

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761150Orig1s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

## NDA/BLA Multi-disciplinary Review and Evaluation

**Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.**

[FDA will complete this section.]

|                                                                |                                                                                                                                                                                                                                                    |
|----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Application Type</b>                                        | Biologics License Application (BLA) 351(a)                                                                                                                                                                                                         |
| <b>Application Number(s)</b>                                   | 761150                                                                                                                                                                                                                                             |
| <b>Priority or Standard</b>                                    | Standard                                                                                                                                                                                                                                           |
| <b>Submit Date(s)</b>                                          | December 18, 2019                                                                                                                                                                                                                                  |
| <b>Received Date(s)</b>                                        | December 18, 2019                                                                                                                                                                                                                                  |
| <b>PDUFA Goal Date</b>                                         | December 18, 2020                                                                                                                                                                                                                                  |
| <b>Division/Office</b>                                         | Division of Oncology 1                                                                                                                                                                                                                             |
| <b>Review Completion Date</b>                                  | December 15, 2020                                                                                                                                                                                                                                  |
| <b>Established Name</b>                                        | Margetuximab-cmkb                                                                                                                                                                                                                                  |
| <b>(Proposed) Trade Name</b>                                   | MARGENZA                                                                                                                                                                                                                                           |
| <b>Pharmacologic Class</b>                                     | HER2-directed antibody antagonist                                                                                                                                                                                                                  |
| <b>Code name</b>                                               | MGAH22                                                                                                                                                                                                                                             |
| <b>Applicant</b>                                               | MacroGenics, Inc.                                                                                                                                                                                                                                  |
| <b>Formulation(s)</b>                                          | 250 mg/10 mL (25 mg/mL) clear to slightly opalescent, colorless to pale yellow or pale brown solution in a single-dose vial                                                                                                                        |
| <b>Dosing Regimen</b>                                          | 15 mg/kg, administered as an intravenous infusion every 3 weeks (21-day cycle)                                                                                                                                                                     |
| <b>Applicant Proposed Indication(s)/Population(s)</b>          | Margenza is indicated in patients with HER2+ metastatic breast cancer who have received [REDACTED] (b) (4)                                                                                                                                         |
| <b>Recommendation on Regulatory Action</b>                     | Approval                                                                                                                                                                                                                                           |
| <b>Recommended Indication(s)/Population(s) (if applicable)</b> | MARGENZA is indicated, in combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease. |

## Table of Contents

|                                                                                                                  |    |
|------------------------------------------------------------------------------------------------------------------|----|
| Reviewers of Multi-Disciplinary Review and Evaluation .....                                                      | 8  |
| Additional Reviewers of Application.....                                                                         | 9  |
| Glossary.....                                                                                                    | 10 |
| 1 Executive Summary .....                                                                                        | 12 |
| 1.1. Product Introduction.....                                                                                   | 12 |
| 1.2. Conclusions on the Substantial Evidence of Effectiveness .....                                              | 12 |
| 1.3. Benefit-Risk Assessment (BRA) .....                                                                         | 14 |
| 1.4. Patient Experience Data.....                                                                                | 19 |
| 2 Therapeutic Context .....                                                                                      | 21 |
| 2.1. Analysis of Condition.....                                                                                  | 21 |
| 2.2. Analysis of Current Treatment Options .....                                                                 | 22 |
| 3 Regulatory Background .....                                                                                    | 29 |
| 3.1. U.S. Regulatory Actions and Marketing History.....                                                          | 29 |
| 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety..... | 31 |
| 4.1. Office of Scientific Investigations (OSI) .....                                                             | 31 |
| 4.2. Product Quality .....                                                                                       | 33 |
| 4.3. Clinical Microbiology .....                                                                                 | 33 |
| 4.4. Devices and Companion Diagnostic Issues .....                                                               | 34 |
| 5 Nonclinical Pharmacology/Toxicology.....                                                                       | 35 |
| 5.1. Executive Summary .....                                                                                     | 35 |
| 5.2. Referenced NDAs, BLAs, DMFs.....                                                                            | 37 |
| 5.3. Pharmacology.....                                                                                           | 37 |
| 5.4. ADME/PK .....                                                                                               | 40 |
| 5.5. Toxicology.....                                                                                             | 42 |
| 5.5.1. General Toxicology.....                                                                                   | 42 |
| 5.5.2. Genetic Toxicology.....                                                                                   | 45 |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
{MARGENZA, margetuximab-cmkb}

|                                                                         |     |
|-------------------------------------------------------------------------|-----|
| 5.5.3. Carcinogenicity.....                                             | 46  |
| 5.5.4. Reproductive and Developmental Toxicology.....                   | 46  |
| 5.5.5. Other Toxicology Studies .....                                   | 47  |
| 6 Clinical Pharmacology.....                                            | 49  |
| 6.1. Executive Summary.....                                             | 49  |
| 6.2. Summary of Clinical Pharmacology Assessment.....                   | 51  |
| 6.2.1. Pharmacology and Clinical Pharmacokinetics .....                 | 51  |
| 6.2.2. General Dosing and Therapeutic Individualization.....            | 52  |
| 6.2.2.1. General Dosing .....                                           | 52  |
| 6.2.2.2. Therapeutic Individualization .....                            | 54  |
| 6.2.2.3. Outstanding Issues .....                                       | 56  |
| 6.3. Comprehensive Clinical Pharmacology Review .....                   | 57  |
| 6.3.1. General Pharmacology and Pharmacokinetic Characteristics.....    | 57  |
| 6.3.2. Clinical Pharmacology Questions.....                             | 63  |
| 7 Sources of Clinical Data .....                                        | 75  |
| 7.1. Table of Clinical Studies.....                                     | 75  |
| 8 Statistical and Clinical Evaluation .....                             | 81  |
| 8.1. Review of Relevant Individual Trials Used to Support Efficacy..... | 81  |
| 8.1.1. CP-MGAH22-04 (SOPHIA, Study 04) .....                            | 81  |
| 8.1.2. Study Results.....                                               | 89  |
| 8.1.3. Supportive Study for Efficacy: CP-MGAH22-01 (Study 01).....      | 112 |
| 8.1.4. Integrated Review of Effectiveness .....                         | 113 |
| 8.1.5. Assessment of Efficacy Across Trials.....                        | 114 |
| 8.1.6. Integrated Assessment of Effectiveness.....                      | 114 |
| 8.2. Review of Safety.....                                              | 117 |
| 8.2.1. Safety Review Approach .....                                     | 118 |
| 8.2.2. Review of the Safety Database .....                              | 119 |
| 8.2.3. Adequacy of Applicant’s Clinical Safety Assessments .....        | 123 |
| 8.2.4. Safety Results.....                                              | 123 |
| 8.2.5. Analysis of Submission-Specific Safety Issues.....               | 141 |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
{MARGENZA, margetuximab-cmkb}

|                                                                                      |     |
|--------------------------------------------------------------------------------------|-----|
| 8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability..... | 144 |
| 8.2.7. Safety Analyses by Demographic Subgroups.....                                 | 145 |
| 8.2.8. Specific Safety Studies/Clinical Trials.....                                  | 147 |
| 8.2.9. Additional Safety Explorations.....                                           | 148 |
| 8.2.10. Safety in the Postmarket Setting.....                                        | 150 |
| 8.2.11. Integrated Assessment of Safety.....                                         | 150 |
| SUMMARY AND CONCLUSIONS.....                                                         | 153 |
| 8.3. Statistical Issues.....                                                         | 154 |
| 8.4. Conclusions and Recommendations.....                                            | 155 |
| 9 Advisory Committee Meeting and Other External Consultations.....                   | 156 |
| 10 Pediatrics.....                                                                   | 157 |
| 11 Labeling Recommendations.....                                                     | 158 |
| 12 Risk Evaluation and Mitigation Strategies (REMS).....                             | 169 |
| 13 Postmarketing Requirements and Commitment.....                                    | 170 |
| 14 Division Director (DHOT) (NME ONLY).....                                          | 172 |
| 15 Division Director (OCP).....                                                      | 173 |
| 16 Division Director (OB).....                                                       | 174 |
| 17 Division Director (Clinical).....                                                 | 175 |
| 18 Office Director (or designated signatory authority).....                          | 176 |
| 19 Appendices.....                                                                   | 177 |
| 19.1. References.....                                                                | 177 |
| 19.2. Financial Disclosure.....                                                      | 180 |
| 19.3. Nonclinical Pharmacology/Toxicology.....                                       | 182 |
| 19.4. OCP Appendices (Technical documents supporting OCP recommendations).....       | 182 |
| 19.4.1 Bioanalytical Method Performance Summary.....                                 | 182 |
| 19.4.2 Pharmacometrics Review.....                                                   | 194 |
| 19.5. Additional Safety Analyses Conducted by FDA.....                               | 208 |

## Table of Tables

|                                                                                                                                                                    |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Table 1: CD16A Biology and Trastuzumab Outcome .....                                                                                                               | 23  |
| Table 2: Treatments Relevant to Proposed Indication in Metastatic Disease (Efficacy).....                                                                          | 24  |
| Table 3: Treatments Relevant to Proposed Indication (Safety).....                                                                                                  | 25  |
| Table 4: Key Regulatory Interactions Related to BLA 761150 .....                                                                                                   | 29  |
| Table 5: Summary of Population Pharmacokinetic Results .....                                                                                                       | 54  |
| Table 6: PPK Predicted Geometric Mean (%CV) Exposure Parameters in 261 Female Patients<br>with MBC who Received 15 mg/kg Q3W .....                                 | 57  |
| Table 7: Listing of Clinical Trials Relevant to this BLA.....                                                                                                      | 76  |
| Table 8: Schedule of Events (CP-MGAH22-04) .....                                                                                                                   | 85  |
| Table 9: Summary of Key SAP Amendments .....                                                                                                                       | 87  |
| Table 10: Subject Disposition (ITT Population; Data Cutoff 10-Oct-2018) .....                                                                                      | 90  |
| Table 11: Major Protocol Deviations (ITT Population; Data Cutoff 10-Oct-2018).....                                                                                 | 92  |
| Table 12: Demographic and Baseline Characteristics (ITT Population; Data Cutoff 10-Oct-2018)<br>.....                                                              | 93  |
| Table 13: Cancer Disease History (ITT Population; Data Cutoff 10-Oct-2018) .....                                                                                   | 94  |
| Table 14: Baseline CD16A, CD32A and CD32B Status (ITT Population; Data Cutoff 10-Oct-2018)<br>.....                                                                | 95  |
| Table 15: Prior Systemic/Hormonal Therapy (ITT Population; Data Cutoff 10-Oct-2018) .....                                                                          | 96  |
| Table 16: Randomization Stratification Factors (ITT Population; Data Cutoff 10-Oct-2018).....                                                                      | 97  |
| Table 17: Study 04 Independently Assessed PFS (ITT Population; Data Cutoff 10-Oct-2018) .....                                                                      | 99  |
| Table 18: Study 04 Overall Survival (ITT Population; Data Cutoff 10-Sep-2019).....                                                                                 | 101 |
| Table 19: Subject Exposure (Safety Population; Data Cutoff 10-Oct-2018) .....                                                                                      | 120 |
| Table 20: Summary of Deaths (Safety Population; Data Cutoff 10-Apr-2019).....                                                                                      | 124 |
| Table 21: Serious Adverse Events (Regardless of Causality) in $\geq 2$ Subjects (Safety Population;<br>Data Cutoff 10-Apr-2019) .....                              | 128 |
| Table 22: Adverse Events Leading to Discontinuation from Whole Study Treatment (Regardless<br>of Causality) (Safety Population; Data Cutoff 10-Apr-2019) .....     | 129 |
| Table 23: Adverse Events Grade $\geq 3$ (Regardless of Causality) in $\geq 4$ Subjects (Safety Population;<br>Data Cutoff 10-Apr-2019) .....                       | 132 |
| Table 24: Adverse Events (Regardless of Causality) in $\geq 5\%$ Subjects (Safety Population; Data<br>Cutoff 10-Apr-2019).....                                     | 133 |
| Table 25: Adverse Reactions in $\geq 5\%$ Subjects (Safety Population; Data Cutoff 10-Apr-2019)..                                                                  | 135 |
| Table 26: FDA Analysis of Treatment Emergent Adverse Events in $\geq 5\%$ of Patients in Study 04<br>data cut off date October 10, 2018. ....                      | 137 |
| Table 27: : FDA Analysis of Laboratory Abnormalities in $\geq 20\%$ of Patients that worsened from<br>baseline in Study 04 data cut off date October 10, 2018..... | 139 |
| Table 28: Summary Method Performance of Bioanalytical Method RES-014 Ver 00, 01, 02 to<br>Measure MGAH22 in Human Serum in CP-MGAH22-01 .....                      | 182 |

|                                                                                                                                    |     |
|------------------------------------------------------------------------------------------------------------------------------------|-----|
| Table 29: Summary Method Performance of Bioanalytical Method RES-014 Ver 03 to Measure MGAH22 in Human Serum in CP-MGAH22-02 ..... | 185 |
| Table 30: Summary of Method RES-014 Ver 03 Modification(s) and Cross-validation Results .                                          | 188 |
| Table 31: Summary Method Performance of Bioanalytical Method ICD 638 to Measure Margetuximab in Human Serum in CP-MGAH22-04 .....  | 190 |
| Table 32: Summary of Method ICD 638 Modification(s) and Cross-validation Results .....                                             | 193 |
| Table 33 General Design/Data Characteristics of Clinical Studies Pooled in Population PK Analysis .....                            | 195 |
| Table 34. Summary of Covariates. ....                                                                                              | 196 |
| Table 35 Margetuximab Population Pharmacokinetic Parameter Estimates (Final Model 103, Study 01, 02, and 04) .....                 | 199 |
| Table 36. Summary of Exposures for Subjects from Study CP-MGAH22-04 .....                                                          | 204 |
| Table 37 PPK Predicted Margetuximab Pharmacokinetic Parameters by Infusion Duration (15 mg/kg Every 3 weeks) .....                 | 204 |
| Table 38 CPH Models for PFS-INV: Final Model.....                                                                                  | 206 |
| Table 39 Summary of Hazard Ratios for PFS with respect to quantiles of CavgSS, Study 04.....                                       | 206 |
| Table 40 Summary of Hazard Ratios for PFS by each quantile vs. placebo* .....                                                      | 206 |
| Table 41. Specific Comments on Applicant’s Final Population PK model .....                                                         | 207 |

### Table of Figures

|                                                                                                                                |     |
|--------------------------------------------------------------------------------------------------------------------------------|-----|
| Figure 1: Schematic of Study Design (CP-MGAH22-04).....                                                                        | 81  |
| Figure 2: Study 04 Independently Assessed PFS (ITT Population; Data Cutoff 10-Oct-2018) ....                                   | 100 |
| Figure 3: Study 04 Independently Assessed PFS - Pre-specified Subgroup Analyses (ITT Population; Data Cutoff 10-Oct-2018)..... | 103 |
| Figure 4: Study 04 Overall Survival - Pre-specified Subgroup Analyses (ITT Population; Data Cutoff 10-Sep-2019).....           | 105 |
| Figure 1 Margetuximab PPK Model Scheme and Model Equations.....                                                                | 198 |
| Figure 2 Goodness of Fit for Study CP-MGAH22-04 .....                                                                          | 200 |
| Figure 3 Visual Predictive Check for Study CP-MGAH22-04, Final Model 103 .....                                                 | 200 |
| Figure 4 Relationship Between Margetuximab Exposure and Tertiles of Body Weight (Final Model 103, Study 04).....               | 201 |
| Figure 5. Relationship Between Margetuximab Exposure and Tertiles of ALB (Final Model 103, Study 04) .....                     | 202 |

## Reviewers of Multi-Disciplinary Review and Evaluation

---

|                                                            |                                                          |
|------------------------------------------------------------|----------------------------------------------------------|
| <b>Regulatory Project Manager</b>                          | Kelly Chiang<br>Clara Lee                                |
| <b>Pharmacology/Toxicology Reviewer(s)</b>                 | Ching-Jey George Chang                                   |
| <b>Pharmacology/Toxicology Team Leader(s)</b>              | Tiffany Ricks                                            |
| <b>Office of Clinical Pharmacology Reviewer(s)</b>         | Krithika Shetty<br>Jeff Kraft<br>Junshan Qiu             |
| <b>Office of Clinical Pharmacology Team Leader(s)</b>      | Pengfei Song<br>Rosane Charlab Orbach<br>Jingyu Jerry Yu |
| <b>Clinical Reviewer</b>                                   | Melanie Royce                                            |
| <b>Clinical Team Leader</b>                                | Christy Osgood                                           |
| <b>Safety Analyst (if applicable)</b>                      | NA                                                       |
| <b>Statistical Reviewer</b>                                | Anup Amatya                                              |
| <b>Statistical Team Leader</b>                             | Mallorie Fiero                                           |
| <b>Associate Director for Labeling (ADL)</b>               | William Pierce                                           |
| <b>Cross-Disciplinary Team Leader</b>                      | Christy Osgood                                           |
| <b>Division Director (DHOT)</b>                            | John Leighton                                            |
| <b>Division Director (OCP)</b>                             | Nam Atiqur Rahman                                        |
| <b>Division Director (OB)</b>                              | Shenghui Tang                                            |
| <b>Division Director (OOD)</b>                             | Laleh Amiri-Kordestani                                   |
| <b>Office Director (or designated signatory authority)</b> | Julia Beaver                                             |

### Additional Reviewers of Application

|                      |                                                                                              |
|----------------------|----------------------------------------------------------------------------------------------|
| <b>OPQ/OBP/DBRR1</b> | Kathryn King<br>Anshu Rastogi<br>Brian Janelsins<br>Wendy Weinberg<br>Kathleen Clouse        |
| <b>OPQ/OBP/IO</b>    | Vicky Borders-Hemphill                                                                       |
| <b>OPQ/OPMA/DBM</b>  | Lindsey Brown<br>Candace Gomez-Broughton<br>Zhong Li<br>Thuy Thanh Nguyen<br>Zihao Peter Qui |
| <b>OPQ/OPRO</b>      | Anh-Thy Ly                                                                                   |
| <b>OPDP</b>          | Maritsa Serlemitsos-Day                                                                      |
| <b>OSI</b>           | Suyoung Tina Chang                                                                           |
| <b>OSE/DEPI</b>      | Richard Scott Swain                                                                          |
| <b>OSE/DMEPA</b>     | Tingting Gao<br>Chi-Ming Alice Tu                                                            |
| <b>PFDD</b>          | Belinda Kallimanis                                                                           |

OPQ=Office of Pharmaceutical Quality  
 OPDP=Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 OSE= Office of Surveillance and Epidemiology  
 DEPI= Division of Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DRISK=Division of Risk Management  
 PFDD= Patient Focus Drug Development

## Glossary

---

|       |                                                 |
|-------|-------------------------------------------------|
| AC    | advisory committee                              |
| ADA   | antidrug antibody                               |
| ADCC  | antibody-dependent cellular cytotoxicity        |
| ADME  | absorption, distribution, metabolism, excretion |
| AE    | adverse event                                   |
| AESI  | adverse event of special interest               |
| ASCO  | American Society of Clinical Oncology           |
| BLA   | biologics license application                   |
| BPCA  | Best Pharmaceuticals for Children Act           |
| BRF   | Benefit Risk Framework                          |
| CBER  | Center for Biologics Evaluation and Research    |
| CBR   | clinical benefit rate                           |
| CDER  | Center for Drug Evaluation and Research         |
| CDRH  | Center for Devices and Radiological Health      |
| CDTL  | Cross-Discipline Team Leader                    |
| CFR   | Code of Federal Regulations                     |
| CI    | confidence interval                             |
| CMC   | chemistry, manufacturing, and controls          |
| CRF   | case report form                                |
| CSR   | clinical study report                           |
| CSS   | Controlled Substance Staff                      |
| DMC   | data monitoring committee                       |
| ECG   | electrocardiogram                               |
| ECOG  | Eastern Cooperative Oncology Group              |
| eCTD  | electronic common technical document            |
| E-R   | exposure response                               |
| ETASU | elements to assure safe use                     |
| FcyR  | Fcy receptor                                    |
| FDA   | Food and Drug Administration                    |
| FISH  | fluorescence in situ hybridization              |
| GCP   | good clinical practice                          |
| GLP   | good laboratory practice                        |
| GRMP  | good review management practice                 |
| HER2  | human epidermal growth factor receptor 2        |
| HR    | hazard ratio                                    |
| ICH   | International Conference on Harmonization       |
| IND   | Investigational New Drug                        |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
{MARGENZA, margetuximab-cmkb}

|           |                                                                         |
|-----------|-------------------------------------------------------------------------|
| IRR       | infusion-related reaction                                               |
| ISE       | integrated summary of effectiveness                                     |
| ISS       | integrated summary of safety                                            |
| ITT       | intent to treat                                                         |
| IV        | intravenous                                                             |
| LVEF      | left ventricular ejection fraction                                      |
| M         | margetuximab                                                            |
| mAb       | monoclonal antibody                                                     |
| MBC       | metastatic breast cancer                                                |
| MedDRA    | Medical Dictionary for Regulatory Activities                            |
| mITT      | modified intent to treat                                                |
| NCCN      | National Comprehensive Cancer Network                                   |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA       | new drug application                                                    |
| NME       | new molecular entity                                                    |
| OCS       | Office of Computational Science                                         |
| OPQ       | Office of Pharmaceutical Quality                                        |
| ORR       | objective response rate                                                 |
| OS        | overall survival                                                        |
| OSE       | Office of Surveillance and Epidemiology                                 |
| OSI       | Office of Scientific Investigation                                      |
| PD        | pharmacodynamics                                                        |
| PFS       | progression-free survival                                               |
| PK        | pharmacokinetics                                                        |
| PMC       | postmarketing commitment                                                |
| PMR       | postmarketing requirement                                               |
| PPK       | population pharmacokinetics                                             |
| PRO       | patient reported outcome                                                |
| Q3W       | every 3 weeks                                                           |
| QW        | once weekly                                                             |
| RECIST    | Response Evaluation Criteria in Solid Tumors                            |
| REMS      | risk evaluation and mitigation strategy                                 |
| SAE       | serious adverse event                                                   |
| SAP       | Statistical Analysis Plan                                               |
| SMQ       | standardized MedDRA query                                               |
| SOC       | system organ class                                                      |
| T         | trastuzumab                                                             |
| T-DM1     | ado-trastuzumab emtansine                                               |
| TEAE      | treatment-emergent adverse event                                        |
| USPI      | United States prescribing information                                   |

## 1 Executive Summary

---

### 1.1. Product Introduction

Margetuximab-cmkb, a HER2/neu receptor antagonist, is a chimeric Fc-engineered IgG1 kappa monoclonal antibody. Margetuximab-cmkb binds to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). Upon binding to HER2-expressing tumor cells, margetuximab-cmkb inhibits tumor cell proliferation, reduces shedding of the HER2 extracellular domain and mediates antibody-dependent cellular cytotoxicity (ADCC).

The Applicant proposed the following indication for BLA 761150:

*Margenza is indicated in patients with HER2+ metastatic breast cancer who have received* <sup>(b) (4)</sup>

The recommended indication for regular approval is:

*MARGENZA is indicated, in combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.*

The recommended dose for margetuximab is 15 mg/kg, administered every 3 weeks as an intravenous infusion over 120 minutes for the initial dose, then over a minimum of 30 minutes in subsequent cycles if prior infusions were well tolerated. On days when both margetuximab and chemotherapy are to be administered, margetuximab may be administered immediately after chemotherapy completion.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends approval of margetuximab, according to 21 Code of Federal Regulations (CFR), Part 601.20, Subpart C of the Biological Licensing Regulations. The basis of this recommendation is a favorable risk-benefit profile for margetuximab when added to chemotherapy in patients with metastatic HER2-positive breast cancer who have received prior anti-HER2 regimens, at least one of which was for metastatic disease. The recommendation for approval is based on efficacy and safety data from study CP-MGAH22-04 (SOPHIA, Study 04). Study 04 was a multicenter, randomized, open-label, active controlled study comparing margetuximab plus chemotherapy to trastuzumab plus chemotherapy in patients with IHC 3+ or ISH-amplified HER2+ metastatic breast cancer. A total of 536 patients were randomized (1:1) to receive either margetuximab 15 mg/kg every 3 weeks plus chemotherapy (n=266) or trastuzumab 8 mg/kg loading dose, followed by 6 mg/kg every 3

weeks thereafter plus chemotherapy (n=270). Study 04 demonstrated a statistically significant difference in the primary endpoint of PFS by blinded independent central review (BICR) with a stratified hazard ratio of 0.76 (95% CI: 0.59, 0.98; p=0.0334). The median PFS in the margetuximab plus chemotherapy arm was 5.8 months (95% CI: 5.5, 7.0) compared to a median PFS of 4.9 months (4.2, 5.6) in the trastuzumab plus chemotherapy arm. Overall survival (OS) was immature (70% of targeted OS events). Median OS was 21.6 months (95% CI: 17.7, 23.8) in the margetuximab plus chemotherapy arm compared to 19.8 months (95% CI: 15.5, 21.2) in the trastuzumab plus chemotherapy arm (HR 0.89; 95% CI: 0.69, 1.13; p=0.2086). The objective response rate (ORR) was 22% (95% CI: 17%, 27%) in the margetuximab plus chemotherapy arm vs 16% (95% CI: 12%, 20%) in the trastuzumab arm. Median duration of response was 6.1 months (4.1, 9.1) vs 6.0 months (4.0, 6.9), respectively.

Overall the toxicity of margetuximab plus chemotherapy is acceptable for the intended population with the use of temporary treatment discontinuations, supportive therapies, and/or standard medical care. The most common adverse reactions (>10%) with margetuximab plus chemotherapy were fatigue/asthenia, nausea, diarrhea, vomiting, constipation, headache, pyrexia, alopecia, abdominal pain, peripheral neuropathy, arthralgia/myalgia, cough, decreased appetite, dyspnea, infusion-related reactions, palmar-plantar erythrodysesthesia, and extremity pain. Infusion related reactions (IRR) are an important safety signal associated with margetuximab plus chemotherapy. In Study 04, IRRs were reported in 13% of patients treated with margetuximab plus chemotherapy. Grade 3 IRRs were reported in 1.5% of margetuximab plus chemotherapy treated patients. Additionally, left ventricular dysfunction is an important class effect of HER2 directed monoclonal antibodies. In Study 04 left ventricular dysfunction occurred in 1.9% of patients treated with margetuximab plus chemotherapy, and patients with a pretreatment left ventricular ejection fraction value of <50%, a prior history of infarction or unstable angina within 6 months, or congestive heart failure NYHA class II-IV were not enrolled in Study 04. Other than these two important adverse reactions, margetuximab plus chemotherapy is associated with an incidence of serious adverse reaction of 16% compared to 18% in the trastuzumab plus chemotherapy arm. The incidence of adverse reaction leading to discontinuation was similar in the two arms occurring in 3% of patients in the margetuximab plus chemotherapy compared to 2.6% of patients in the trastuzumab plus chemotherapy arm. Fatal adverse reactions occurred in 1.1% of patients treated with margetuximab plus chemotherapy compared to 0.8% of patients treated with trastuzumab plus chemotherapy.

In summary, margetuximab plus chemotherapy for the treatment of adult patients with advanced or metastatic HER-2 positive breast cancer and who have received two or more prior anti-HER2 based regimens, at least one in the metastatic setting demonstrates a favorable benefit-risk profile with adequate evidence to recommend approval. All disciplines were in agreement with approval of margetuximab, or did not identify any outstanding issues that precluded approval.

### 1.3. Benefit-Risk Assessment (BRA)

#### Benefit-Risk Summary and Assessment

Margetuximab, a HER2/neu receptor antagonist chimeric Fc-engineered IgG1 kappa monoclonal antibody, is recommended for approval for the treatment, in combination with chemotherapy of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

In the United States (US), breast cancer is the most common cancer in women, with more than 260,000 new cases and 40,000 deaths annually. Metastatic breast cancer is categorized into different histopathological subtypes based on expression of ER, PR, and HER2. Approximately 20-25% of patients with breast cancer have HER2-positive tumors. HER2-positive disease is associated with a more aggressive tumor and a younger patient population.

Current standard of care for first-line metastatic HER2-positive breast cancer in the US is the combination of trastuzumab, pertuzumab, and a taxane. T-DM1 is the preferred second-line option. Lapatinib in combination with capecitabine is approved for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. Fam-trastuzumab deruxtecan-nxki, a HER2-directed antibody and topoisomerase inhibitor conjugate, is approved under the accelerated approval program for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. Neratinib is a kinase inhibitor indicated in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting. Tucatinib, a tyrosine kinase inhibitor of HER2 was approved in combination with trastuzumab and capecitabine for the treatment of patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting. Although treatment with anti-HER2 therapies has improved the disease outcomes for patients with unresectable or metastatic HER2-positive breast cancer, patients invariably progress. There remains an unmet need for further effective therapies for metastatic HER2-positive breast cancer, especially in later lines of therapy.

Study CP-MGAH22-04 (Study 04, SOPHIA, NCT02492711) is a multicenter, randomized, open-label, active-controlled trial of margetuximab plus chemotherapy vs trastuzumab plus chemotherapy in patients with advanced or metastatic HER2-positive breast cancer who had received prior treatment with other anti-HER2 therapies. A total of 536 patients were randomized (1:1) to margetuximab plus chemotherapy (n=266) or

trastuzumab plus chemotherapy (n=270). Randomization was stratified by chemotherapy choice (capecitabine, eribulin, gemcitabine, or vinorelbine), number of lines of therapy in the metastatic setting ( $\leq 2$ ,  $> 2$ ), and number of metastatic sites ( $\leq 2$ ,  $> 2$ ). Patients received margetuximab intravenously at a dose of 15 mg/kg every 3 weeks administered over 120 minutes for the initial administration and then over 30 to 120 minutes thereafter. Trastuzumab was given intravenously at an initial dose of 8 mg/kg over 90 minutes, followed by 6 mg/kg over 30 minutes every 3 weeks thereafter. Patients were treated with margetuximab or trastuzumab plus with chemotherapy until disease progression or unacceptable toxicity. Study 04 demonstrated a statistically significant difference in the primary endpoint of PFS by BICR. The median PFS in the margetuximab plus chemotherapy arm was 5.8 months (95% CI: 5.5, 7.0) compared to a median PFS of 4.9 months (95%CI: 4.2, 5.6) in the trastuzumab plus chemotherapy arm corresponding to a stratified hazard ratio of 0.76 (95% CI: 0.59, 0.98). The OS results are immature (70% of targeted OS events). The median OS was 21.6 months (95% CI: 17.7, 23.8) in the margetuximab plus chemotherapy arm compared to 19.8 months (95% CI: 15.5, 21.2) in the trastuzumab plus chemotherapy arm (HR 0.89; 95% CI: 0.69, 1.13;  $p=0.2086$ ). The final OS will be provided as part of an agreed upon post marketing commitment (PMC). The objective response rate (ORR) was 22% (95% CI: 17%, 27%) in the margetuximab plus chemotherapy arm vs 16% (95% CI: 12%, 20%) in the trastuzumab arm. Median duration of response was 6.1 months (95% CI: 4.1, 9.1) vs 6.0 months (95% CI: 4.0, 6.9), respectively.

A major review issue with this application was that the magnitude of improvement in median PFS per BIRC was shorter than the imaging interval of 6 weeks. However, as trastuzumab plus chemotherapy is an active control, there is a reasonable assurance that margetuximab plus chemotherapy confers, at the minimum, the same amount of benefit, if not more, as trastuzumab plus chemotherapy in this disease setting. There is not a requirement that a therapy for regular approval be better than that of available therapies. Additionally, the Applicant conducted a post-hoc interval censored analysis of PFS to assess sensitivity of primary analysis results with respect to imaging interval. The median PFS estimated with this approach in the margetuximab plus chemotherapy arm was 5.6 months (95% CI: 5.62-5.82) and in trastuzumab plus chemotherapy arm was 4.4 months (95% CI: 3.52-4.76). These results provide further assurance of robustness of primary analysis results.

An additional review issue was that the subgroup of patients with Fc-receptor CD16A-158 V/V homozygote appeared to have different outcomes in a direction unfavorable to margetuximab plus chemotherapy compared to overall study population and other subgroups. This is a mechanistically unexpected finding because margetuximab is specifically Fc-engineered to provide higher affinity, compared to trastuzumab, to both F-carriers and V/V alleles. Further post-hoc analysis accounting for moderate imbalance in prognostics factors did not yield a satisfactory explanation for this observed anomaly. Nonetheless, the subgroup analysis result should be interpreted with caution due to a small sample size (n=69), possible imbalances in patient known/unknown characteristics between treatment arms, and no clear mechanistic basis to support the observed heterogeneity. More studies will be required to explain and better understand this apparent incongruity. Additional information

pertinent to CD16A (FCaGR3A) F158V genotype and patient outcome from clinical trials that correlate CD16A (FCGR3A) F158V genotype with trial efficacy endpoints to further characterize the clinical benefit of margetuximab will be provided as part of an agreed upon PMC.

The safety of margetuximab plus chemotherapy was evaluated in Study 04. A total of 530 patients enrolled received at least one dose of study treatment. These included a total of 264 patients on the margetuximab plus chemotherapy arm and 266 patients on the trastuzumab plus chemotherapy arm. The most common adverse reactions (>10%) experienced by patients in the margetuximab plus chemotherapy arm were fatigue/asthenia, nausea, diarrhea, vomiting, constipation, headache, pyrexia, alopecia, abdominal pain, peripheral neuropathy, arthralgia/myalgia, cough, decreased appetite, dyspnea, infusion-related reactions, palmar-plantar erythrodysesthesia, and extremity pain. Serious adverse reactions occurred in 16% of patients who received margetuximab plus chemotherapy. Serious adverse reactions in > 1% of patients included febrile neutropenia (1.5%), neutropenia/neutrophil count decrease (1.5%) and infusion related reactions (1.1%). Serious adverse reactions occurred in 18% of patients who received trastuzumab plus chemotherapy. Serious adverse reaction in >1% of patients included febrile neutropenia (3.8%), pleural effusion (1.5%), pyrexia (1.5%), and cellulitis (1.5%). Fatal adverse reactions occurred in 1.1% of patients who received margetuximab plus chemotherapy, including viral pneumonia (0.8%) and aspiration pneumonia (0.4%). Fatal adverse reactions occurred in 0.8% of patients who received trastuzumab plus chemotherapy, including viral pneumonia (0.4%) and acute kidney injury (0.4%).

The prescribing information includes a Boxed Warning to advise health professionals of the risk of left ventricular dysfunction and embryo-fetal toxicity. In Study 04 left ventricular dysfunction occurred in 1.9% of patients treated with margetuximab plus chemotherapy; however, since this is a known class effect of HER2 directed monoclonal antibodies, margetuximab was not studied in patients with pretreatment LVEF value of < 50%, a prior history of myocardial infarction or unstable angina within 6 months, or congestive heart failure NYHA class II-IV. IRRs are an additional important adverse reaction in Study 04. In Study 04, IRRs were reported by 13% of patients on the margetuximab plus chemotherapy arm. Grade 3 IRRs were reported in 1.5% of margetuximab treated patients. IRRs leading to interruption of treatment occurred in 9% in patients treated with margetuximab plus chemotherapy. One patient (0.4%) on margetuximab discontinued treatment due to IRR. The prescribing information contains a warning and precaution to inform health care professionals about the risk of IRRs in patients treated with margetuximab.

Overall, the benefit-risk profile for margetuximab plus chemotherapy based upon results from Study 04 is favorable. Although the PFS improvement is only 0.9 months, margetuximab plus chemotherapy represents a new treatment option for patients with HER2-positive advanced/metastatic breast cancer whose disease has progressed on prior HER2-based therapies in the metastatic setting and patients may benefit from having an alternative therapy to trastuzumab combinations. MARGENZA (margetuximab) is recommended for approval for the

following indication: MARGENZA is indicated, in combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

| Dimension                                 | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Conclusions and Reasons                                                                                                                                                                                     |
|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <a href="#">Analysis of Condition</a>     | <ul style="list-style-type: none"> <li>Breast cancer is the most common cancer in women, with more than 260,000 new cases and 40,000 deaths annually.</li> <li>HER2-positive breast cancer comprises approximately 20 to 25% of the entire breast cancer population.</li> <li>HER2 gene amplification or HER2 protein overexpression in breast cancer tumors is associated with more aggressive clinical disease and historically poorer prognosis.</li> <li>Advanced or metastatic HER2-positive breast cancer is incurable.</li> </ul>                                                                                                                                                                                                                                                                                                                           | <p><b>Advanced or metastatic HER2-positive breast cancer is a serious and life-threatening condition with an ongoing unmet medical need.</b></p>                                                            |
| <a href="#">Current Treatment Options</a> | <ul style="list-style-type: none"> <li>Treatment goals for metastatic HER2-positive breast cancer are palliative in nature to delay disease progression, prolong survival, and reduce cancer-related symptoms.</li> <li>The combination of trastuzumab, pertuzumab, and taxane is an FDA approved treatment for patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.</li> <li>T-DM1 is FDA approved for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane.</li> <li>Other standard options can include fam-trastuzumab deruxtecan-nxki, neratinib or lapatinib plus capecitabine, tucatinib plus capecitabine and trastuzumab, or trastuzumab combined with another chemotherapeutic agent.</li> </ul> | <p><b>There is an unmet medical need to improve the outcomes of patients with HER2-positive advanced or metastatic breast cancer whose disease has progressed on available HER2-directed therapies.</b></p> |

| Dimension                                       | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><a href="#">Benefit</a></p>                  | <ul style="list-style-type: none"> <li>The efficacy of margetuximab plus chemotherapy was evaluated in Study 04, a multicenter, randomized, open-label, active controlled trial of margetuximab plus chemotherapy versus trastuzumab plus chemotherapy in patients with advanced or metastatic HER2-positive who have received prior anti-HER2 based regimens in the metastatic setting.</li> <li>Median PFS in the margetuximab plus chemotherapy arm was 5.8 months (95% CI: 5.5, 7.0) compared to 4.9 months (95% CI: 4.2, 5.6) in the trastuzumab plus chemotherapy arm (HR = 0.76; 95% CI: 0.59, 0.98; p = 0.033).</li> <li>OS was immature (70% of targeted OS events). Median OS was 21.6 months (95%CI: 17.7, 23.8) in the margetuximab plus chemotherapy arm compared to 19.8 months (95% CI: 15.5, 21.2) in the trastuzumab plus chemotherapy arm (HR 0.89; 95% CI: 0.69, 1.13; p=0.2086).</li> <li>The ORR was 22% (95% CI: 17%, 27%) in the margetuximab plus chemotherapy arm vs 16% (95% CI: 12%, 20%) in the trastuzumab arm. Median duration of response was 6.1 months (95%CI: 4.1, 9.1) vs 6.0 months (95%CI: 4.0, 6.9), respectively.</li> </ul> | <p><b>Study 04 resulted in a statistically significant difference in PFS when margetuximab plus chemotherapy was compared to trastuzumab plus chemotherapy. Although the PFS improvement is only 0.9 months, margetuximab plus chemotherapy represents a replacement therapy for trastuzumab plus chemotherapy and patients may benefit from having an alternative therapy.</b></p> <p><b>Overall survival was immature; however no apparent detriment was observed in patients who received margetuximab plus chemotherapy compared to those that received trastuzumab plus chemotherapy.</b></p> |
| <p><a href="#">Risk and Risk Management</a></p> | <ul style="list-style-type: none"> <li>Common adverse reactions observed &gt;10% of patients treated with margetuximab plus chemotherapy on Study 04 were fatigue/asthenia, nausea, diarrhea, vomiting, constipation, headache, pyrexia, alopecia, abdominal pain, peripheral neuropathy, arthralgia/myalgia, cough, decreased appetite, dyspnea, infusion-related reactions, palmar-plantar erythrodysesthesia, and extremity pain.</li> <li>Three percent of patients discontinued margetuximab plus chemotherapy due to an adverse reaction and 2.6% of patients discontinued trastuzumab plus chemotherapy due to an adverse reaction</li> <li>Fatal adverse reactions occurred in 1.1% of patients who received</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                     | <p><b>Margetuximab demonstrated acceptable tolerability for the indicated population with a serious and life-threatening disease.</b></p> <p><b>The safe use of margetuximab plus chemotherapy can be managed through appropriate labeling, including boxed warning for left ventricular dysfunction and embryofetal toxicity as well as a warning and precaution for infusion</b></p>                                                                                                                                                                                                             |

| Dimension | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Conclusions and Reasons                         |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
|           | margetuximab plus chemotherapy and in 0.8% of patients who received trastuzumab plus chemotherapy. <ul style="list-style-type: none"> <li>• Serious adverse reactions occurred in 16% of patients who received margetuximab plus chemotherapy and in 18% of patients who received trastuzumab plus chemotherapy, respectively.</li> <li>• Dose interruptions due to an adverse reaction occurred in 11% of patients who received margetuximab plus chemotherapy and 3.0% of patients who received trastuzumab plus chemotherapy, respectively.</li> </ul> | <b>related reactions. No REMS is indicated.</b> |

#### 1.4. Patient Experience Data

##### Patient Experience Data Relevant to this Application (check all that apply)

|                          |                                                                                                                                                                                                                                                                                   |                                        |                                                                                                                                    |                      |
|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| <input type="checkbox"/> | The patient experience data that was submitted as part of the application, include:                                                                                                                                                                                               | Section where discussed, if applicable |                                                                                                                                    |                      |
| x                        | Clinical outcome assessment (COA) data, such as                                                                                                                                                                                                                                   |                                        |                                                                                                                                    |                      |
|                          | <table border="0"> <tr> <td data-bbox="338 911 401 951">x</td> <td data-bbox="401 911 1409 951">Patient reported outcome (PRO)</td> </tr> </table>                                                                                                                                | x                                      | Patient reported outcome (PRO)                                                                                                     | <b>Section 8.1.2</b> |
| x                        | Patient reported outcome (PRO)                                                                                                                                                                                                                                                    |                                        |                                                                                                                                    |                      |
|                          | <table border="0"> <tr> <td data-bbox="338 951 401 992"><input type="checkbox"/></td> <td data-bbox="401 951 1409 992">Observer reported outcome (ObsRO)</td> </tr> </table>                                                                                                      | <input type="checkbox"/>               | Observer reported outcome (ObsRO)                                                                                                  | Not applicable       |
| <input type="checkbox"/> | Observer reported outcome (ObsRO)                                                                                                                                                                                                                                                 |                                        |                                                                                                                                    |                      |
|                          | <table border="0"> <tr> <td data-bbox="338 992 401 1032"><input type="checkbox"/></td> <td data-bbox="401 992 1409 1032">Clinician reported outcome (ClinRO)</td> </tr> </table>                                                                                                  | <input type="checkbox"/>               | Clinician reported outcome (ClinRO)                                                                                                | Not applicable       |
| <input type="checkbox"/> | Clinician reported outcome (ClinRO)                                                                                                                                                                                                                                               |                                        |                                                                                                                                    |                      |
|                          | <table border="0"> <tr> <td data-bbox="338 1032 401 1073"><input type="checkbox"/></td> <td data-bbox="401 1032 1409 1073">Performance outcome (PerFO)</td> </tr> </table>                                                                                                        | <input type="checkbox"/>               | Performance outcome (PerFO)                                                                                                        | Not applicable       |
| <input type="checkbox"/> | Performance outcome (PerFO)                                                                                                                                                                                                                                                       |                                        |                                                                                                                                    |                      |
|                          | <table border="0"> <tr> <td data-bbox="264 1073 327 1154"><input type="checkbox"/></td> <td data-bbox="327 1073 1409 1154">Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)</td> </tr> </table> | <input type="checkbox"/>               | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | Not applicable       |
| <input type="checkbox"/> | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)                                                                                                                                                |                                        |                                                                                                                                    |                      |
|                          | <table border="0"> <tr> <td data-bbox="264 1154 327 1235"><input type="checkbox"/></td> <td data-bbox="327 1154 1409 1235">Patient-focused drug development or other stakeholder meeting summary reports</td> </tr> </table>                                                      | <input type="checkbox"/>               | Patient-focused drug development or other stakeholder meeting summary reports                                                      | Not applicable       |
| <input type="checkbox"/> | Patient-focused drug development or other stakeholder meeting summary reports                                                                                                                                                                                                     |                                        |                                                                                                                                    |                      |
|                          | <table border="0"> <tr> <td data-bbox="264 1235 327 1276"><input type="checkbox"/></td> <td data-bbox="327 1235 1409 1276">Observational survey studies designed to capture patient experience data</td> </tr> </table>                                                           | <input type="checkbox"/>               | Observational survey studies designed to capture patient experience data                                                           | Not applicable       |
| <input type="checkbox"/> | Observational survey studies designed to capture patient experience data                                                                                                                                                                                                          |                                        |                                                                                                                                    |                      |
|                          | <table border="0"> <tr> <td data-bbox="264 1276 327 1317"><input type="checkbox"/></td> <td data-bbox="327 1276 1409 1317">Natural history studies</td> </tr> </table>                                                                                                            | <input type="checkbox"/>               | Natural history studies                                                                                                            | Not applicable       |
| <input type="checkbox"/> | Natural history studies                                                                                                                                                                                                                                                           |                                        |                                                                                                                                    |                      |
|                          | <table border="0"> <tr> <td data-bbox="264 1317 327 1364"><input type="checkbox"/></td> <td data-bbox="327 1317 1409 1364">Patient preference studies (e.g., submitted studies or scientific publications)</td> </tr> </table>                                                    | <input type="checkbox"/>               | Patient preference studies (e.g., submitted studies or scientific publications)                                                    | Not applicable       |
| <input type="checkbox"/> | Patient preference studies (e.g., submitted studies or scientific publications)                                                                                                                                                                                                   |                                        |                                                                                                                                    |                      |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
{MARGENZA, margetuximab-cmkb}

|                          |                                                                                                       |                |
|--------------------------|-------------------------------------------------------------------------------------------------------|----------------|
| <input type="checkbox"/> | Other: (Please specify)                                                                               | Not applicable |
| <input type="checkbox"/> | Patient experience data that was not submitted in the application, but was considered in this review. |                |

**X**

---

Christy Osgood, MD  
Cross-Disciplinary Team Leader

## 2 Therapeutic Context

---

### 2.1. Analysis of Condition

#### The Applicant's Position:

Worldwide, breast cancer is the most common cancer and a primary cause of cancer mortality in women (1). Lifetime risk of breast cancer in North American women is about 12% (32). Median age at time of breast cancer diagnosis was 62 during 2012-2016. In 2019, an estimated 268,600 new cases of invasive breast cancer will occur in the US, and 41,760 women are expected to die from the disease. Early breast cancer is surgically resectable and potentially curable (1). Advanced breast cancer comprises locally advanced and metastatic breast cancer (MBC). MBC remains incurable despite treatment, with a median overall survival (OS) of about 2-3 years and a 5-year survival of about 25% (5).

HER2 is overexpressed in 15-25% of breast cancers and is associated with more aggressive disease than HER2-negative breast cancer. Before trastuzumab's 1998 marketing authorization, HER2 overexpression was associated with poor prognosis (8, 15). Since then, prognosis has steadily improved with multiple add-ons to or refinements of trastuzumab to achieve the current standard of care with HER2-targeting therapies (Table 2 and Table 3). Sequenced first-line and second-line therapies prolong survival. Still, an unmet need for new treatments persists. This need is especially notable among patients with HER2+ metastatic disease who develop treatment resistance, as well as cumulative toxicities, after multiple lines of HER2-targeted therapy combined with cytotoxic chemotherapy. Line after line of therapy can adversely affect quality of life. In part, because breast cancer is more prevalent in an older population, approved treatments are associated with toxicity (Table 3). Patients who do not tolerate toxicities of emerging third-line therapies for pretreated HER2+ breast cancer will benefit from additional HER2-targeted treatment options that can be combined with multiple chemotherapy options.

#### The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment. Antibody-based therapies such as trastuzumab, pertuzumab, and T-DM1 have indeed changed the treatment landscape and significantly improved prognosis of patients with HER2+ breast cancer. Additionally, provided patients have good performance status, they can be offered more therapies if toxicities are not prohibitive. FDA agrees with the Applicant that additional, better tolerated therapies are needed. However, it must be recognized that patients who are living longer also have more opportunity of developing brain metastasis. Thus, the greatest unmet medical need in this setting is treatment that controls both systemic and CNS disease.

## 2.2. Analysis of Current Treatment Options

### The Applicant's Position:

US standard of care for first-line HER2-positive MBC is a combination of trastuzumab, pertuzumab, and taxane from the CLEOPATRA trial (**Table 2**). The preferred second-line option is ado-trastuzumab emtansine (T-DM1) based on the EMILIA study. After disease progression on first-line and second-line therapy, ASCO and NCCN guidelines recommend third-line or greater HER2-targeted therapy-based treatment. Evidence suggests that ongoing trastuzumab remains clinically active after progression on trastuzumab (**39, 40**). In a Phase 3 study, continuation of trastuzumab plus capecitabine improved objective response rate (ORR) and time to progression (HR: 0.69, 95% CI: 0.48, 0.97) versus capecitabine alone in HER2-positive breast cancer progressing during trastuzumab treatment (**39**). Other options include lapatinib plus capecitabine, other chemotherapy, trastuzumab, or trastuzumab with other chemotherapy. For hormone receptor-positive, HER2+ disease, endocrine therapy may be used in place of chemotherapy. Although lapatinib and trastuzumab are often used in this setting, insufficient evidence supports use of one regimen over another.

New therapies for pretreated HER2+ MBC include trastuzumab deruxtecan and tucatinib. Trastuzumab deruxtecan demonstrated an ORR of 60.3% in a Phase 2 trial (**Table 2**). Tucatinib, combined with capecitabine, generated a survival benefit versus capecitabine alone (HR: 0.66; 95% CI: 0.50, 0.88), including in patients with active brain disease (**24**).

### Antibody Immune Mechanism, CD16A Genetics, and Trastuzumab Clinical Outcomes

Antitumor activity of trastuzumab results from direct (Fc-independent) and immune cell-mediated (Fc-dependent) modes of action. Direct binding to tumor cells overexpressing HER2 inhibits oncogenic signaling, inhibits proliferation, and induces apoptosis (**14**). Direct binding also blocks HER2 extracellular domain cleavage/shedding, preventing formation of membrane-associated HER2 p95 protein, which has constitutive oncogenic activity (**23**).

Engagement of immune cells (NK cells, macrophages, antigen-presenting cells) with trastuzumab-coated tumor cells occurs via Fc:FcγR interactions, which induce innate immune responses such as antibody-dependent cellular cytotoxicity (ADCC) (**26**). Patients with higher circulating NK cell counts exhibit higher levels of trastuzumab-mediated ADCC activity, which is associated with increased tumor responsiveness (**12, 38**). Furthermore, increased numbers of tumor-associated NK cells are seen in patients treated with trastuzumab, with responsive patients' tumors having larger numbers of tumor-infiltrating NK cells (**2, 12**). Trastuzumab therapy associates with increased HER2-specific antibody and T-cell responses, which in turn

associate with improved clinical outcomes (17, 28, 36). In addition, trastuzumab-mediated antitumor vaccinal effects may promote long-term immunity against HER2-positive cancers (4).

Low-affinity FcγRs that regulate immune effector cell function include 2 activating receptors, FcγRIIIA (CD16A) and FcγRIIA (CD32A), and 1 inhibitory receptor, FcγRIIB (CD32B). Monocytes, macrophages, and dendritic cells express all 3 of these receptors. NK cells mainly express only CD16A, and B lymphocytes express only CD32B.

CD16A is the Fc receptor that triggers ADCC by NK cells (26) (see Table 1). Two human CD16A polymorphic variants (allotypes) exhibit different binding affinities for human IgG1 Fc (158V – higher affinity, 158F – lower affinity) (7). Most humans (~85%) carry at least 1 allele for the lower binding CD16A-158F allotype, including F/V heterozygotes and F/F homozygotes. NK cells from CD16A-158V/V homozygotes exhibit greater IgG1 binding and generally mediate ADCC with increased potency. This biology explains the observation that therapeutic benefit from trastuzumab in breast cancer, cetuximab in head and neck cancer, and rituximab in lymphoma accrues mostly to higher affinity CD16A-158V/V homozygotes (11, 21, 25, 29, 34). Adjuvant trastuzumab recipients with one or more 158F alleles have less favorable disease-free survival than CD16A-158V/V homozygotes, relative to those treated with chemotherapy alone (11). This finding extends earlier work showing more favorable progression-free survival (PFS) for CD16A-158V/V homozygotes (25). Thus, CD16A-158F carriers, representing up to 85% of the HER2+ patient population, may not benefit maximally from trastuzumab therapy, although it is routinely used in later lines of treatment.

**Table 1: CD16A Biology and Trastuzumab Outcome**

| CD16A-158 Genotype | Population Prevalence                     | IgG1 Binding Affinity (K <sub>D</sub> , nM) (range) | IgG1 NK Cell Binding (MFI ± SD)               | ADCC Stimulation                                            | Disease Free Survival (HR) (95% CI) <sup>a</sup> |
|--------------------|-------------------------------------------|-----------------------------------------------------|-----------------------------------------------|-------------------------------------------------------------|--------------------------------------------------|
| V/V                | ~15-20%                                   | 411 (403-419)                                       | 1,814 ± 507                                   | Greater                                                     | 0.118 (0.05-0.28)                                |
| V/F                | ~40-45%                                   | -                                                   | 1,257 ± 608                                   | Intermediate                                                | 0.336 (0.23-0.48)                                |
| F/F                | ~35-40%                                   | 1066 (981-1150)                                     | 913 ± 317                                     | Lesser                                                      | 0.713 (0.51-1.01)                                |
| <b>Implication</b> | V/V homozygotes are a minority population | V allotype has higher affinity for IgG1 Fc          | V/V NK cells bind more IgG1 than F/F NK cells | V/V effector cells generally activate ADCC most effectively | V alleles associate with greatest benefit        |
| <b>Reference</b>   | (19, 22, 34, 35)                          | (33)                                                | (18)                                          | (25, 27, 30, 38)                                            | (11, 25)                                         |

<sup>a</sup> Disease-free survival HR is for subjects with early stage HER2+ breast cancer treated with doxorubicin and cyclophosphamide plus paclitaxel, with or without 1 year of trastuzumab in the NSABP-B31 trial (11).  
 Abbreviation: MFI: mean fluorescence intensity.

**Table 2: Treatments Relevant to Proposed Indication in Metastatic Disease (Efficacy)**

| Product<br>USPI Source Date                                       | Combination                  | Indication/<br>Line of Therapy | Study                | Number<br>of<br>Subjects | PFS<br>(median;<br>months) | OS<br>(median;<br>months) | ORR<br>(%)        | Duration of<br>Response<br>(median;<br>months) | Time to<br>Progression<br>(median;<br>months) |
|-------------------------------------------------------------------|------------------------------|--------------------------------|----------------------|--------------------------|----------------------------|---------------------------|-------------------|------------------------------------------------|-----------------------------------------------|
| <b>FDA Approved Treatments</b>                                    |                              |                                |                      |                          |                            |                           |                   |                                                |                                               |
| HERCEPTIN® (trastuzumab)<br>Revised: 11/2018                      | + chemotherapy               | 1L HER2+ MBC                   | Study 5              | 235                      | nr                         | 25.1                      | 45                | 8.3                                            | 7.2                                           |
|                                                                   | Monotherapy                  | 2L HER2+ MBC                   | Study 6              | 222                      | nr                         | nr                        | 14                | nr                                             | nr                                            |
| PERJETA® (pertuzumab)<br>Revised: 01/2020                         | + trastuzumab<br>+ docetaxel | 1L HER2+ MBC                   | CLEOPATRA            | 402                      | 18.5                       | 56.5                      | 80.2              | 20.2                                           | nr                                            |
| TYKERB® (lapatinib)<br>Revised: 12/2018                           | + letrozole                  | 1L HER2+ HR+ MBC               | nr                   | 111                      | 8.3 <sup>a</sup>           | nr                        | 27.9              | nr                                             | nr                                            |
|                                                                   | + capecitabine               | 2L HER2+ MBC                   | nr                   | 198                      | nr                         | 17.5 <sup>a, b</sup>      | 23.7              | nr                                             | 6.3 <sup>a</sup>                              |
| KADCYLA® (T-DM1)<br>Revised: 05/2019                              | Monotherapy                  | 2L HER2+ MBC                   | EMILIA               | 495                      | 9.6                        | 30.9                      | 43.6              | 12.6                                           | nr                                            |
| NERLYNX® (neratinib)<br>Revised: 02/2020                          | + capecitabine               | 3L HER2+ MBC                   | NALA                 | 307                      | 5.6                        | 21.0                      | 32.8              | 8.5                                            | nr                                            |
| ENHERTU® (fam-trastuzumab<br>deruxtecan-nxki)<br>Revised: 12/2019 | Monotherapy                  | 3L HER2+ MBC <sup>c</sup>      | DESTINY-<br>Breast01 | 184                      | nr                         | nr                        | 60.3              | 14.8                                           | nr                                            |
| <b>Other Treatments</b>                                           |                              |                                |                      |                          |                            |                           |                   |                                                |                                               |
| Margetuximab                                                      | + chemotherapy               | 3L HER2+ MBC                   | Study 04             | 266                      | 5.8                        | 21.6                      | 22.1 <sup>d</sup> | 6.1                                            | nr                                            |

Note: Cross-study comparisons may be subject to selection bias. Margetuximab data from Study 04, data cutoff 10-Oct-2018, except OS (data cutoff 10-Sep-2019).

- a Reported in weeks. Converted to months manually (assuming 30 days/month) to aid comparison.
- b After 2-year follow-up of subjects receiving lapatinib + chemotherapy and lapatinib alone crossed over to lapatinib + chemotherapy. N = 207.
- c Approved under accelerated approval based on ORR and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- d Study 04 Response Evaluable Population, N = 262.

Abbreviations: HR: hormone receptor; nr: not reported in USPI.

**Table 3: Treatments Relevant to Proposed Indication (Safety)**

| Product                                                                          | Initial Approval/USPI Source Date  | Breast Cancer Indication(s)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Dosage Regimen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Important Safety and Tolerability Issues                                                                                                                                                                |
|----------------------------------------------------------------------------------|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>FDA Approved Treatments</b>                                                   |                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                         |
| HERCEPTIN® (trastuzumab)<br><br>Humanized mAb that targets the HER2/neu receptor | September 1998<br>Revised: 11/2018 | <u>Adjuvant HER2-overexpressing breast cancer:</u><br>Treatment of node positive or node negative (ER/PR negative or with 1 high risk feature) breast cancer <ul style="list-style-type: none"> <li>• as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel</li> <li>• as part of a treatment regimen with docetaxel and carboplatin</li> <li>• as a single agent following multimodality anthracycline-based therapy.</li> </ul> <u>HER2-overexpressing MBC:</u> <ul style="list-style-type: none"> <li>• In combination with paclitaxel for first-line treatment of MBC</li> <li>• As a single agent for treatment of breast cancer in patients who received 1 or more chemotherapy regimens for metastatic disease.</li> </ul> | <u>Adjuvant Breast Cancer:</u> Total 52 weeks as either: <ul style="list-style-type: none"> <li>• Initial dose of 4 mg/kg IV over 90 minutes, then 2 mg/kg IV over 30 minutes weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin) One week after the last weekly dose of trastuzumab, administer 6 mg/kg IV over 30–90 minutes Q3W, or</li> <li>• As a single agent within 3 weeks after completion of multimodality, anthracycline-based chemotherapy: Initial dose of 8 mg/kg IV over 90 minutes, then 6 mg/kg IV over 30–90 minutes Q3W</li> </ul> <u>MBC:</u> Initial dose of 4 mg/kg IV over 90 minutes, then 2 mg/kg IV over 30 minutes weekly until disease progression. | <u>Boxed Warnings:</u><br>CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, AND PULMONARY TOXICITY<br><br><u>Warnings and Precautions:</u><br>Exacerbation of chemotherapy-induced neutropenia |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

| Product                                                                                                 | Initial Approval/USPI Source Date | Breast Cancer Indication(s)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Dosage Regimen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Important Safety and Tolerability Issues                                                                                                                                                                                                                                                                                                                                |
|---------------------------------------------------------------------------------------------------------|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PERJETA®<br>(pertuzumab)<br><br>Humanized mAb that targets the HER2/neu receptor                        | June 2012<br>Revised:<br>01/2020  | In combination with trastuzumab and docetaxel for treatment of patients with HER2+ MBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.<br><br>In combination with trastuzumab and chemotherapy as: <ul style="list-style-type: none"> <li>neoadjuvant treatment of patients with HER2+, locally advanced, inflammatory, or early stage breast cancer as part of a complete treatment regimen for EBC</li> <li>adjuvant treatment of patients with HER2+ EBC at high risk of recurrence.</li> </ul>       | 840 mg IV over 60 minutes, followed by 420 mg IV over 30 to 60 minutes Q3W<br><u>MBC:</u><br>Administer PERJETA, trastuzumab, or trastuzumab hyaluronise-oysk, and docetaxel Q3W<br><u>Neoadjuvant:</u><br>Administer PERJETA, trastuzumab, or trastuzumab hyaluronise-oysk, and chemotherapy preoperatively Q3W for 3 to 6 cycles<br><u>Adjuvant:</u><br>Administer PERJETA, trastuzumab, or trastuzumab hyaluronise-oysk, and chemotherapy postoperatively Q3W for a total of 1 year (up to 18 cycles) | <u>Boxed Warnings:</u><br>LEFT VENTRICULAR DYSFUNCTION, EMBRYO-FETAL TOXICITY<br><u>Warnings and Precautions:</u><br>Infusion-related reactions, hypersensitivity reactions/anaphylaxis<br><u>Contraindications:</u><br>Known hypersensitivity to pertuzumab or its excipients                                                                                          |
| TYKERB®<br>(lapatinib)<br><br>Dual tyrosine kinase inhibitor that interrupts HER2/neu and EGFR pathways | March 2007<br>Revised:<br>12/2018 | In combination with capecitabine, for treatment of patients with advanced or MBC whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. Patients should have disease progression on trastuzumab prior to initiation of treatment with lapatinib in combination with capecitabine.<br><br>In combination with letrozole for treatment of postmenopausal women with hormone receptor-positive MBC that overexpresses the HER2 receptor for whom hormonal therapy is indicated. | <u>HER2+ MBC:</u><br>1250 mg (5 tablets) orally once daily on Days 1-21 continuously in combination with capecitabine 2000 mg/m <sup>2</sup> /day on Days 1-14 in a repeating 21-day cycle<br><br><u>Hormone receptor-positive HER2+ MBC:</u><br>1500 mg (6 tablets) orally once daily continuously in combination with letrozole 2.5 mg once daily                                                                                                                                                      | <u>Boxed Warnings:</u><br>HEPATOTOXICITY<br><u>Warnings and Precautions:</u><br>Decreases in left ventricular ejection fraction, diarrhea, interstitial lung disease and pneumonitis, QT interval prolongation, severe cutaneous reactions, fetal harm<br><u>Contraindications:</u><br>Known severe hypersensitivity (e.g., anaphylaxis) to lapatinib or its components |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

| Product                                                                                                           | Initial Approval/USPI Source Date                              | Breast Cancer Indication(s)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Dosage Regimen                                                                                                                                                                                                                                                                                                                                                          | Important Safety and Tolerability Issues                                                                                                                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| KADCYLA®<br>(ado-trastuzumab emtansine; T-DM1)<br><br>HER2-targeted antibody and microtubule inhibitor conjugate  | February 2013<br>Revised:<br>05/2019                           | As a single agent, for treatment of patients with HER2+ MBC who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: <ul style="list-style-type: none"> <li>Received prior therapy for metastatic disease, or</li> <li>Developed disease recurrence during or within 6 months of completing adjuvant therapy</li> </ul> As a single agent for adjuvant treatment of patients with HER2+ EBC who have residual invasive disease after neoadjuvant taxane and trastuzumab-based therapy. | 3.6 mg/kg IV infusion Q3W (21-day cycle) – first infusion over 90 minutes, subsequent infusions over 30 minutes if prior infusions were well tolerated<br><u>MBC:</u> until disease progression or unmanageable toxicity<br><u>EBC:</u> total of 14 cycles unless there is disease recurrence or unmanageable toxicity                                                  | <u>Boxed Warnings:</u><br>HEPATOTOXICITY, CARDIAC TOXICITY, EMBRYO-FETAL TOXICITY<br><u>Warnings and Precautions:</u><br>Pulmonary toxicity; infusion-related reactions, hypersensitivity reactions; hemorrhage; thrombocytopenia; neurotoxicity |
| NERLYNX®<br>(neratinib)<br><br>Kinase inhibitor that irreversibly binds to EGFR, HER2, and HER4                   | July 2017<br>Revised:<br>02/2020                               | As a single agent, for the extended adjuvant treatment of adult patients with HER2-positive EBC, to follow adjuvant trastuzumab-based therapy.<br>In combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.                                                                                                                                                                    | <u>Adjuvant EBC:</u><br>240 mg (6 tablets) orally once daily, continuously until disease recurrence for up to 1 year<br><u>Advanced or MBC:</u><br>240 mg (6 tablets) orally once daily on Days 1-21 of a 21-day cycle plus capecitabine (750 mg/m <sup>2</sup> orally twice daily) on Days 1-14 of a 21-day cycle until disease progression or unacceptable toxicities | <u>Boxed Warnings:</u><br>No boxed warning<br><u>Warnings and Precautions:</u><br>Diarrhea, hepatotoxicity, embryofetal toxicity                                                                                                                 |
| ENHERTU®<br>(fam-trastuzumab deruxtecan-nxki)<br><br>HER2-directed antibody and topoisomerase inhibitor conjugate | December 2019<br>(Accelerated Approval)<br>Revised:<br>12/2019 | Treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.                                                                                                                                                                                                                                                                                                                                                            | 5.4 mg/kg IV infusion Q3W (21-day cycle) until disease progression or unacceptable toxicity                                                                                                                                                                                                                                                                             | <u>Boxed Warnings:</u> INTERSTITIAL LUNG DISEASE, EMBRYO-FETAL TOXICITY<br><u>Warnings and Precautions:</u><br>Neutropenia, left ventricular dysfunction                                                                                         |

Note: trastuzumab biosimilars OGVIRI, HERZUMA, ONTRUZANT, TRAZIMERA, and KANJINTI are not presented in this table. Labelled warnings and precautions are identical to those of HERCEPTIN®.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of current treatment options for patients with HER2+ metastatic breast cancer in the U.S. with the following additions and clarifications:

- Although the standard-of-care second-line treatment is T-DM1 based on results from the EMILIA clinical trial, it may also be a first-line treatment option for those who are rapidly progressing after adjuvant therapy. In the EMILIA trial, patients with HER2+ breast cancer who developed disease recurrence during or within six months of adjuvant therapy with trastuzumab and a taxane were also eligible and 12% received T-DM1 as first-line treatment in the metastatic setting.
- On December 20, 2019, the FDA granted accelerated approval to fam-trastuzumab deruxtecan for patients with unresectable or metastatic HER2+ breast cancer who received two or more prior anti-HER2-based regimens in the metastatic setting based on the results of DESTINY-Breast01 trial. All patients were exposed to T-DM1 prior to enrollment.
- On February 25, 2020, the FDA granted regular approval to neratinib in combination with capecitabine for patients with advanced or metastatic HER2+ breast cancer who received two or more prior anti-HER2-based regimens in the metastatic setting based on the results of the NALA trial. Patients were not required to receive prior T-DM1 but 54.3% were exposed to T-DM1 prior to enrollment.
- Despite these treatment options, no treatment has shown a clinically meaningful and statistically significant OS benefit in the post-T-DM1 setting with the exception of tucatinib, which was granted regular approval on April 17, 2020. The basis for approval was the HER2CLIMB study (n=612 patients), a randomized (2:1), double-blind, placebo-controlled trial which enrolled patients with advanced unresectable or metastatic HER2+ breast cancer, including those with brain metastasis, who had received prior trastuzumab, pertuzumab, and T-DM1. In terms of patients with brain metastasis, 48% of patients had a presence or history of brain metastases at baseline; of these patients, 40% had treated and stable brain metastases, 37% had treated but radiographically progressing brain metastases, and 23% had untreated brain metastases. Patients received either tucatinib 300 mg or placebo orally twice daily, with trastuzumab intravenously or subcutaneously at standard doses, and capecitabine 1000 mg/m<sup>2</sup> orally twice daily on days 1 to 14 of each 21-day cycle. The estimated median PFS assessed by BICR for patients on the tucatinib arm was 7.8 months (95% CI: 7.5, 9.6) versus 5.6 months (95% CI: 4.2, 7.1) for patients on the control arm, with a hazard ratio of 0.54 (95% CI: 0.42, 0.71; p<0.00001). Median OS was 21.9 months (95% CI: 18.3, 31.0) in the tucatinib arm compared to 17.4 months (95% CI: 13.6, 19.9) in the control arm (HR: 0.66, 95% CI 0.50, 0.87, p=0.00480).
- The correlation of FCGR polymorphism and efficacy of HER-2 directed antibody therapy is an evolving issue. Association of polymorphisms in FCGR2A and FCGR3A and degree of trastuzumab benefit are based primarily on retrospective analysis. Furthermore, except

for one (i.e., NSABP-B31), most of these trials included only a limited number of patients (~50-100 total patients). In general, the higher-affinity alleles (e.g., V genotype) in FCGR3A appear to receive greater benefit from trastuzumab therapy compared to patient carriers of the low-affinity allele (i.e., F genotype).

### 3 Regulatory Background

#### 3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Margetuximab is not yet marketed. There is no postmarketing experience.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

#### 3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Margetuximab has been developed under IND 107768 for treatment of HER2+ carcinomas since 2010. Key US pre-submission regulatory activities are outlined in **Table 4**.

**Table 4: Key Regulatory Interactions Related to BLA 761150**

| Type of Interaction/ Meeting                       | Date        | Purpose of Interaction/Meeting                                                                                                                                                                                                                                                                                                          |
|----------------------------------------------------|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Type B (Pre-Phase 3) CMC Meeting                   | 30-Apr-2014 | To seek Agency input on proposed pre-Phase 3 CMC development plans and design of a comparability study to bridge drug substance scale-up and manufacturing site changes (b) (4) processes) for drug supply in a previous Phase 3 study with a different indication.                                                                     |
| Type B (EOP2) Clinical and Nonclinical Meeting     | 30-Jan-2015 | To seek feedback regarding the clinical development plan for margetuximab, including the proposed Phase 3 pivotal registration enabling study (Study 04). Further development of the nonclinical toxicology program for margetuximab was also discussed.                                                                                |
| Type C Clinical Meeting: T-DM1 Prior Use           | 01-Dec-2016 | To seek feedback on Study 04 design, specifically requirements for prior anti-HER2 therapy in defining the patient population, criteria for assessment of clinical benefit based on PFS, and procedures for addressing sparse data in statistical strata.                                                                               |
| Type C Clinical Meeting Request: Infusion Substudy | 09-Jan-2018 | To seek feedback on the planned Study 04 infusion substudy cohort to evaluate safety and tolerability of sequential reductions in margetuximab infusion duration from 120 minutes in Cycle 1 to 30 minutes in Cycles 2 and beyond. In addition, FDA's agreement was sought on the strategy to include substudy data in the planned BLA. |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

| Type of Interaction/ Meeting                                | Date        | Purpose of Interaction/Meeting                                                                                                                                                                                                                                                                                                                                                                                             |
|-------------------------------------------------------------|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Fast Track designation                                      | 12-Jan-2018 | Granted Fast Track designation for treatment of patients with metastatic or locally advanced HER-2 positive breast cancer who have previously been treated with anti-HER2-target therapy.                                                                                                                                                                                                                                  |
| Type C Clinical Meeting Request: Study Data Standardization | 23-Oct-2018 | To seek feedback on the margetuximab Study Data Standardization and Integration Plan for a planned BLA submission. FDA's input was also sought on clinical and statistical data presentation considerations for the pivotal study, as well as clinical trials that support the planned BLA.                                                                                                                                |
| Type C CMC Meeting: Late Stage Development Topics           | 06-Dec-2018 | To seek feedback on several proposed CMC development topics, to help guide MacroGenics during late stages of product development, and to ensure proposed development approaches support product licensure. Topics were related to cell line clonality, specifications, adequacy of potency assays for commercial release testing, implementation of a process-specific host cell protein assay, and leachables monitoring. |
| Type B (Pre-BLA) Meeting: Clinical and Nonclinical          | 06-May-2019 | To seek feedback on the plans for clinical and non-clinical format and content of the BLA.                                                                                                                                                                                                                                                                                                                                 |
| Type B (Pre-BLA) Meeting: CMC                               | 06-May-2019 | To seek feedback on the content and format of CMC portions of the BLA to ensure a well-organized and complete submission.                                                                                                                                                                                                                                                                                                  |

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of regulatory interactions in reference to this BLA application.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

---

### 4.1. Office of Scientific Investigations (OSI)

The Division of Oncology 1 consulted OSI to perform inspections with the following objectives:

- Verify efficacy endpoints
- Evaluate identification, documentation and reporting of adverse events
- Assess general compliance with the investigational plan and Good Clinical Practice (GCP)

Three sites were selected for clinical inspection based on a relatively high numbers of patient enrollment (all 3 sites) plus either a complaint (site# US025), high risk ranking (site# US035), or better efficacy in the study drug population (site# US043).

The inspection findings verified the Applicant's reported clinical data with source records at the three study sites. There were no substantial Good Clinical Practice (GCP) compliance deficiencies identified at these sites.

Based on the results of these inspections, the data reported by these investigator sites appear acceptable and supportive of this BLA. A summary of the findings from these inspections are below.

- Site# US025: Dr. William Gradishar  
Reason selected: High enrollment in 2018 and a complaint.

This clinical investigator site was inspected between February 20 – 28, 2020. This site screened 18 subjects and enrolled 9 subjects; 1 subject withdrew consent before receiving the investigational product. All 9 of the enrolled subjects were reviewed comprehensively during the inspection.

The inspection evaluated the following documents: IRB approval letters and correspondence; monitoring reports; consent forms, subject medical records, financial disclosure reports, case report forms, drug accountability records, site signature and responsibility logs; and site training documentation.

The primary efficacy endpoint was verifiable for all subjects, except for one. There was no under-reporting of adverse events.

Generally, this clinical investigator appeared to be compliant with Good Clinical Practices except for the items below for which a Form FDA 483 was issued:

1. An investigation was not conducted in accordance with the investigational plan. Specifically, RECIST 1.1 worksheet/assessments were delayed.
2. Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation. Specifically, inspection noted failure to maintain copies of “Test Article Accountability Log” forms and no source documentation for the cause of death for 2 subjects, both assigned to the margetuximab plus chemotherapy treatment group.

The deficiencies described above were deemed unlikely to have significant impact on the overall safety or efficacy data of the study with acceptable corrective action taken. Data submitted by this clinical site appear acceptable in support of this application.

OSI Classification: Voluntary corrective action taken.

- Site #US035: Dr. Raul Oyola

Reason selected: High enrollment and high-risk ranking.

This clinical investigator site was inspected between June 22 – June 25, 2020. This was Dr. Oyola’s second FDA inspection. The previous inspection was a For Cause inspection as a result of a complaint received by the Division of Good Clinical Practice Compliance, conducted on October 22 – 25, 2018 covering the same clinical study (Study 04) as this inspection. In the prior inspection, no Form FDA 483 (Inspectional Observations) was issued and it was classified as NAI.

The current inspection evaluated the primary endpoints, verification of line listings, adverse events, and study procedures that took place after the date of the previous inspection. This site screened 9 subjects and enrolled 7 subjects; among the 7 enrolled subjects, 4 subjects discontinued the study due to disease progression. All 7 subjects were reviewed comprehensively during the inspection.

Source documents for the raw data used to assess the primary endpoint were verifiable at the study site. No under-reporting of adverse events was noted.

This clinical investigator appeared to be compliant with Good Clinical Practices. The inspection found no significant deficiencies, with no Form FDA 483 issued.

OSI Classification: No action indicated.

- Site US043: Dr. Gail Wright

Reason selected: High enrollment and better efficacy in the study drug population.

This clinical investigator site was inspected between June 12- June 22, 2020. this site screened 19 subjects and enrolled 16 subjects. Among the 16 enrolled subjects, 16 subjects completed the study treatment; all 16 were reviewed comprehensively during the inspection. The inspection evaluated the following documents: Protocols and amendments, monitoring visits and correspondence, informed consent forms, subject medical records, oversight of the study, site's training activities and implementation of study procedures, adherence to and documentation of protocol-required visits, administration of the investigational product, financial disclosure reports, case report forms, IRB approval letters and correspondence, notifications and correspondence between the Sponsor and the Principal Investigator, delegation of study responsibilities, drug accountability records, investigational product control, and storage, site signature and responsibility logs, and site training documentation.

Source documents for the raw data used to assess the primary endpoint were verifiable at the study site. No under-reporting of adverse events was noted.

This clinical investigator appeared to be compliant with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued.

OSI Classification: No action indicated.

## 4.2. Product Quality

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761150 for MARGENZA manufactured by MacroGenics, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of MARGENZA is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert. Refer to the detailed review by the product quality team for further details, including issues discussed with the Applicant that were satisfactorily resolved.

For issues discussed with the Applicant for product quality and addressed as postmarketing commitments (PMCs), refer to Section 13 of this Assessment Aid for the PMCs.

## 4.3. Clinical Microbiology

The application has been reviewed with regards to microbial control, product quality and sterility assurance by the Clinical Microbiology review team. The application is recommended for approval with the establishment of a post-marketing commitment to conduct a media fill using the margetuximab primary container closure system. Refer to the detailed review by the

clinical microbiology team for further details. Refer to Section 13 of this Assessment Aid for the Postmarketing commitments for clinical microbiology.

#### 4.4. **Devices and Companion Diagnostic Issues**

In CP-MGAH22-04 (SOPHIA, Study 04), the tumor HER2 status was determined locally on the most recently available tumor biopsy collected from the patient (either archival tissue samples or on fresh tissue samples). Confirmatory IHC testing is not required for study entry.

The Applicant did not propose the use of a companion diagnostic or an FDA-approved test to select patients with HER2+ breast cancer. The Center for Devices and Radiologic Health (CDRH) had no issue with this population of patients being selected for margetuximab treatment without a companion diagnostic device, since in the clinical setting patients were screened for HER2 amplification for previous HER2-directed therapies. Refer to the CDRH consult review by Drs. Banu Saritas-Yildirim, Soma Ghosh and Reena Philip for further details.

## 5 Nonclinical Pharmacology/Toxicology

---

### 5.1. Executive Summary

#### The FDA's Assessment:

Margetuximab (MGAH22) is a (b) (4) chimeric Fc-modified IgG1 kappa monoclonal antibody (mAb) and comprises a (b) (4) fragment of variable region (Fab) based on mouse clone 4D5, the parental murine antibody precursor to trastuzumab. This Fab of margetuximab binds the extracellular domain (ECD) of human epidermal growth factor receptor 2 (HER2/ErbB2), preserving the HER2 antigen-binding properties exhibited by trastuzumab. Margetuximab has a single point mutation in the light chain variable region (N65S) that removes an N-glycosylation site. The engineered Fc domain of margetuximab contains mutations (L235V, F243L, R292P, Y300L, and P396L) that increase affinity for human activating FcγRIIIA (CD16A) and decrease affinity for human inhibitory FcγRIIB (CD32B).

The Applicant submitted a biologics license application (BLA) for margetuximab, in combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive (HER2+) breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease. The proposed dose regimen for margetuximab is 15 mg/kg/dose through an intravenous (IV) infusion once every 3 weeks in 21-day cycles.

To support proof of concept, the Applicant conducted nonclinical pharmacology studies to demonstrate mode of action and anti-tumor activity of margetuximab. Margetuximab binds to HER2 with an equilibrium dissociate constant ( $K_D$ ) of 2.8 nM. When compared to trastuzumab, margetuximab has enhanced binding for CD16A-158V, lower affinity allele CD16A-158F, and C1q by 4.2-, 4.7-, and 12.9-fold, respectively, and reduced binding for CD32B by 6.9-fold. Margetuximab shows an anti-proliferative effect in HER2+ cancer cell lines, which is Fc-independent. Margetuximab exhibits anti-tumor activity equal to or better than RES120 [with wild-type (WT) Fc] for breast cancer, particularly for HER2 2+ and 3+ cancers, in mouse xenograft models.

Margetuximab mediates antibody-dependent cytotoxicity (ADCC) in HER2-positive cancer cell lines using effector cells from human donors of all CD16A genotypes and promotes NK-cell activation and cytolytic activity. Margetuximab triggers release of IL-2, IL-4, and IL-10 from human peripheral blood mononuclear cells (PBMCs) with various CD16A and CD32A genotypes but only in the presence of HER2 antigen. The nonclinical pharmacology data submitted in the BLA submission demonstrate that the Established Pharmacological Class (EPC) of "HER2/neu receptor antagonist" is appropriate based on its pharmacological activity and prior EPC for related FDA-approved products.

The Applicant conducted GLP-compliant 6-week (doses up to 150 mg/kg/dose) and 13-week (doses up to 100 mg/kg/dose) repeat-dose toxicology studies of margetuximab in cynomolgus monkeys. Margetuximab was administered through IV infusion once weekly. No target organs for margetuximab were identified, nor were there margetuximab-related increased release of IFN- $\gamma$ , IL-2, IL-5, IL-6, IL-10, or TNF- $\alpha$  in serum. Margetuximab treatment resulted in partially reversible decreases in blood CD3-/CD159a+ and CD16+/CD159a+ NK cells when compared to vehicle controls. Exposure to margetuximab, in terms of AUC, increased with an increase in dose and was similar between sexes. Half-life ( $T_{1/2}$ ) of margetuximab in monkeys ranged from 5.3 to 9.7 days, and the average accumulation index for margetuximab was 2.2 at the end of dosing.

Dedicated fertility studies were not needed or conducted to support marketing of Margenza for the current indication. In repeat-dose toxicity studies of up to 13-week duration, margetuximab had no effect on male and female reproductive organs in sexually mature cynomolgus monkeys.

The Applicant conducted a GLP-compliant enhanced pre- and postnatal development (ePPND) toxicology study in pregnant cynomolgus monkeys. Margetuximab was administered at doses of 0, 50, and 100 mg/kg/dose IV once every 3 weeks from gestational day 20 (GD20) to delivery. The ePPND study did not require a loading dose to achieve clinically relevant exposures. Margetuximab-related adverse effects included 3<sup>rd</sup> trimester oligohydramnios, increased incidence of abortion/stillbirth primarily due to hypersensitivity reactions, placental transfer of margetuximab, and microscopic findings of immature renal tubules in infants. Margetuximab-related mortality occurred for one infant due to a severe renal injury after maternal exposure to 100 mg/kg. Renal injury was characterized by elevated serum urea nitrogen and creatinine concentrations, decreased kidney weights, and microscopic findings of immature nephrons in infants after maternal exposure to 50 or 100 mg/kg margetuximab. Oligohydramnios and associated renal toxicity are class effects of HER2-directed antibodies. In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of oligohydramnios. Because of the potential for serious adverse reactions to a developing fetus, women should use effective contraception during Margenza treatment and for 4 months following the last dose.

There is no information regarding presence of margetuximab in human milk, effects on the breastfed child, or effects on milk production. Published data suggest human IgG is present in human milk but does not enter neonatal or infant circulation in substantial amounts. Patients should consider developmental and health benefits of breastfeeding along with the mother's clinical need for Margenza treatment and any potential adverse effects on the breastfed child or from the underlying maternal condition. This consideration should also take into account the Margenza washout period of 4 months.

The nonclinical pharmacology and toxicology data submitted by the Applicant support the approval of Margenza for the proposed indication.

## 5.2. Referenced NDAs, BLAs, DMFs

### The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for margetuximab.

### The FDA's Assessment:

FDA agrees.

## 5.3. Pharmacology

### Primary Pharmacology

### The FDA's Assessment:

#### Molecular Binding

In a molecular binding study applying enzyme-linked immunosorbent assay (ELISA), the binding of margetuximab and trastuzumab to ECD of HER2 was comparable with EC<sub>50</sub> values of 28.7 and 27.3 ng/mL, respectively. Binding of margetuximab (modified Fc) and RES120 (WT Fc) to HER2 ECD was also comparable with EC<sub>50</sub> values of 39.3 and 45.8 ng/mL, respectively (Study RND MGAH22-09-1012). In a molecular binding study applying surface plasmon resonance (SPR), K<sub>D</sub> values were similar for margetuximab and trastuzumab in the presence or absence of pertuzumab, suggesting that both margetuximab and trastuzumab bind to HER2 independently from pertuzumab (Study MGAH22-BIND).

In a molecular binding study applying SPR, margetuximab showed enhanced binding to human activating FcγRIIIA genotypes CD16A-158V and CD16A-158F with 4.2-fold and 4.7-fold higher affinity, respectively, compared to trastuzumab. Margetuximab also showed reduced binding to human inhibitory FcγRIIB (CD32B) when compared to trastuzumab with 6.9-fold lower affinity. Margetuximab showed an increase in C1q binding compared to trastuzumab with 12.9-fold higher affinity (Study MGAH22-BIND).

In a molecular binding study applying SPR, margetuximab Fc domain showed enhanced binding to activating cynomolgus Fc receptors CD16A and CD32A but also increased binding to inhibitory Fc receptor CD32B. SPR analysis showed stronger binding to cynomolgus monkey CD16A and CD32B than to human CD16A (both h158V and h158F) and CD32B whereas binding to cynomolgus CD32A was intermediate to that of human CD32A-131H and CD32A-131R. Given

the increased binding to activating monkey Fc receptors, cynomolgus monkey is an appropriate species for the safety assessment for margetuximab (Study RND-MGAH22-09-1004).

In a molecular binding assay applying SPR, the modified Fc domain of margetuximab, when compared with Ch4D5 (WT Fc), showed an enhanced 3-fold binding to mFcγRIV (mER2), which does not have a human homolog. The modified Fc domain reduced binding to mFcγRIII (mCD16), mFcγRII (mCD32), and mFcγRI (mCD64). Due to these differences, results from mouse xenograft models with human tumor cells may be limited in evaluating the anti-tumor effects of the modified Fc domain of margetuximab (Study RND MGAH22-09-1013).

### In Vitro Activity

In an in vitro cytotoxicity study, margetuximab and trastuzumab inhibited the proliferation of HER2+ BT474 and SKBR-3 breast cancer cell lines with comparable EC<sub>50</sub> values (0.08-0.10 µg/mL with BT474 cells and 0.05-0.10 µg/mL with SKBR-3 cells) and maximal inhibition (E<sub>max</sub>) (56% inhibition for BT474 cells and 21%-28% for SKBR-3 cells). The EC<sub>50</sub> values for the combination of margetuximab + pertuzumab or trastuzumab + pertuzumab were comparable to those of margetuximab or trastuzumab alone while their E<sub>max</sub> values were additive in the combination therapy. In addition, the variants of margetuximab with WT Fc domains (ch4D5, RES120) or an inactivated Fc domain (ch4D5-N297Q) exhibited comparable E<sub>max</sub> values to those of margetuximab and trastuzumab under all conditions tested, demonstrating that the anti-proliferative activity mediated by margetuximab is Fc-independent (Study MGAH22 ACT2).

In a cell biology assay applying CellTiter-Glo method (proliferation assay) and flow cytometry (apoptosis assay), margetuximab (modified Fc) and RES120 (WT Fc) induced a similar degree of anti-proliferative activity against HER2+ breast cancer cell line SKBR-3 (trastuzumab-sensitive) but did not inhibit the proliferation of JIMT-1 (trastuzumab-resistant) after 3 or 6 days of treatment. Margetuximab and RES120 triggered a similarly low degree of apoptosis (2%-11%) in HER2+ cell lines SKBR-3, JIMT-1, ZR75-1, or MCF-7, while camptothecin, the positive control, induced a significant degree of apoptosis (16%-45%) in all of those 4 HER2+ breast cancer cell lines. The Fc modifications made to margetuximab did not affect the antiproliferative activity or apoptosis of HER2-responsive cell lines tested (Study RND-MGAH22-09-1009).

Margetuximab, trastuzumab, and pertuzumab bound similarly, in terms of E<sub>max</sub> and EC<sub>50</sub>, to cell surface HER2 antigen on breast cancer cell lines, SKBR-3 and JIMT-1. Margetuximab reduced HER2 ECD shedding on SKBR-3 cells by 65% at a concentration of 1 µg/mL. Similar results were observed with trastuzumab and Ch4D5-N297Q (inactivated Fc). Margetuximab, trastuzumab, and pertuzumab did not mediate complement-dependent cytotoxicity (CDC) in HER2+ cells, even though margetuximab demonstrated 12.9-fold higher affinity for C1q compared to trastuzumab (Study MGAH22-ACT).

The modified Fc domain of margetuximab increased ADCC of HER2+ N87 and SKBR-3 cell lines in the presence of NK cells from donors with all CD16A genotypes (F/F, V/F, or V/V). Margetuximab also demonstrated greater NK-cell activation by enhancing expression of CD137, Ki67, granzyme B, and perforin and causing death of target cells (N87 and SKBR-3). Ch4D5-N297Q (inactivated Fc) was much less effective in inducing these NK-cell responses than margetuximab and trastuzumab, demonstrating that the anti-HER2 antibody-mediated NK cell responses were Fc-dependent. A 1:1 combination of margetuximab + pertuzumab maintained higher ADCC activity than a 1:1 combination of trastuzumab + pertuzumab (Study MGAH22-ACT).

#### In Vivo Anti-Tumor Activity

Margetuximab activities were demonstrated in in vivo efficacy studies applying different mouse xenograft models with HER2+ human breast cancer lines. Margetuximab dose-dependently increased anti-tumor activity equal to or better than RES120 (WT Fc) for trastuzumab-sensitive HER2+ BT474 breast cancer. Margetuximab also showed dose-dependent enhanced activity against trastuzumab-resistant JIMT-1 compared to RES120 in a hCD16A knock-in transgenic mouse model expressing low-binding allele CD16A-158F, while no enhancement was noted in mCD16-/- mice (Study RND-MGAH22-09-1007).

#### Secondary Pharmacology

##### The Applicant's Position:

The engineered Fc domain of margetuximab does not increase cytokine release in vitro, compared with trastuzumab. In vivo cynomolgus monkey studies demonstrated that cytokine release after IV margetuximab is absent or non-specific.

##### The FDA's Assessment:

FDA agrees with Applicant's assessment.

#### Safety Pharmacology

##### The Applicant's Position:

No dedicated safety pharmacology studies were performed with margetuximab. Safety pharmacology endpoints were evaluated in toxicology studies per ICH S6(R1) and ICH S7A guidelines. Cardiovascular (CV) safety assessment in a 6-week study of weekly margetuximab in cynomolgus monkeys (**Report UOK00019**) found no margetuximab-related changes in blood pressure, heart rate or ECG intervals. Similarly, no margetuximab-related neurological observations or changes in respiration, body temperature, or above CV parameters were observed after weekly 1-hour IV infusions for at least 13 weeks (**Report 8321179**).

##### The FDA's Assessment:

FDA agrees with Applicant's assessment.

#### 5.4. ADME/PK

##### The Applicant's Position:

Pharmacokinetic parameters for margetuximab were determined in cynomolgus monkeys (**Reports UOK00021, UOK00019, 8321179, and 8329256**). Margetuximab exposure increased with dose. PK was characterized by slow elimination and limited extravascular distribution. CL and  $V_{ss}$  describe essentially linear repeat-dose TK across the 15 to 100 mg/kg range. Exposure differences between males and females across doses and dose cycles were considered minor. Weekly dosing resulted in accumulation ratios of 2.3 and 2.1 for males and females, respectively. By contrast, dosing at 3-week intervals resulted in accumulation ratios ranging from 1 to 1.09 for pregnant females. Margetuximab serum half-life was comparable between male and female monkeys across studies with a range of 127–233 hours (5.3–9.7 days) for males and 137–205 hours (5.7–8.5 days) for females. Measurable serum margetuximab in infants was consistent with placental transfer from maternal to fetal circulation.

Margetuximab produced a minimal immunogenic response in cynomolgus monkeys. Positive confirmation of ADA following margetuximab administration was detected in 6 of 108 animals across all 4 studies, primarily at lower dose levels. A more rapid decline in margetuximab serum concentrations was observed in animals that had confirmed ADAs.

##### The FDA's Assessment:

FDA agrees with the Applicant's assessment. See table below for additional pharmacokinetic results.

##### Data (presented by FDA):

| Type of Study                                                                                                                                                                             | Major Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>TK data from general toxicology studies</b><br>13-Week GLP intravenous infusion chronic toxicity study with margetuximab in cynomolgus monkeys with a 10-week recovery (Study 8321179) | Differences in exposure to margetuximab between males and females after the first dose were not significant. After the 7 <sup>th</sup> and 13 <sup>th</sup> doses, mean $C_{max}$ values for females were 77% to 83% of male values, respectively.<br><br>Mean clearance (CL) for margetuximab was 0.25-0.35 mL/hr/kg in females and 0.19-0.29 mL/hr/kg in males. No differences in CL or $V_{ss}$ across dose groups were noted, except in females after the 13 <sup>th</sup> dose when CL at 100 mg/kg was higher than that at 15 mg/kg.<br><br>Males (at Dose 13) |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

|                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                          | <p><math>T_{1/2}</math> (hr) at 15, 50, and 100 mg/kg/dose: 149, 203, and 171, respectively.<br/> <math>C_{max}</math> (<math>\mu\text{g/mL}</math>) at 15, 50, and 100 mg/kg/dose: 753, 2369, and 4099, respectively.<br/> <math>AUC_{0-168}</math> (<math>\text{hr}\cdot\mu\text{g/mL}</math>) at 15, 50, and 100 mg/kg/dose: 126473, 534208, and 772523, respectively.<br/> <math>AUC_{0-168}</math> accumulation ratio (<math>AUC_{0-168}</math> Dose 13/<math>AUC_{0-168}</math> Dose 1) at 15, 50, and 100 mg/kg/dose: 1.9, 2.3, and 2.0, respectively.</p> <p>Females (at Dose 13)<br/> <math>T_{1/2}</math> (hr) at 15, 50 and 100 mg/kg/dose: 177, 153, and 157, respectively.<br/> <math>C_{max}</math> (<math>\mu\text{g/mL}</math>) at 15, 50 and 100 mg/kg/dose: 591, 1815, and 3157, respectively.<br/> <math>AUC_{0-168}</math> (<math>\text{hr}\cdot\mu\text{g/mL}</math>) at 15, 50 and 100 mg/kg/dose: 126002, 340900, and 550618, respectively.<br/> <math>AUC_{0-168}</math> accumulation ratio (<math>AUC_{0-168}</math> Dose 13/<math>AUC_{0-168}</math> Dose 1) at 15, 50, and 100 mg/kg/dose: 2.1, 1.9, and 1.9, respectively.</p> |
| <p><b>TK data from reproductive toxicology studies</b><br/>         Enhanced pre- and postnatal developmental toxicity study with margetuximab in cynomolgus monkeys (Study 8329256)</p> | <p>Except for maternal monkeys with apparent ADA, exposure to margetuximab (in terms of <math>C_{max}</math> and <math>AUC_{0-168}</math>) during the gestational phase (post 1<sup>st</sup>, 4<sup>th</sup>, and 7<sup>th</sup> doses) at 50 or 100 mg/kg was dose-proportional with no apparent accumulation after 7 doses.</p> <p>Dose 7:<br/> <math>C_{max}</math> (<math>\mu\text{g/mL}</math>) at 50 and 100 mg/kg/dose: 1399 and 2835, respectively<br/> <math>AUC_{0-168}</math> (<math>\text{hr}\cdot\mu\text{g/mL}</math>) at 50 and 100 mg/kg/dose: 146558 and 314547, respectively<br/> <math>C_{max}</math> accumulation ratio (<math>C_{max}</math> Dose 7/<math>C_{max}</math> Dose 1) at 50 and 100 mg/kg/dose: 1.09 and 1.00, respectively<br/> <math>AUC_{0-168}</math> accumulation ratio (<math>AUC_{0-168}</math> Dose 7/<math>AUC_{0-168}</math> Dose 1) at 50 and 100 mg/kg/dose: 1.09 and 1.05, respectively</p>                                                                                                                                                                                                                   |
| <p><b>Human PK data (Trial CP-MGAH22-04):</b></p>                                                                                                                                        | <p><math>C_{max}</math> (CV in %):</p> <ul style="list-style-type: none"> <li>• Cycle 1: 356 (21.4%) <math>\mu\text{g/mL}</math></li> <li>• Steady-state: 466 (19.5%) <math>\mu\text{g/mL}</math></li> </ul> <p><math>AUC_{0-21d}</math> (CV in %):</p> <ul style="list-style-type: none"> <li>• Cycle 1: 2490 (19%) <math>\mu\text{g}\cdot\text{day/mL}</math></li> <li>• Steady-state: 4120 (21%) <math>\mu\text{g}\cdot\text{day/mL}</math></li> </ul> <p><math>T_{1/2}</math> (CV in %): 19.2 (28.3%) days<br/>         Margetuximab washout period:</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

|  |                                                                              |
|--|------------------------------------------------------------------------------|
|  | 71 days (10 weeks) in 50% patients<br>110 days (16 weeks) in 95% of patients |
|--|------------------------------------------------------------------------------|

## 5.5. Toxicology

### 5.5.1. General Toxicology

#### The Applicant's Position:

Margetuximab was well tolerated by male and female cynomolgus monkeys by 1-hour IV infusion as either a single dose of 50 mg/kg (**Report UOK00021**) or 6 weekly doses of 0, 15, 50 or 150 mg/kg/dose (**Report UOK00019**). These data support a no-observed-adverse-effect level (NOAEL) of 150 mg/kg/dose. Thirteen (13) weeks of margetuximab dosing at 0, 15, 50, or 100 mg/kg/dose was well tolerated, with exception of 1 moribund animal at 100 mg/kg/dose (**Report 8321179**). Necropsy findings in this moribund animal suggested decreased red cell production and/or hemolysis. However, no clear mechanism could be determined, and no similar findings were observed for any other animal receiving margetuximab. No cardiac-related toxicities were observed in study animals including margetuximab-related changes in serum troponin I, ECG assessments, or pathologic findings in heart tissue.

These 6- and 13-week GLP margetuximab toxicology studies provided up to more than a 10-fold safety margin in comparison to human mean steady state  $C_{max}$  (475  $\mu\text{g/mL}$ ) at the recommended 15 mg/kg dose (see **Section 6**). In the 6-week study, mean  $C_{max}$  fold differences at the 150 mg/kg/dose on Day 36 were 14.5 $\times$  and 23.2 $\times$  in males and females, respectively. In the 13-week study, mean  $C_{max}$  fold differences at the 100 mg/kg/dose after the 13th dose were 8.6 $\times$  and 6.6 $\times$  in males and females, respectively.

#### The FDA's Assessment:

In general, FDA agrees with the Applicant's assessment. See below for study results. For exposure multiple calculations, FDA used the human mean steady-state  $C_{max}$  of 466  $\mu\text{g/mL}$  for margetuximab (Trial CP-MGAH22-04).

#### Data (presented by FDA):

##### **Study title/ number: 13-Week GLP intravenous infusion chronic toxicity study with margetuximab in cynomolgus monkeys with a 10-week recovery (Study 8321179)**

- One drug-related early mortality occurred on Day 71 in one female at 100 mg/kg/dose with manifestations including marked non-regenerative anemia and hypocellularity in bone marrow.

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
{MARGENZA, margetuximab-cmkb}

- Drug-related partially reversible decreases in CD3-/CD159a+ and CD16+/CD159a+ NK cells, particularly on Day 8 following the first dose but with lesser magnitude after subsequent doses.
- No target organs for margetuximab were identified in monkeys.

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 15, 50, and 100 mg/kg/dose; once weekly for 13 consecutive weeks (13 doses)  
Route of administration: IV infusion (1 hour)  
Formulation/Vehicle: Sterile saline  
Species/Strain: Cynomolgus monkeys  
Number/Sex/Group: Main study: 4/sex/group  
Recovery: 2/sex/group  
Age: 4-10 years old  
Satellite groups/ unique design: None / None  
Deviation from study protocol affecting interpretation of results: No

**Observations and Results: changes from control**

| Parameters            | Major findings                                                                                                                                                    |
|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Mortality</b>      | One female at 100 mg/kg/dose was moribund sacrificed on Day 71 due to the predose clinical findings of being hypoactive, hunched, pale and hypothermic on Day 71. |
| <b>Clinical Signs</b> | No drug-related clinical signs of toxicity were noted in surviving monkeys.                                                                                       |
| <b>Body Weights</b>   | No drug-related changes in body weight were noted.                                                                                                                |
| <b>Ophthalmoscopy</b> | No drug-related ophthalmic findings were noted.                                                                                                                   |
| <b>ECG</b>            | No drug-related ECG findings were noted.                                                                                                                          |
| <b>Hematology</b>     | Drug-related changes in hematology parameters included a decrease in RBC mass in females at 100 mg/kg but no significant effects on reticulocytes.                |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

| Dose Level (Males)                  | 0    |      | 15  | 50 | 100 |     |
|-------------------------------------|------|------|-----|----|-----|-----|
| Day                                 | 93   | 163  | 93  | 93 | 93  | 163 |
| n                                   | 6    | 2    | 6   | 6  | 6   | 2   |
| RBC (10 <sup>6</sup> /μL)           | 5.52 | 6.20 | 6↓  | 2↑ | 6↓  | 9↓  |
| Hg (g/dL)                           | 12.8 | 15.1 | 2↓  | 1↓ | 5↓  | 8↓  |
| Hct (%)                             | 42.1 | 45.7 | 2↓  | 1↓ | 4↓  | 2↓  |
| Reticulocytes (10 <sup>3</sup> /μL) | 38.0 | 31.7 | 12↑ | 6↑ | 23↑ | 65↑ |

\*: p<0.05

Values in margetuximab-treated groups are percent changes to their respective controls.

| Dose Level (Females)                | 0    |      | 15 | 50 | 100  |     |
|-------------------------------------|------|------|----|----|------|-----|
| Day                                 | 93   | 163  | 93 | 93 | 93   | 163 |
| n                                   | 6    | 2    | 6  | 6  | 5    | 2   |
| RBC (10 <sup>6</sup> /μL)           | 5.03 | 5.51 | 4↑ | 2↓ | 8↓   | 12↑ |
| Hg (g/dL)                           | 11.7 | 13.7 | 2↑ | 3↓ | 13↓* | 5↓  |
| Hct (%)                             | 39.3 | 46.3 | 1↑ | 2↓ | 10↓* | 2↓  |
| Reticulocytes (10 <sup>3</sup> /μL) | 55.2 | 43.6 | 6↓ | 5↓ | 22↑  | 35↑ |

\*: p<0.05

Values in margetuximab-treated groups are percent changes to their respective controls.

|                           |                                                                                                                                                                                 |
|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical Chemistry</b> | Drug-related partially reversible changes in clinical chemistry parameters included increases in globulin and urea nitrogen and a decrease in A/G ratio, particularly in males. |
|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| Dose Level (Males)    | 0   |     | 15  | 50   | 100  |     |
|-----------------------|-----|-----|-----|------|------|-----|
| Day                   | 93  | 163 | 93  | 93   | 93   | 163 |
| n                     | 6   | 2   | 6   | 6    | 6    | 2   |
| Globulin (g/dL)       | 2.7 | 2.4 | 4↑  | 15↑* | 19↑* | 8↑  |
| Urea Nitrogen (mg/dL) | 13  | 18  | 23↑ | 62↑* | 46↑* | 11↑ |
| A/G Ratio             | 1.6 | 1.9 | 0   | 19↓* | 12↓  | 5↑  |

\*: p<0.05

Values in margetuximab-treated groups are percent changes to their respective controls.

| Dose Level (Females)  | 0   |     | 15  | 50  | 100  |     |
|-----------------------|-----|-----|-----|-----|------|-----|
| Day                   | 93  | 163 | 93  | 93  | 93   | 163 |
| n                     | 6   | 2   | 6   | 6   | 5    | 2   |
| Globulin (g/dL)       | 2.5 | 3.4 | 8↑  | 16↑ | 36↑* | 6↓  |
| Urea Nitrogen (mg/dL) | 16  | 18  | 31↑ | 38↑ | 19↑  | 0   |
| A/G Ratio             | 1.5 | 1.3 | 0   | 13↓ | 27↓  | 8↑  |

\*: p<0.05

Values in margetuximab-treated groups are percent changes to their respective controls.

|                                                |                                                              |
|------------------------------------------------|--------------------------------------------------------------|
| <b>Urinalysis</b>                              | No drug-related changes in urinalysis parameters were noted. |
| <b>Gross Pathology</b>                         | No drug-related gross pathology findings were noted.         |
| <b>Organ Weights</b>                           | No drug-related changes in organ weights were noted.         |
| <b>Histopathology</b><br>Adequate battery: Yes | No drug-related microscopic findings were noted.             |

|                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Cytokines and Immunophenotype Profiles</b> | <p>Cytokines<br/>No drug-related increases in IFN-<math>\gamma</math>, IL-2, IL-4, IL-5, IL-6, IL-10, or TNF-<math>\alpha</math> were noted.</p> <p>Immunophenotype Profiles<br/>No drug-related changes were noted in circulating counts of total leukocytes (CD45+), total T cells (CD45+CD3+), helper T cells (CD3+CD4+), cytotoxic T cells (CD3+CD8+), B cells (CD45+CD20+), or monocytes (CD45+CD14+).</p> <p>Drug-related, partially reversible decreases in CD3-/CD159a+ and CD16+/CD159a+ NK cells were noted, particularly on Day 8 following the first dose but with lesser magnitude after subsequent doses. This finding was consistent with the mechanism of action of margetuximab in enhancing engagement of NK cells extravascularly by the modified Fc domain.</p> |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**Study title/ number: A 6-week toxicity and toxicokinetic study of MGAH22 administered by weekly intravenous infusion to cynomolgus monkeys with an 8-week recovery period (Study UOK00019)**

Results from Study UOK00019 were reviewed previously under IND 107768 and are summarized below.

In a GLP-compliant 6-week repeat-dose toxicology study in monkeys, MGAH22 (margetuximab) was administered at doses of 15, 50, and 150 mg/kg/week through IV infusion with an 8-week recovery period. MGAH22 was well tolerated in monkeys. MGAH22-related findings included a decrease in NK cells with no correlating change in NK cell cytolytic activity, and an increase in IL-6 noted on Day 1 at 4 hours postdose. Eight percent (1/13) of monkeys receiving MGAH22 had anti-MGAH22 antibodies. MGAH22-related microscopic findings included minimal to moderate pleural fibrosis at 150 mg/kg/week at the end of the dosing phase (males only) and recovery (females only) phase. The  $C_{max}$  and  $AUC_{0-inf}$  of MGAH22 were generally dose-proportional with greater clearance on Day 1 than on Day 36 and a  $T_{1/2}$  of approximately 7-9 days.

### 5.5.2. Genetic Toxicology

The Applicant's Position:

Not performed per ICH S6(R1).

The FDA's Assessment:

FDA agrees that genetic toxicology studies are not needed to support approval of Margenza.

### 5.5.3. Carcinogenicity

The Applicant's Position:

Not performed per ICH S6(R1), ICH S1A, and ICH S9.

The FDA's Assessment:

FDA agrees that carcinogenicity studies are not needed to support approval of Margenza for the proposed indication.

### 5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Per ICH S9, no studies were performed to evaluate margetuximab effects on fertility or early embryonic development. No studies were performed to evaluate effects of margetuximab administered to offspring.

An enhanced pre- and postnatal development (ePPND) study was conducted in cynomolgus monkeys (**Report 8329256**) to evaluate potential effects of margetuximab on pregnancy, embryo-fetal development, parturition, and postnatal development. Pregnant female monkeys were administered vehicle control article, 50 or 100 mg/kg/dose margetuximab via 1-hour IV infusion once every 3 weeks beginning on gestation day 20 through delivery. Postnatal survival, growth, and development of offspring were assessed for 3 months. No differences in gestation length; prenatal loss (abortions); fetal heart rates; maternal clinical pathology; maternal or infant clinical observations, body weights, or body weight change; infant grip strength, external, morphological, neurobehavioral observations; infant skeletal development; hematology; or coagulation were noted for margetuximab dosed animals compared to control animals. Treatment with margetuximab during pregnancy resulted in low amniotic fluid, beginning on gestation day 75, in maternal animals administered 50 or 100 mg/kg/dose. Margetuximab-related mortality occurred for one infant after maternal exposure to 100 mg/kg due to kidney findings. Fetal loss in three maternal animals was attributed to hypersensitivity reactions that occurred during dosing in response to ADAs. Clinical pathology changes included higher serum urea nitrogen and creatinine concentrations in 17% and 12% of infants from maternal groups administered 50 or 100 mg/kg/dose, respectively. Clinical pathology changes were associated with decreased kidney weights and microscopic findings of immature nephrons in infants after maternal exposure of 50 or 100 mg/kg/dose. The kidney findings in infants after maternal exposure to 50 or 100 mg/kg/dose and infant loss after maternal exposure to 100 mg/kg were defined as severe. Hence, a NOAEL was not determined. Measurable serum margetuximab was observed in all infants born from maternal animals having measurable serum margetuximab during lactation. These data are consistent with placental transfer of margetuximab from maternal to fetal circulation.

The FDA's Assessment:

In general, FDA agrees with the Applicant's assessment. See table below for study design.

Prenatal and Postnatal Development

**Study title/ number: Enhanced pre- and postnatal development toxicity study with margetuximab in cynomolgus monkeys (Study 8329256)**

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Dose and frequency of dosing:

0, 50, and 100 mg/kg/dose

Route of administration:

IV infusion (in 1 hour)

Formulation/Vehicle:

Sterile saline

Species/Strain:

Cynomolgus monkeys

Number/Sex/Group:

18 Females/group

Satellite groups:

None

Study design:

Margetuximab was administered at doses of 0, 50, and 100 mg/kg/dose IV every 3 weeks from gestational day 20 (GD20) to delivery in pregnant cynomolgus monkeys.

Deviation from study protocol

None

affecting interpretation of results:

**5.5.5. Other Toxicology Studies**

The Applicant's Position:

**Local Tolerance**

Stand-alone local tolerance (irritation) studies were not conducted. Instead, local tolerance after IV administration was evaluated within general toxicology studies per ICH M3(R2) and European Medicines Agency (EMA) "Guideline on non-clinical local tolerance testing of medicinal products". No effects related to local tolerance were observed in any of the general toxicity studies (**Reports UOK00021, UOK00019, 8321179**).

**Tissue Cross-Reactivity**

Four tissue cross-reactivity studies with margetuximab were conducted in normal human and cynomolgus monkey tissues, each with comparison to trastuzumab. Two non-GLP studies were performed on human tissues (**Reports RND-MGAH22-09-1005** and **IM1827**) and one GLP-compliant study each was performed on human (**Report IM1744**) and cynomolgus monkey (**Report IM1745**) tissues. These studies revealed margetuximab staining patterns consistent with reported sites of HER2 expression on human and cynomolgus monkey tissues. Direct comparison of margetuximab and trastuzumab revealed similar tissue staining.

The FDA's Assessment:

FDA agrees with the Applicant's assessment on local tolerance.

Tissue cross reactivity studies were reviewed under IND 107768. Margetuximab and trastuzumab showed similar binding to human and monkey tissues, and there were minimal differences between binding of margetuximab to human and monkey tissues.

X

X

---

George Ching-Jey Chang  
Primary Reviewer

Tiffany Ricks  
Supervisor

## 6 Clinical Pharmacology

---

### 6.1. Executive Summary

#### The FDA's Assessment:

Margetuximab is a chimeric IgG1- $\kappa$  monoclonal antibody that binds to the extracellular domain of HER2. The Fc-domain of margetuximab is engineered at 5 amino acid residues, conferring increased binding to both allotypes (158F or V) of the activating Fc receptor Fc $\gamma$ RIIIA (CD16A), and decreased binding to inhibitory Fc receptor Fc $\gamma$ RIIB (CD32B).

The proposed indication is the treatment of patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease, in combination with chemotherapy. The proposed margetuximab dosing regimen is 15 mg/kg every 3 weeks (Q3W), administered as an IV infusion over 120 minutes for the initial dose, then over a minimum of 30 minutes for all subsequent doses.

Primary evidence of efficacy and safety in the proposed indication at the 15 mg/kg Q3W dosage is derived from the randomized, active comparator-controlled phase 3 Study CP-MGAH22-04 (Study 04). The sequential primary endpoints of Study 04 were PFS, followed by OS. Study 04 met one of its primary objectives with a PFS prolongation of 0.9 months in the margetuximab + chemotherapy arm (median PFS = 5.8 months) compared to the trastuzumab + chemotherapy arm (median PFS = 4.9 months) and a hazard ratio of 0.76 (95% CI: 0.593, 0.979) favoring margetuximab. Interim OS analysis (70% of target OS events) showed that the margetuximab + chemotherapy arm had median OS of 21.6 months compared to 19.8 months in the trastuzumab + chemotherapy arm. In the pivotal Study 04, all margetuximab doses were administered as an IV infusion over 120 mins. Safety, tolerability and PK in a non-randomized infusion sub-study in Study 04 support the proposed 30 min infusion duration in Cycle 2 and beyond.

The Clinical Pharmacology review evaluated the acceptability of the proposed dosing regimen, the effect of Fc $\gamma$  receptor polymorphisms on the response to margetuximab and the pharmacokinetics of margetuximab over the dosage range of 0.1 mg/kg Q1W to 18 mg/kg Q3W. The proposed dosing regimen is acceptable. Based on exploratory analyses in Study 04, while patients carrying the CD16A low-affinity F allele (F/F or F/V) appeared to benefit from margetuximab vs trastuzumab, the HR of 1.776 for PFS showed a trend in favor of trastuzumab over margetuximab in the subgroup of patients with the CD16A V/V genotype.

The Agency will issue a Post Marketing Commitment to develop an adequately validated assay for neutralizing antibody and assess the neutralizing antibodies against margetuximab in Study

04 and the infusion sub-study.

**Recommendations:**

The Office of Clinical Pharmacology has reviewed the information submitted in BLA 761150. This BLA is approvable from a clinical pharmacology perspective for the following indication: MARGENZA is indicated, in combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

The key review issues with specific recommendations and comments are summarized below:

| Review Issue                                                             | Recommendations and Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pivotal and Supportive evidence of effectiveness</b>                  | <p>Primary evidence of effectiveness at the proposed dosage is established in the pivotal phase 3 trial, Study 04. The proposed regimen is supported by a statistically significant PFS prolongation (by blinded independent review) of 0.9 months in the margetuximab + chemotherapy arm (median PFS = 5.8 months) compared to the trastuzumab + chemotherapy arm (median PFS = 4.9 months) with a hazard ratio of 0.76 (95% CI: 0.593, 0.979; stratified log-rank p-value = 0.0334) favoring margetuximab.</p> <p>The second interim OS analysis (70% of target OS events) showed the margetuximab + chemotherapy arm had median OS = 21.6 months compared to 19.8 months in the trastuzumab + chemotherapy arm.</p> |
| <b>General dosing instructions</b>                                       | <p>The recommended dosing regimen in adult patients is 15 mg/kg every 3 weeks (Q3W), administered as an IV infusion over 120 minutes for the initial dose, then over a minimum of 30 minutes for all subsequent doses.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Dosing in patient subgroups (intrinsic and extrinsic factors)</b>     | <p>Recommended dosing is based on body weight. No other dose modifications are recommended for intrinsic or extrinsic factors.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Labeling</b>                                                          | <p>The review team has specific content and formatting change recommendations.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Bridge between the to-be-marketed and clinical trial formulations</b> | <p>The to-be-marketed liquid formulation was used throughout the clinical development program. Two DP manufacturing processes were used at different manufacturing sites. DP evaluated in pivotal Study 04 was from a single DS/DP process, and the process is the same as the to-be-marketed DP.</p>                                                                                                                                                                                                                                                                                                                                                                                                                  |

| Review Issue | Recommendations and Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|              | <i>(Source: section 2.3.P-Drug Product Summary, section 2.7.1-Summary of Biopharmaceutical Studies and Associated Analytical Methods)</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>PMC</b>   | There is one clinical pharmacology PMC:<br><br>Conduct a study to assess neutralizing antibody (nAb) responses against margetuximab in Study CP-MGAH22-04 and the infusion sub-study (CP-MGAH22-04) with an adequately validated nAb assay. NAb responses should be evaluated in all confirmed anti-drug antibody positive samples from Study CP-MGAH22-04 and the infusion substudy. Provide the final report and include information on the level of margetuximab in each patient’s test sample at each sampling point, an assessment of the effect of nAb development on the anti-tumor activity of margetuximab in individual patients, and the nAb assessment data set. |

## 6.2. Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

#### The Applicant’s Position:

Margetuximab clinical pharmacology has been characterized by population pharmacokinetic (PPK) and exposure-response (E-R) analyses of studies included in the application.

PK parameters were derived by PPK analysis of data from 261 patients with HER2+ MBC in Study 04 receiving the recommended 15 mg/kg IV Q3W dose. Geometric mean values (percent coefficient of variations) for clearance, steady state volume of distribution, and terminal half-life were 0.221 L/day (24%), 5.47 L (22%), and 19.2 days (28%), respectively. Time to steady-state was 2 months, and accumulation ratio was approximately 2. After margetuximab discontinuation, concentrations in at least 95% of metastatic breast cancer patients decreased to about 3% of the population-predicted steady-state trough serum concentration (97% washout) by 4 months. Reducing infusion time from 120 to 30 min had no influence on margetuximab exposure parameters.

E-R analysis of efficacy suggests PFS and OS are associated with margetuximab exposure. E-R analysis of safety suggests no correlation between probability of AEs and steady state margetuximab exposure.

The FDA's Assessment:

FDA agrees with the Applicant's position.

## 6.2.2. General Dosing and Therapeutic Individualization

### 6.2.2.1. General Dosing

Data:

Initial human dose regimens were informed by in vitro and in vivo pharmacological data, toxicology data, and interspecies scaling of monkey PK data to humans. Dose ranging Study 01 identified 6 mg/kg once weekly (QW), or 15 mg/kg Q3W, as potentially effective margetuximab dose regimens. Safety, PK, and clinical activity at 6 mg/kg QW and 15 mg/kg Q3W doses appeared similar in subjects with relapsed or refractory HER2+ carcinomas, including breast cancer. Both 6 mg/kg QW and 15 mg/kg Q3W dosing regimens were taken forward in Study 02.

FDA was consulted regarding Study 04 margetuximab and trastuzumab dose regimens (Type B End of Phase 2 meeting, 30-Jan-2015; **Table 4**). Dose selection rationale was included in the study protocol. A margetuximab dose regimen of 15 mg/kg Q3W was chosen for 3 reasons: 1) it was tolerable and clinically active; 2) it was less burdensome to patients than weekly dosing; and 3) it achieved target PK exposure.

Interim data from 88 subjects enrolled in Study 04 Infusion Substudy demonstrate tolerability of reduced duration margetuximab infusions starting from Cycle 2 (**Section 8.2.8**). In the Infusion Substudy, margetuximab was administered IV over 120 minutes in Cycle 1, then over 30 minutes in Cycle 2 onwards. Infusion-related reactions (IRRs) were ≤ Grade 2 and occurred predominantly during the first (120 minute) administration, as seen in randomized Study 04. From Cycle 2 onward, despite reduced infusion time, 1 subject only (1.1%) had a Grade 1 IRR. No ≥ Grade 3 IRRs were seen. Reduction of infusion duration to 30 minutes for Cycle 2 and beyond does not adversely affect margetuximab safety or increase IRR risk or severity.

The Applicant's Position:

The proposed dose regimen is 15 mg/kg as an IV infusion over 120 minutes for the initial dose and then over a minimum of 30-minute infusion every 3 weeks (Q3W) for all subsequent doses. On days when both margetuximab and chemotherapy are administered, margetuximab may be administered immediately after chemotherapy completion.

In Study 04, margetuximab at 15 mg/kg dose Q3W provided steady-state target exposure in 99% of subjects (N = 261) above the 30 µg/mL target threshold concentration for margetuximab clinical activity. Furthermore, the 19-day terminal half-life supports administration of 15 mg/kg Q3W. Given observed PPK, E-R, efficacy, and safety data, the margetuximab 15 mg/kg Q3W

dose regimen offers an acceptable benefit-risk profile in subjects with pretreated, advanced HER2+ MBC.

Interim data from 88 subjects enrolled in Study 04 Infusion Substudy demonstrate tolerability of reduced duration margetuximab infusions starting from Cycle 2. Pharmacometric modeling indicates that changing margetuximab infusion time from 120 to 30 minutes has minimal effect on exposure parameters. Minimal, if any, effects on efficacy or safety of margetuximab are expected.

#### The FDA's Assessment:

FDA agrees that the proposed dosing regimen of 15 mg/kg as an IV infusion over 120 minutes for the initial dose and then over a minimum of 30-minute infusion every 3 weeks (Q3W) for all subsequent doses is acceptable. The proposed 15 mg/kg Q3W dosing regimen is supported by the observed PFS benefit of 0.9 months over the active comparator trastuzumab in Study 04, acceptable safety and supportive PK data from Studies 01, 02, 04. The proposed infusion duration of 120 mins in Cycle 1 followed by 30 mins in Cycle 2 and beyond is supported by safety data from 72 patients in Stage A2 (n=8) and B (n=64) of the Study 04 infusion sub-study who received accelerated infusions over approximately 30 mins at or after Cycle 2. Observed PK data from Stage A2 and B of the infusion sub-study and population PK-based simulations support that margetuximab exposure is not markedly altered by the shorter the infusion duration.

FDA makes the following clarifications regarding the Applicant's position:

- As stated, the Applicant utilized a putative target steady-state trough concentration of 30 µg/mL, because population PK modeling of trastuzumab predicted a median Cycle 1 trough concentration of 29.4 µg/mL per the Herceptin USPI. As margetuximab is derived from the same parent antibody as trastuzumab, binds to the same epitope in subdomain IV of the ECD of HER2 as trastuzumab with a similar binding affinity (equilibrium dissociation constant by surface plasmon resonance is 2.8 and 2.3 nM for margetuximab and trastuzumab respectively), has similar EC50 of binding to cell surface Her2, similar Fc-independent non-clinical activity and increased Fc-dependent non-clinical ADCC activity, this overall approach is reasonable. However, FDA utilized a target steady-state trough concentration value of 50 µg/mL where applicable, because the median steady-state trastuzumab C<sub>trough</sub> in breast cancer patients (with the approved recommended trastuzumab Q3W dosing regimen) is 47.4 µg/mL per the Herceptin USPI. Based on population PK predicted values, in Study 04, the 15 mg/kg dose Q3W margetuximab dosage provided steady-state target exposure above the 50 µg/mL target threshold in > 95% of subjects.
- The Applicant's statement 'PK at 6 mg/kg QW and 15 mg/kg Q3W doses appeared similar in subjects with relapsed or refractory HER2+ carcinomas, including breast cancer' in the data

section, refers to an initial population PK analysis of data from Study 01 which indicated that estimated steady-state AUC over a 4-week cycle at 6 mg/kg Q1W (with dosing on days 0, 7, and 14) and C<sub>trough</sub> (end of cycle) were similar to AUC over a dose interval of 3 weeks and C<sub>trough</sub> at 15 mg/kg Q3W. (Source: Study report ‘Margetuximab (MGAH22) Population Pharmacokinetic Analysis of the Data from Study CP-MGAH22-01’ )

### 6.2.2.2. Therapeutic Individualization

Data:

PPK analysis of demographic and other covariates that may influence margetuximab PK identified baseline body weight (BW), sex, albumin, and tumor burden as significant covariates of linear clearance (CL). Baseline BW and sex were also significant covariates of volume parameters. Overall, observed variability in margetuximab PK and magnitude of covariate effects suggest that none of these factors has a clinically meaningful effect that would require dose adjustment. These and other covariate effects are presented in **Table 5**.

**Table 5: Summary of Population Pharmacokinetic Results**

| Category       | Covariate Investigated   | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Demo-graphics  | Effect of body weight    | Baseline subject BW in the PPK dataset ranged from 34–151 kg with a median of 65 kg (N=261). Margetuximab clearance and volume parameters increased with BW. Weight-based dosing generated comparable trough concentration (C <sub>trough</sub> ) and average concentration in a 3-week dosing interval (C <sub>avg</sub> ) values across the range of BWs. C <sub>max</sub> slightly increased with increasing BW, with about 25% differences between subjects from the lower and upper BW tertiles. There was considerable overlap in distributions of exposure parameters across BW tertiles. These results support weight-based dosing of margetuximab. |
|                | Effect of sex            | Of 349 subjects in PPK analysis, 29 (8.3%) were males. There was considerable overlap in distributions of exposure parameters between male and female subjects. Considering margetuximab PK variability (approximately 30–33%) and magnitude of covariate effects (≤35%), dose adjustment of margetuximab is not needed. Of note, all subjects on margetuximab in Study 04 were females.                                                                                                                                                                                                                                                                    |
|                | Effect of race           | White, Black or African American, Asian, and Other were 200, 16, 20, and 25, respectively, of 261 total subjects in Study 04. PPK analysis indicated no differences among races in steady-state margetuximab median C <sub>trough</sub> and C <sub>avg</sub> exceeding 15%.                                                                                                                                                                                                                                                                                                                                                                                 |
|                | Effect of age            | In PPK analysis (N=261), subject age ranged from 29 to 83 years with a median of 56 years in Study 04. There were no differences in first dose or steady-state exposure among age groups (29 to 50 years; 51 to 59 years, and 60 to 83 years [tertiles of age]). These data indicate no effect of age on margetuximab PK.                                                                                                                                                                                                                                                                                                                                   |
| Organ function | Effect of renal function | Margetuximab PK in renal impairment was inferred from PPK analysis. Of 261 female Study 04 subjects, 184, 63, and 14 had normal renal function, mild, or moderate renal impairment, respectively. Subjects with severe renal                                                                                                                                                                                                                                                                                                                                                                                                                                |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

| Category           | Covariate Investigated                                       | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|--------------------|--------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                    |                                                              | impairment were excluded due to study eligibility criteria. Individual exposure values indicated no meaningful differences among groups studied.                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                    | Effect of hepatic function                                   | Of 261 female subjects from Study 04 in the PPK analysis, 149, 110, 2, and 0 subjects were categorized as having normal hepatic function or mild, moderate, or severe hepatic impairment, respectively. The range of hepatic impairment was limited due to Study 04 liver function eligibility criteria. Margetuximab exposures were similar for subjects with mild hepatic impairment versus normal hepatic function. The small sample size with moderate hepatic impairment (N=2) did not allow meaningful comparison of exposures in this group to subjects with normal hepatic function.    |
| Con-comitant drugs | Effect of chemotherapy                                       | Of the 349 total subjects, 261 subjects from Study 04 received concomitant chemotherapy (capecitabine [N=68], gemcitabine [N=35], eribulin [N=66], or vinorelbine [N=92]), and 88 subjects from Studies 01 and 02 received monotherapy. PPK analysis indicated that concurrent chemotherapy did not have an effect on margetuximab PK parameters. Differences in steady-state margetuximab median C <sub>trough</sub> , C <sub>max</sub> , and C <sub>avg</sub> did not exceed 13% across the chemotherapies. Furthermore, there was considerable overlap in Cycle 1 or steady-state exposures. |
| Infusion duration  | Effect of duration of infusion                               | Simulations were performed to assess for effect of a shorter 30-minute infusion, compared to 120-minute infusions, on margetuximab PK (N=261). Exposure differences were less than 1%, suggesting that clinical results based on 30-minute margetuximab infusions should be similar to those of 120-minute infusions.                                                                                                                                                                                                                                                                           |
| Disease state      | Effect of albumin                                            | Baseline albumin ranged from 24 to 50 g/L with a median of 41 g/L (N=349) and had a significant influence on margetuximab CL. Subjects with baseline albumin of 29 g/L (2.5th percentile) had 25% higher CL, whereas subjects with baseline albumin of 47 g/L (97.5th percentile) had 10% lower CL than subjects with median baseline albumin of 41 g/L. These differences were not considered clinically meaningful as weight-based dosing generated comparable exposures across the range of albumin concentrations.                                                                          |
|                    | Effect of tumor burden                                       | Baseline tumor burden of subjects in PPK analysis ranged from 2 to 317 mm with a median of 85 mm (N=349). PPK analysis indicated a modest increase of margetuximab CL with increased tumor burden. Subjects with baseline tumor burden of 12.4 mm (2.5th percentile) had 12% lower CL and subjects with baseline tumor burden of 153.0 mm (97.5th percentile) had 7% higher CL than subjects with baseline tumor burden of 100 mm. Given margetuximab PK variability (approximately 30–33%) and modest magnitude of covariate effect, dose adjustment is not needed.                            |
| Pharmacogenomics   | Effect of FcγR genotypes                                     | Impact of FcγR genotypes of CD16A, CD32A, and CD32B on margetuximab exposures were evaluated in 261 subjects in Study 04. PPK analysis showed no effect of these covariates on margetuximab PK.                                                                                                                                                                                                                                                                                                                                                                                                 |
| Other              | Effects of ADA, LDH, HER2 expression, ECOG score, metastatic | In the final PPK model, ADA (N=4 and 257 ADA+ and ADA-, respectively), LDH (median [range]: 3.77 [1.7 to 97.8] μkat/L), HER2 expression by IHC (0 [N=10], 1 [3], 2 [N=149], and 3 [N=183]), ECOG score (0, 1, or 2), number of metastatic sites (≤ 2 versus > 2), and number of prior regimens of therapy (≤ 2 versus > 2) were not significant covariates.                                                                                                                                                                                                                                     |

| Category | Covariate Investigated    | Results |
|----------|---------------------------|---------|
|          | sites, and prior regimens |         |

The Applicant's Position:

No margetuximab dose adjustment is needed based on demographic or other covariates. Baseline covariates without clinically meaningful effects on margetuximab PK include sex, age, race, mild or moderate renal impairment, mild hepatic impairment, albumin, LDH, ADA status, HER2 expression level, ECOG score, genetic variations, tumor burden, number of metastatic sites, number of prior regimens of therapy, and concurrent chemotherapies.

The FDA's Assessment:

FDA agrees with the Applicant's position.

### 6.2.2.3. Outstanding Issues

The Applicant's Position:

The effect of severe renal impairment on margetuximab PK could not be investigated by PPK analysis since no subjects had severe renal impairment because of Study 04 protocol eligibility criteria. Nonetheless, renal clearance likely plays a minimal role in margetuximab disposition due to this antibody's ~149 kDa molecular weight. For mAbs generally, effects requiring dosage adjustment are considered unlikely (9), and no margetuximab dosage adjustment for severe renal impairment is proposed.

Due to protocol eligibility criteria for hepatic function, no subjects with severe hepatic impairment were enrolled in Study 04. Therefore, the effect of severe hepatic impairment on the PK of margetuximab could not be assessed.

The FDA's Assessment:

There is limited or no information regarding the impact of severe renal impairment (n=1 in Study 01) and moderate (n=2) or severe (n=0) hepatic impairment on the safety and PK of margetuximab. Margetuximab PK is not expected to be markedly altered in these populations.

The bioanalytical performance of the current neutralizing antibody assay is inadequate (please refer to the OBP review for further details). To support reporting of neutralizing antibody incidence in labeling, one PMC will be issued:

1. Conduct a study to assess neutralizing antibody (nAb) responses against margetuximab in Study CP-MGAH22-04 and the infusion sub-study (CP-MGAH22-04) with an adequately

validated nAb assay. NAb responses should be evaluated in all confirmed anti-drug antibody positive samples from Study CP-MGAH22-04 and the infusion substudy. Provide the final report and include information on the level of margetuximab in each patient's test sample at each sampling point, an assessment of the effect of nAb development on the anti-tumor activity of margetuximab in individual patients, and the nAb assessment data set.

### 6.3. Comprehensive Clinical Pharmacology Review

#### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

##### The Applicant's Position:

**Pharmacology:** Margetuximab targets HER2 overexpressed on the tumor cell surface. After binding HER2, margetuximab (1) inhibits tumor cell proliferation, (2) blocks shedding of HER2 extracellular domain and (3) mediates tumor cell lysis by engaging immune effector cells. Margetuximab Fc engineering seeks to increase immune activation beyond trastuzumab. Nonclinical assays confirm increased potency of margetuximab, relative to trastuzumab in NK cell activation and stimulation of ADCC. In addition, HER2-specific T-cells and antibodies increased in margetuximab treated patients.

**Pharmacokinetics:** Margetuximab PK in subjects with cancer is nonlinear, consistent with target-mediated drug disposition. Margetuximab disposition is described by a 2-compartment model with zero order IV infusion, parallel linear and Michaelis-Menten elimination from the central compartment. At lower doses (< 3.0 mg/kg), exposure increases more than proportionally to dose. At higher doses ( $\geq$  3.0 mg/kg), margetuximab exhibits linear PK, and exposure increases approximately proportionally to dose. After IV margetuximab 15 mg/kg Q3W in females with MBC (N = 261), PPK predicted margetuximab exposure parameters after the first dose and at steady-state are presented in **Table 6**.

**Table 6: PPK Predicted Geometric Mean (%CV) Exposure Parameters in 261 Female Patients with MBC who Received 15 mg/kg Q3W**

| Period       | C <sub>max</sub> <sup>a</sup><br>( $\mu\text{g/mL}$ ) | AUC <sup>b</sup><br>( $\mu\text{g}\cdot\text{day/mL}$ ) | C <sub>trough</sub> <sup>c</sup><br>( $\mu\text{g/mL}$ ) |
|--------------|-------------------------------------------------------|---------------------------------------------------------|----------------------------------------------------------|
| First Dose   | 356 (21%)                                             | 2490 (19%)                                              | 54.6 (32%)                                               |
| Steady-state | 466 (20%)                                             | 4120 (21%)                                              | 106 (33%)                                                |

a Maximum serum concentration

b Area under the curve in a dosing interval of 21 days

c Trough serum concentration

See also **Section 6.2.1**.

**Pharmacodynamics:** Margetuximab 15 mg/kg Q3W achieves target margetuximab  $C_{\text{trough}} \geq 30 \mu\text{g/mL}$  in 94% of subjects after first dose and in 99% at steady-state. Margetuximab has no clinically relevant effect on cytokines.

**Pharmacogenomics:** HER2 3+ expression associates with a lower hazard of progression. The disease progression hazard trends higher in high binding CD16A-158V/V homozygotes, relative to subjects carrying low affinity CD16A-158F alleles.

**Drug Interaction Potential:** Margetuximab is not expected to modulate concomitant chemotherapy exposure since metabolic pathways differ for antibodies versus small molecule chemotherapy drugs. Coadministration of capecitabine, gemcitabine, eribulin, or vinorelbine results in similar margetuximab exposure.

**Immunogenicity:** Four of 263 Study 04 subjects (1.5%) treated with margetuximab plus chemotherapy tested positive for treatment-emergent ADA. No subjects had neutralizing antibodies. None of 66 subjects in Study 01 and 22 subjects in Study 02 tested positive for treatment-emergent ADA. Immunogenicity appears to have no clinically meaningful effect on margetuximab PK, safety, or efficacy.

**Cardiac Intervals, Including QT Prolongation Potential:** ECG intervals revealed no marked differences between margetuximab and trastuzumab treatment groups. More subjects on margetuximab had heart rate  $> 100$  bpm than those on trastuzumab, coincident with increased concomitant IRRs on margetuximab. There were no AEs related to QTc interval changes.

SMQ analysis of Torsade/QTc prolongation did not identify potential safety issues for margetuximab (**Section 8.2.5**). In Study 04, categorical analysis of cardiac intervals revealed no notable differences between baseline and end of treatment in either treatment group. There was no evidence that margetuximab induced cardiac conduction abnormalities.

**Population Pharmacokinetics:** See **Section 6.2.2.2**.

**E-R Analysis of Efficacy:** PFS correlated with exposure in margetuximab recipients. However, even in subjects with lowest margetuximab exposure (1st Quartile), PFS was no worse than overall trastuzumab plus chemotherapy control PFS. PFS was longer in subjects with HER2 IHC 3+ expression. PFS was shorter for subjects with higher body surface area (BSA), lower age, and higher LDH. In exploratory analysis, PFS was shorter for CD16A-158V/V homozygotes. There were no differences in exposure-PFS relationships among margetuximab recipients with different CD16A alleles.

OS correlated with exposure. Although this relationship was significant without covariates, it was not significant when identified prognostic factors (albumin and LDH) were added to the model. OS was shorter for subjects with either lower baseline albumin or higher baseline LDH.

Probability of objective response appeared to increase with exposure. Except for clinical benefit rate (CBR) by independent review committee, these relationships did not reach statistical significance.

**E-R Analysis of Safety:** Margetuximab exposure did not correlate with probability of adverse events, serious adverse events (SAEs), IRRs, left ventricular dysfunction, neutropenia, febrile neutropenia, and vascular disorders.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. An overview of margetuximab ADME and clinical PK information based on the FDA's assessment are presented in Table 1:

**Table 1: General Pharmacology and Pharmacokinetic Characteristics**

| PHYSICOCHEMICAL PROPERTIES                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemical structure and molecular weight</b> | <p>Margetuximab is a chimeric IgG1-κ monoclonal antibody that binds to the extracellular domain of HER2. Margetuximab was derived from 4D5, the murine precursor to the trastuzumab and binds the same epitope in subdomain IV of the extracellular domain (ECD) of HER2 as trastuzumab. The HER2 binding affinity and Fc-independent in vitro activity of margetuximab are similar to trastuzumab. The Fc domain of margetuximab is engineered at 5 amino acid residues, conferring increased binding to both allotypes (158F or V) of the activating Fc receptor FcγRIIIA (CD16A) and decreased binding to inhibitory Fc receptor FcγRIIB (CD32B).</p> <p>The molecular weight of Margetuximab is 149 kDa.</p> <p><i>(Source: 2.6.2 Pharmacology written summary and 2.3.S Drug substance summary)</i></p> |
| PHARMACOLOGY                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Mechanism of action</b>                     | <p>Margetuximab binds to HER2 overexpressed on the tumor cell surface and (1) inhibits tumor cell proliferation, (2) blocks shedding of HER2 extracellular domain and (3) mediates tumor cell lysis by engaging immune effector cells. Please refer to non-clinical review for the FDA's assessment of the non-clinical pharmacology data.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Active moiety</b>                           | Margetuximab                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

| <b>QT/QTc prolongation</b>                                  | As a monoclonal antibody, margetuximab is not expected to cause QT prolongation (please see QT IRT review for additional information).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                              |                                          |                              |                                          |            |           |            |            |              |           |            |           |
|-------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|------------------------------------------|------------------------------|------------------------------------------|------------|-----------|------------|------------|--------------|-----------|------------|-----------|
| <b>GENERAL INFORMATION</b>                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                              |                                          |                              |                                          |            |           |            |            |              |           |            |           |
| <b>Bioanalytical assay</b>                                  | A validated enzyme-linked immunosorbent assay (ELISA; RES-014 Vers 00, 01, & 02 which was refined to RES-014 Vers 03) and a validated electrochemiluminescent (ECL) immunoassay (Method ICD 638) were used to measure serum margetuximab concentrations in the clinical studies included in this BLA (please see Section 19.4).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                              |                                          |                              |                                          |            |           |            |            |              |           |            |           |
| <b>Patient PK vs. healthy subject (HS) PK</b>               | Margetuximab PK have not been evaluated in healthy subjects.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                              |                                          |                              |                                          |            |           |            |            |              |           |            |           |
| <b>Steady-state exposure at the proposed dosing regimen</b> | <p>FDA verified the population PK-predicted margetuximab exposure parameters reported in Table 6 of the Applicant's position (summarized below). Based on population PK analyses, in Study 04 margetuximab 15 mg/kg Q3W achieves margetuximab C<sub>trough</sub> ≥ 50 µg/mL in ~67% of patients after the first dose and in ~97% at steady-state.</p> <p><b>Applicant's Table 6: PPK Predicted Geometric Mean (%CV) Exposure Parameters in 261 Female Patients with MBC who Received 15 mg/kg Q3W</b></p> <table border="1"> <thead> <tr> <th>Period</th> <th>C<sub>max</sub><sup>a</sup> (µg/mL)</th> <th>AUC<sup>b</sup> (µg•day/mL)</th> <th>C<sub>trough</sub><sup>c</sup> (µg/mL)</th> </tr> </thead> <tbody> <tr> <td>First Dose</td> <td>356 (21%)</td> <td>2490 (19%)</td> <td>54.6 (32%)</td> </tr> <tr> <td>Steady-state</td> <td>466 (20%)</td> <td>4120 (21%)</td> <td>106 (33%)</td> </tr> </tbody> </table> <p>a Maximum serum concentration<br/>                     b Area under the curve in a dosing interval of 21 days<br/>                     c Trough serum concentration</p> | Period                       | C <sub>max</sub> <sup>a</sup> (µg/mL)    | AUC <sup>b</sup> (µg•day/mL) | C <sub>trough</sub> <sup>c</sup> (µg/mL) | First Dose | 356 (21%) | 2490 (19%) | 54.6 (32%) | Steady-state | 466 (20%) | 4120 (21%) | 106 (33%) |
| Period                                                      | C <sub>max</sub> <sup>a</sup> (µg/mL)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | AUC <sup>b</sup> (µg•day/mL) | C <sub>trough</sub> <sup>c</sup> (µg/mL) |                              |                                          |            |           |            |            |              |           |            |           |
| First Dose                                                  | 356 (21%)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 2490 (19%)                   | 54.6 (32%)                               |                              |                                          |            |           |            |            |              |           |            |           |
| Steady-state                                                | 466 (20%)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 4120 (21%)                   | 106 (33%)                                |                              |                                          |            |           |            |            |              |           |            |           |
| <b>Maximum tolerated dose or exposure</b>                   | In the phase 1 Study 01, margetuximab was evaluated over the dosage range of 0.1 mg/kg to 6 mg/kg Q1W (on Days 1, 8, and 15 of 28-day cycles <sup>1</sup> ) and 10 mg/kg to 18 mg/kg Q3W <sup>1</sup> . The margetuximab MTD was not reached in this study. In Study 01, no DLTs were observed at the highest dose level tested, 18 mg/kg Q3W; 1 patient each in the 3mg/kg Q1W and 10 mg/kg Q3W cohorts experienced DLTs.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                              |                                          |                              |                                          |            |           |            |            |              |           |            |           |
| <b>Dose proportionality</b>                                 | Margetuximab undergoes both linear and non-linear elimination. The reviewer conducted a non-compartmental analysis of margetuximab PK data after a single dose in Study 01 over the dosage range of 0.1 mg/kg to 6 mg/kg Q1W and 10 mg/kg to 18 mg/kg Q3W <sup>1</sup> . Based on a power model analysis of the resulting NCA parameters conducted by the reviewer, margetuximab maximum observed concentrations (first PK timepoint is 1 hour post the end of infusion) after a single dose increased in a dose proportional manner from 0.1 mg/kg to 18 mg/kg (slope: 0.99; 95% CI: 0.94-1.03) and margetuximab                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                              |                                          |                              |                                          |            |           |            |            |              |           |            |           |

|                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                       | AUC0-21d after a single dose increased in an approximately dose proportional manner over the 10 -18 mg/kg dose range (slope: 1.11; 95% CI: 0.7-1.5). Sparse PK data collected over a dose interval at steady-state are inadequate to enable a similar analysis of dose proportionality at steady-state.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Accumulation</b>   | Based on geometric mean population PK derived exposures, margetuximab steady-state accumulation at the 15 mg/kg Q3W dosage is in the range of 1-2 fold (accumulation ratio = 1.9 based on Ctrough, 1.65 based on AUC0-21d and 1.3 based on Cmax).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Variability</b>    | Following administration of margetuximab 15 mg/kg Q3W to female patients with breast cancer, the inter-subject variability (CV%) in steady-state margetuximab AU <sub>Ctau</sub> , C <sub>max</sub> , and C <sub>trough</sub> was 21%, 19.5% and 32.6%, respectively based on population PK analysis.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Immunogenicity</b> | <p>Please see OBP review regarding the bioanalytical performance of the ADA and neutralizing antibody assays in Study 04 including the infusion sub-study. The performance of the current neutralizing antibody is inadequate; the sensitivity of the assay in the presence of the observed margetuximab systemic concentrations has not been demonstrated.</p> <p>In the pivotal Study 04, 263 patients had immunogenicity assessment at baseline and 240 patients had immunogenicity assessment at baseline and at least one time point post-dose. Of the 263 patients with immunogenicity assessment at baseline, 17 (6.5%) patients were positive for anti-margetuximab antibodies at baseline. Of the 240 patients who had immunogenicity assessment at baseline and at least one time point post-dose, 4 (1.7%) patients were positive for anti-margetuximab antibodies on or after therapy (treatment-emergent anti-drug antibodies). Of these 4 patients, anti-margetuximab antibodies were detected prior to Cycle 7 in 1 patient, and more than 2 months after the last margetuximab dose in 3 patients. Two additional patients tested positive for anti-margetuximab antibodies at baseline and also tested positive on therapy. One subject had a baseline titer of 300 and was ADA positive at Cycle 3 with a titer of 300. The second subject had a positive antibody response at baseline with a titer of 9600, which persisted until Cycle 7 then dropped at Cycle 9 to a titer of 4800.</p> <p>In the infusion sub-study of Study 04, 80 patients had immunogenicity assessment at baseline and 52 patients had immunogenicity assessment at baseline and at least one time point post-dose. Of the 80 patients</p> |

|                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                     | <p>with immunogenicity assessment at baseline, 2 (2.5%) patients were positive for anti-margetuximab antibodies at baseline. Of the 52 patients who had immunogenicity assessment at baseline and at least one time point post-dose, 2 (3.8%) patients were positive for anti-margetuximab antibodies on or after therapy (treatment-emergent anti-drug antibodies). Of these 2 patients, anti-margetuximab antibodies were detected prior to Cycle 3 in 1 patient, and more than 6 months after the last margetuximab dose in 1 patient.</p> <p>Due the limited number of patients who were positive for anti-margetuximab antibodies during treatment with margetuximab, the impact of anti-margetuximab antibodies on the PK, safety and efficacy of margetuximab is not definitively known. Therefore, and in order to support reporting of neutralizing antibody incidence in labeling, FDA determined that the Applicant should conduct a PMC study to assess the development of neutralizing antibodies against margetuximab in Study 04 and the infusion sub-study using an adequately validated assay.</p> <p>Study 01 and 02 utilized a different anti-drug antibody assay than that used in Study 04. Please see OBP review regarding the performance of this assay. In Study 01, 64 patients had immunogenicity assessment at baseline and at least one time point post dose. One patient in this study (dosed at 15 mg/kg Q3W) tested positive for anti-margetuximab antibodies at baseline and also on therapy, no patients had treatment emergent anti-margetuximab antibodies. In Study 02, 20 patients had immunogenicity assessment at baseline and at least one time point post dose and no patient tested positive for anti-margetuximab antibodies.</p> |
| <b>ABSORPTION</b>                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Bioavailability</b>                              | Complete as margetuximab is administered via IV infusion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>TMAX</b>                                         | Close to end of infusion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>DISTRIBUTION</b>                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Volume of distribution (Vd)</b>                  | Population PK-derived mean (SD) steady-state volume of distribution of margetuximab in female patients with breast cancer is 5.6 (1.31) L.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>ELIMINATION</b>                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Terminal elimination half-life and clearance</b> | The PK of margetuximab are described by a 2-compartment model with parallel non-specific linear and Michaelis-Menten elimination. Total margetuximab clearance increases with decreasing concentrations. In the linear concentration range, the population PK-derived mean (SD) terminal elimination half-life (t <sub>1/2</sub> ) of margetuximab in female patients                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

|                                   |                                                                                                                                         |
|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
|                                   | with breast cancer is 20 (6.42) days and the mean linear clearance is 0.228 (0.0565) L/day.                                             |
| <b>Metabolism</b>                 | As a monoclonal antibody, margetuximab is expected to be metabolized into small peptides by catabolic pathways.                         |
| <b>Excretion</b>                  | Monoclonal antibodies do not undergo significant renal excretion.                                                                       |
| <b>Drug interaction liability</b> | No formal drug-drug interaction studies have been conducted with margetuximab. No CYP enzyme or transporter-mediated DDIs are expected. |

<sup>1</sup> Dosing in Study 01 was as follows:

- 0.1, 0.3, 1, 3, 6 mg/kg IV on Days 1, 8, 15, 22 of 50-day Cycle 1; then Q1W on Days 1, 8, and 15 of 28-day cycles
- 10, 15, 18 mg/kg on Days 1 and 22 of 50-day Cycle 1, then Q3W Day 1 of 21-day cycle

### 6.3.2. Clinical Pharmacology Questions

#### 6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

##### Data:

Clinical pharmacology of margetuximab derives from 3 human studies (Phase 1 Study 01, Phase 2 Study 02, and Phase 3 Study 04), including a Study 04 Infusion. These studies provided safety, efficacy, PK, PD, genetics, and ADA data that support the margetuximab clinical pharmacology profile.

Study 01 examined safety, clinical pharmacology, immunogenicity, and clinical activity of margetuximab over escalating doses in subjects with pre-treated HER2+ cancers. Doses investigated ranged from 0.1 to 6 mg/kg QW and 10 to 18 mg/kg Q3W. No maximum tolerated dose was reached. Single-agent margetuximab was well tolerated with detectable clinical activity. PPK analysis estimated steady-state AUC over a 4-week cycle at 6 mg/kg QW (dosing on Days 0, 7, and 14) to be near AUC over a 3-week cycle at 15 and 18 mg/kg Q3W. Steady state C<sub>trough</sub> values were also similar and exceeded the 30 µg/mL target for margetuximab clinical efficacy. Study 01 results informed Study 02, then Study 04.

Study 02 rationale followed nonclinical observation of improved ADCC activity of margetuximab versus wild-type Fc variant against lower HER2 expressing (IHC 2+) JIMT-1 cells (**BLA – Section 2.6.2.2.4.1**). Also, 8 (40%) of 20 Study 01 subjects with no or low HER2 overexpression (IHC 0–2 and FISH non-amplified) had stable disease (**Study 01 CSR – Table 16**). Therefore, Study 02 focused on subjects who were IHC 1+ or 2+ FISH non-amplified. Administered IV dose levels were 6.0 mg/kg QW on Days 1, 8, and 15 of every 28-day cycle and 15 mg/kg Q3W. This trial stopped after meeting discontinuation criteria (b) (4)

(b) (4). Study 02 PK supported Study 04 dosing regimen refinement to 15 mg/kg Q3W with chemotherapy.

Study 04 compared margetuximab and trastuzumab, each with chemotherapy, in subjects with advanced HER2+ breast cancer after prior anti-HER2 therapy. Standard of care chemotherapy options were Investigator selected before randomization, including capecitabine, eribulin, gemcitabine, and vinorelbine. Subjects received margetuximab (15 mg/kg as a 120-minute IV infusion) or trastuzumab (first as a 90-minute IV infusion in Cycle 1, then a 30-minute IV infusion from Cycle 2 onward) on Day 1 of a 3-week cycle. In primary independent blinded PFS analysis, margetuximab 15 mg/kg Q3W plus chemotherapy led to a 24% PFS risk reduction over trastuzumab plus chemotherapy ( $p = 0.033$ ; **Table 17** and **Figure 2**). Immature interim OS evaluation nominally favored margetuximab without statistical significance (**Table 18**). Clinical safety of margetuximab overall appeared similar to that of trastuzumab.

The Study 04 Infusion Substudy evaluated safety and tolerability of reduced infusion time after Cycle 1. Margetuximab was infused IV over 120 minutes in Cycle 1, then over 30 minutes in Cycle 2 and beyond. A 30-minute infusion duration from Cycle 2 onward did not adversely affect IRR risk or severity (see **Section 8.2.8**).

Studies 01, 02, and 04 data supported PPK and E-R analyses of margetuximab. PPK analysis indicated that (1) linear clearance and volume of distribution increase with BW, supporting weight-based dosing; (2) an approximate 19-day half-life supports Q3W (21 day) dosing; (3) the proposed regimen achieved target  $C_{trough}$  in 94% of subjects after first infusion and > 99% of subjects at steady state; and (4) reducing infusion time from 120 to 30 minutes in Cycle 2 onward has minimal impact on exposure. E-R analysis supports the margetuximab 15 mg/kg Q3W dosing regimen with chemotherapy. Importantly, E-R for efficacy indicates that higher exposure correlates with better efficacy, whereas E-R for safety supported that AEs did not increase with increasing exposure.

#### The Applicant's Position:

The clinical pharmacology program provides supportive evidence of effectiveness of margetuximab. E-R analyses demonstrated that margetuximab had a positive benefit to risk ratio at the 15 mg/kg Q3W dosing regimen. PPK analyses support weight-based dosing, administration Q3W, target concentration attainment in > 99% of subjects, and infusion time reduction from 120 minutes in Cycle 1 to 30 minutes in all subsequent Q3W cycles.

#### The FDA's Assessment:

Overall FDA agrees with the Applicant's position that the clinical pharmacology data provide supportive evidence of efficacy. Primary evidence of efficacy and acceptable safety of margetuximab at the 15 mg/kg Q3W dosage in the proposed indication was established in

Study 04. As supportive clinical pharmacology evidence, in Study 04, margetuximab achieved steady-state C<sub>trough</sub> values associated with PD activity in non-clinical studies. Based on population PK model predicted values, in Study 04, the 15 mg/kg dose Q3W margetuximab dosage attained target exposure above the 50 µg/mL target threshold in ~67% of patients after the first dose and in ~97% of patients at steady-state. Reducing the duration of infusion in ≥ Cycle 2 did not markedly affect the exposure of margetuximab (see section 6.3.2.2). E-R analyses of the data in patients in Study 04 treated at 15 mg/kg Q3W indicate that there is a trend towards longer PFS with higher exposure (see section 6.3.2.2). None of the safety endpoints evaluated in the E-R analysis showed a meaningful relationship with exposure at the 15 mg/kg Q3W dosage.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

Integrated assessment of in vitro, preclinical, laboratory, and clinical data over a range of margetuximab doses enabled iterative examination of margetuximab clinical pharmacology, immunogenicity, efficacy, and safety. Study 01 and Study 02 monotherapy data were used sequentially to support dose rationale and regimen for Phase 3 Study 04 (15 mg/kg Q3W) with chemotherapy.

A dose ranging Phase 1 Study 01 of margetuximab monotherapy identified 6.0 mg/kg QW or 15 mg/kg Q3W as recommended Phase 2 doses. Clinical activity at 6.0 mg/kg QW and 15 mg/kg dose Q3W were similar, as were margetuximab AUC and C<sub>trough</sub>. Both regimens generated C<sub>trough</sub> concentrations above the 30 µg/mL target threshold concentration for margetuximab clinical activity. These 2 dosing regimens were used in Phase 2 Study 02 that investigated monotherapy margetuximab in subjects with HER2 low expressing advanced breast cancer. Study 02 was discontinued early (b) (4)

Preclinical xenograft studies indicated that, similar to trastuzumab plus chemotherapy, margetuximab plus chemotherapy may be effective in subjects with HER2+ MBC after prior anti-HER2+ therapies. Therefore, Phase 3 Study 04 compared margetuximab 15 mg/kg Q3W plus chemotherapy with trastuzumab plus chemotherapy for treatment of subjects with pretreated HER2+ MBC. The 15 mg/kg Q3W regimen was selected due to similar safety and antitumor activity as the 6 mg/kg QW regimen as well as increased convenience. Statistically significant and clinically meaningful improvement was observed in efficacy parameters. The safety profile was similar to that of trastuzumab.

PPK analysis indicated: (1) both linear clearance and volume of distribution increase with BW supporting weight-based dosing; (2) half-life of approximately 19 days supported Q3W (21 day)

dosing; (3) the proposed regimen achieved target  $C_{trough}$  in 94% after first infusion and > 99% at steady state; and (4) reducing infusion time from 120 to 30 minutes in Cycle 2 and beyond had minimal impact on margetuximab exposure parameters, suggesting any effects of reduced infusion duration on efficacy or safety are expected to be minimal.

E-R analyses supported the margetuximab 15 mg/kg Q3W dosing regimen with chemotherapy. E-R for efficacy indicated that higher exposure was associated with better efficacy, whereas E-R for safety supported that AEs did not increase with increasing exposure.

#### The Applicant's Position:

The proposed dosing regimen is acceptable for the general patient population for which the indication is being sought. The proposed dose regimen is 15 mg/kg as an IV infusion over 120 minutes for the initial dose and then over a minimum of 30-minute infusion Q3W for all subsequent doses. On days when both margetuximab and chemotherapy are administered, margetuximab may be administered immediately after chemotherapy completion.

Cumulative efficacy data across 2 studies (Studies 04 and 01) and safety data across the 3 studies included in this application (Studies 04, 01, and 02; **Table 7**), including Study 04 Infusion Substudy, support a positive benefit/risk profile for margetuximab at the target dose in the target indication. Additionally, E-R analyses for efficacy and key safety variables from Study 04 further support the positive benefit/risk profile for the 15 mg/kg Q3W dosing regimen. In conclusion, the 15 mg/kg Q3W regimen was safe and effective for treatment of subjects with HER2+ MBC having limited effective treatment choices.

#### The FDA's Assessment:

FDA agrees that the proposed margetuximab dosing regimen of 15 mg/kg Q3W is acceptable for the general patient population, as this dosage reasonably balances safety and efficacy. The proposed dosage level is supported by safety and efficacy data in Study 04 and the infusion sub-study as well as PK data from Studies 01, 02, 04 and the infusion sub-study in Study 04.

In the phase 1, dose escalation Study 01, no marked dose-response with treatment-related AEs, grade  $\geq 3$  adverse events or SAEs were observed with margetuximab monotherapy from 3 mg/kg Q1W to 18 mg/kg Q3W. No DLTs were observed at the 18 mg/kg Q3W dose level; though 1 patient each in the 3 mg/kg Q1W and 10 mg/kg Q3W cohorts experienced DLTs. The MTD was therefore not reached up to the highest dose levels tested 18 mg/kg Q3W in Study 01.

In the pivotal study, Study 04, a high mean (SD) relative dose intensity of 93.8 (11)% over the duration of treatment was observed at the 15 mg/kg Q3W dosage, which was not significantly affected by the shorter infusion duration in the infusion sub-study in Study 04 (mean [SD]

relative dose intensity in Stages A2+B= 94.7 [11%]). The tolerability of the 15 mg/kg Q3W dosage in Study 04 and the infusion sub-study was acceptable as described in Table 2.

**Table 2: Tolerability of 15 mg/kg Q3W Margetuximab**

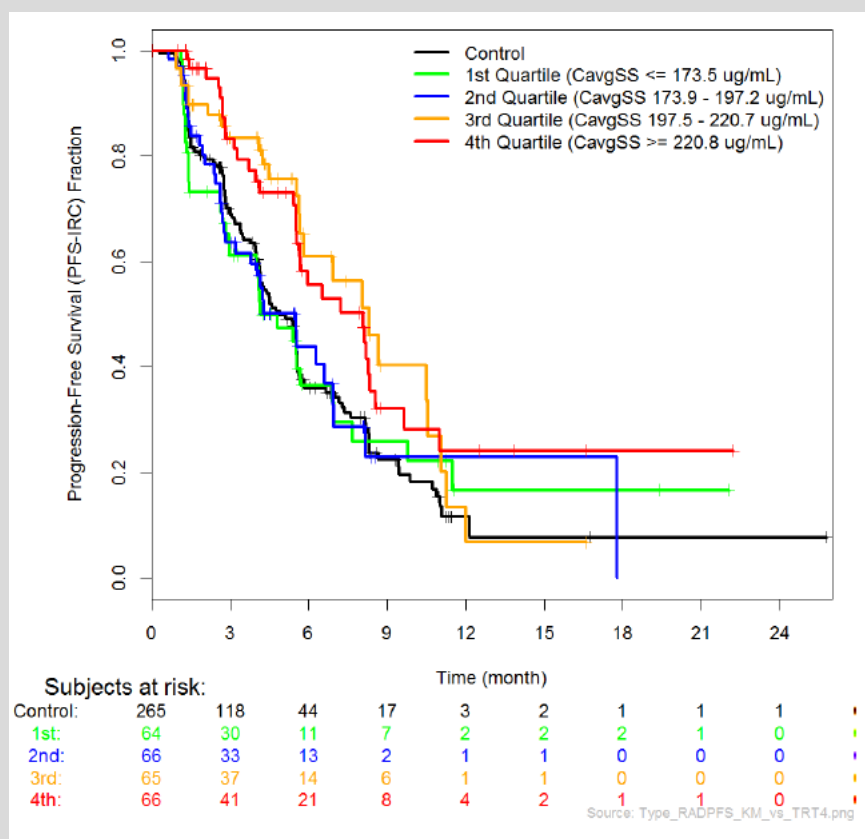
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <b>Margetuximab (M) + chemotherapy main study (N=264)</b> | <b>Margetuximab (M) + chemotherapy infusion sub-study (Stage A2+ B; n=80)</b> | <b>Trastuzumab (T) + chemotherapy main study (n=265)</b> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <b>Number of patients (%)</b>                             |                                                                               |                                                          |
| <b>Study drug interruptions due to AE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 27 (10.2)                                                 | 19 (23.8)                                                                     | 7 (2.6)                                                  |
| <b>Dose delays due to AE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 44 (16.7)                                                 | 18 (22.5)                                                                     | 70 (26.4)                                                |
| <b>M/T discontinuation due to AE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 11 (4.2)                                                  | 3 (3.8)                                                                       | 9 (3.4)                                                  |
| <b>Infusion interruptions due to AE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 22 (8.3)                                                  | 15 (18.8)                                                                     | 5 (1.9)                                                  |
| <b>Infusion terminations due to AE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 10 (3.8)                                                  | 2 (2.5)                                                                       | 0 (0)                                                    |
| <b>Dose intensity (% Mean ± SD)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 93.8 ± 11                                                 | 94.7 ± 11                                                                     | 94.4 ± 10                                                |
| Notes: <ul style="list-style-type: none"> <li>• No margetuximab dose reductions were permitted per the Study 04 protocol.</li> <li>• Infusion-related reactions were the most common cause of study drug interruption in the pivotal study (23 [8.7 %]) and infusion sub-study (15 [18.8%]). In the infusion sub-study, infusion-related reactions were observed mainly during the initial 120-minute margetuximab infusion. Only one subject in Stage B reported a (Grade 1) infusion-related reaction in Cycle 2.</li> </ul> |                                                           |                                                                               |                                                          |

*Source: Reviewer generated*

Efficacy of margetuximab in combination with chemotherapy (capecitabine, gemcitabine, eribulin or vinorelbine) compared to the active control comparator trastuzumab +chemotherapy was established in the pivotal Study 04. PFS and OS were sequential primary endpoints in Study 04. Patients treated with margetuximab 15 mg/kg Q3W +chemotherapy had a PFS prolongation by blinded independent review of 0.9 months (median PFS = 5.8 months) compared to patients treated with the trastuzumab +chemotherapy arm (median PFS = 4.9 months) with a hazard ratio of 0.76 (95% CI: 0.593, 0.979; stratified log-rank p-value = 0.0334) favoring margetuximab. The second interim OS analysis (70% of target OS events) showed the margetuximab + chemotherapy arm had median OS = 21.6 months compared to 19.8 months in the trastuzumab + chemotherapy arm.

Exposure-response analysis with margetuximab safety and efficacy are limited to data from patients treated at a single dose level i.e. the 15 mg/kg Q3W dosage in Study 04. No meaningful exposure-response relationships between margetuximab CavgSS and the probability of any grade or grade  $\geq 3$  AEs, SAEs, IRRs (no relationship with CavgSS, Cycle 1 Cmax and CmaxSS), left ventricular dysfunction, neutropenia, febrile neutropenia, or vascular disorders were observed in Study 04 over the margetuximab exposure range achieved at the 15 mg/kg Q3W dosage (see section 19.4). As discussed in section 19.4, a cox proportional hazard (CPH) analysis identified a statistically significant trend towards longer PFS with increasing margetuximab exposure (CavgSS) in Study 04 over the margetuximab exposure range achieved at the 15 mg/kg Q3W dosage. Kaplan-Meier plots indicate PFS in subjects in the lowest quartile of margetuximab exposure was no worse than the trastuzumab plus chemotherapy control (Figure 1).

**Figure 1: Kaplan-Meier Plot for Time to PFS-IRC by Quartiles of Exposure**



Source: Applicant's exposure response analysis

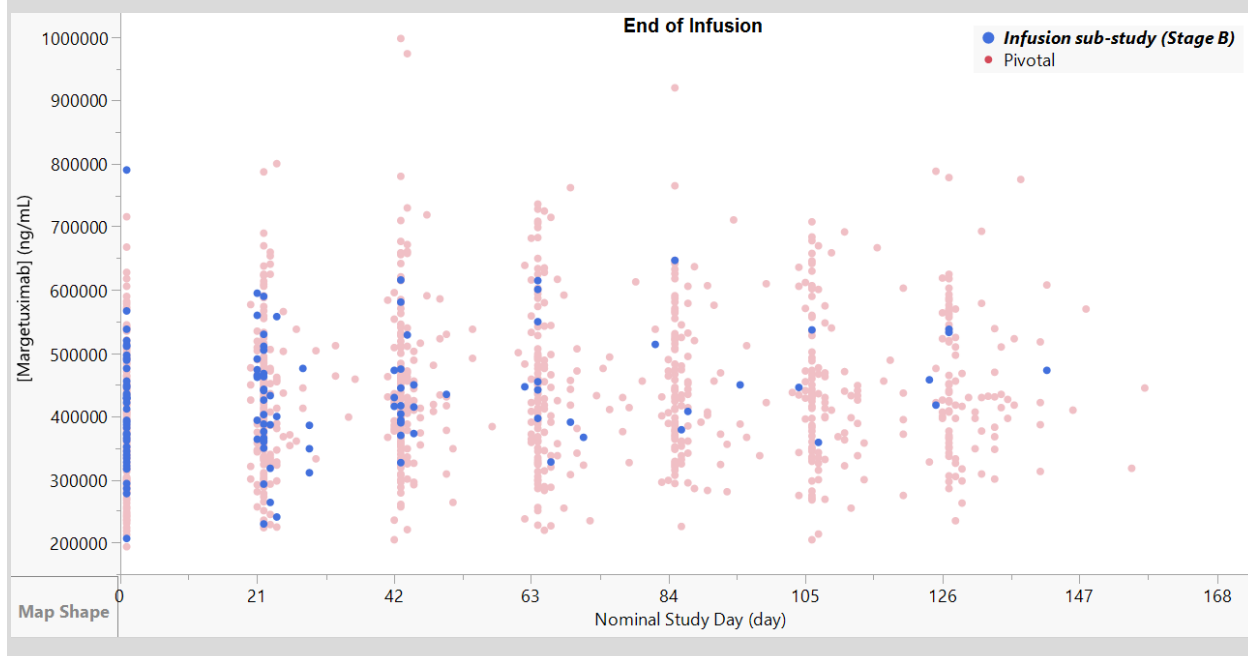
A trend towards longer OS with increasing margetuximab exposure (CavgSS) was also observed in the CPH analysis, however this relationship was not statistically significant after accounting for identified prognostic factors. Additionally, as OS data used in the exposure-response

analysis are immature, this relationship is interpreted with caution. Kaplan-Meier plots suggest shorter OS in the lowest quartile of margetuximab exposure compared to trastuzumab treated patients. However, as indicated, this analysis was conducted with immature OS data and this finding may be due to subjects in the first quartile of the margetuximab arm being compared to all subjects in the control arm. Therefore, no conclusions were drawn based on the exposure-response analysis with OS. The margetuximab exposure-response relationship with OS will be revisited when updated exposure-response analyses with the final OS data set are available.

The 15 mg/kg Q3W dosing regimen in the pivotal Study 04 achieved a geometric mean (CV%) steady-state Ctrough of 106 µg/mL. This provides supportive evidence of the adequacy of the proposed dosage, as the attained Ctrough is adequate based on the exposure range associated with margetuximab non-clinical PD activity (non-clinical PD studies identified a putative range of target concentrations from < 1 to 100 µg/mL) and clinical steady-state trough of trastuzumab per the Herceptin USPI (47.4 µg/mL in breast cancer patients with the Q3W dosing schedule). Based on population PK model predicted values, in Study 04, the 15 mg/kg dose Q3W margetuximab dosage attained target exposure above the 50 µg/mL target threshold in ~67% of patients after the first dose and in ~ 97% of patients at steady-state.

Modification of the infusion duration from 120 min to 30 min in Cycle 2 and beyond did not markedly impact exposure of margetuximab based on the observed data (at end of infusion and pre-dose) and using population PK model-based simulations.

**Figure 2: Observed margetuximab end of infusion concentrations in pivotal Study 04 (120 min infusion duration for all doses) and Stage B patients in the infusion sub-study (30 min infusion duration in Cycle 2 and beyond)**



69

Version date: July 24, 2019 (ALL NDA/ BLA reviews)

**Disclaimer: In this document, sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect positions of FDA.**

*Source: Reviewer's analysis*

Safety experience with this approach in the pivotal Study 04 and the infusion sub-study in Study 04 support the administration of margetuximab immediately after chemotherapy completion on days when both margetuximab and chemotherapy are administered.

### 6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

#### Data:

PPK analysis of demographic and other covariates that may influence margetuximab PK identified baseline body weight, sex, albumin, and tumor burden as significant covariates of linear CL. Baseline body weight and sex were also significant covariates of volume parameters. Overall margetuximab PK variability (approximately 30–33%) and magnitude of covariate effects suggest that none of these factors has a clinically meaningful effect that necessitates dose adjustment (**Section 6.2.2.1**). Covariates with no clinically important PPK-based margetuximab PK effects include age, race, sex, HER2 expression level, ECOG score, albumin, genetic variations, number of metastatic sites, tumor burden, number of prior therapy lines, concurrent chemotherapies (**Section 6.2.2.1**).

The impact of renal or hepatic Impairment on margetuximab PK is described in **Section 6.2.2.1**.

#### The Applicant's Position:

An alternative dosing regimen or management strategy is not required for subpopulations based on intrinsic patient factors. Given reassuring PPK and AE by subgroup analyses, no dose adjustment or management strategy is needed in special groups, including older patients and those with mild or moderate renal or mild hepatic impairment. Currently, there is no data to inform if margetuximab dose should be adjusted in severe renal or moderate or severe hepatic impairment. Treatment seems reasonable despite lack of data based on known pharmacology of monoclonal antibodies.

#### The FDA's Assessment:

FDA agrees that no dosage adjustment or alternative management strategies are needed for subpopulations based on intrinsic factors of age (29 to 83 years), sex, race (Caucasian, Black, Asian), mild (CLcr 60 to 89 mL/min) or moderate (CLcr 30 to 59 mL/min) renal impairment, mild hepatic impairment (total bilirubin  $\leq$  ULN and AST  $>$  ULN or total bilirubin 1 to 1.5 times ULN and any AST), albumin (24 to 50 g/L), FcγR (CD16A, CD32A and CD32B) genotype, HER2 expression level (0 to 3 by IHC), baseline ECOG score (0-2), tumor burden (2 – 317 mm) and number of metastatic sites ( $\leq$  2 or  $>$ 2), based on the population PK analyses. FDA also agrees

that based on the population PK model the number of prior therapies ( $\leq 2$  or  $>2$ ) or concurrent chemotherapies (capecitabine, gemcitabine, eribulin and vinorelbine) do not have a meaningful impact on margetuximab exposure.

There is limited or no information regarding the impact of severe renal impairment (n=1) and moderate (n=2) or severe (n=0) hepatic impairment on the safety and PK of margetuximab and no dose recommendations can be made in these populations. However, as monoclonal antibodies do not undergo renal excretion and population PK analyses did not identify creatinine clearance (25.6 – 150 mL/min) as a significant covariate influencing margetuximab PK, margetuximab PK is not expected to be markedly altered in severe renal impairment. Population PK predictions of exposure in the 2 patients with moderate hepatic impairment suggest margetuximab exposure in these patients is within the range of that in patients with normal hepatic function.

Circulating levels of soluble HER2 (sHER2) ECD were not measured in Study 04 to enable an assessment of circulating sHER2 levels on margetuximab exposure or treatment response.

In Study 04, the Applicant conducted predefined, non-alpha allocating exploratory analyses of PFS (BIRC) by CD16A (CD16A-158F or V), CD32A (CD32A-131H or R), and CD32B (CD32B-232I or T) genotype. Of the 536 enrolled patients, a total of 506 (94.4%) patients had blood samples centrally genotyped (Applicant's Table 14, Section 8) by polymerase chain reaction (PCR) and Sanger sequencing.

While patients carrying the CD16A low-affinity F allele (F/F or F/V) appeared to benefit from margetuximab vs trastuzumab, the HR for PFS showed a trend in favor of trastuzumab over margetuximab in the subgroup of patients with the CD16A V/V genotype (HR=1.776, Applicant's Figure 3, Section 8). CD32A and CD32B allelic variants did not appear to be associated with a differential response. Results from an FDA exploratory analysis adjusting for selected potential prognostic factors suggest that imbalances in age, ECOG status, previous lines of therapy, and body surface area (BSA) do not explain the apparent negative outcome in the CD16A V/V subgroup (see FDA assessment, Section 8.1.2).

It is possible that results were due to a small sample size, as there were only 69 patients (37 margetuximab vs. 32 trastuzumab) with the V/V genotype in the study. In the absence of a clear mechanistic basis, this finding should be replicated in ongoing and future trials to determine whether the CD16A V/V genotype (approximately 15% of the overall population) negatively impacts the response to margetuximab as compared to trastuzumab. The Applicant has agreed to a post-marketing commitment (PMC) to provide additional CD16A F158V genotype and patient outcome data from ongoing studies. This information will be used to further characterize the clinical benefit of margetuximab and may inform product labeling. For details on this PMC refer to Section 13.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

**Food-drug interaction:** Clinical food-drug interaction studies were not conducted because margetuximab is administered intravenously.

**Drug-drug interaction:** As an IgG1 monoclonal antibody, margetuximab elimination is likely by pathways similar to those of other antibodies, including nonspecific proteolysis or endocytosis, Fcγ or complement receptor-mediated clearance, and target-mediated clearance (16). Non-specific clearance is presumed primary (3). These pathways are not known to be inhibited or induced by drugs. Thus, it is unlikely that other drugs will substantially affect margetuximab PK.

Still, literature reports suggest that therapeutic proteins can modulate cytokines that indirectly influence CYP enzyme and drug transporters gene expression (6). Such effects might alter systemic exposure and/or clinical response of concomitantly administered drugs that are substrates for affected CYP enzymes or transporters. Margetuximab treatment resulted in small in magnitude transient changes in circulating cytokines in monkeys that were dose independent but not significantly different from the vehicle control group (27). In Study 01, no consistent pattern of cytokine production after margetuximab administration was seen in limited samples analyzed. Infusion reactions occurred without significant elevations of measured cytokines, and cytokine elevations occurred without concomitant clinical infusion reactions. Hence, cytokine elevations after margetuximab administration are considered not to be clinically meaningful.

Hence, proposed chemotherapies capecitabine, eribulin, gemcitabine, and vinorelbine are unlikely to have PK drug-drug interactions with margetuximab. Capecitabine (XELODA® USPI) and gemcitabine (GEMZAR® USPI) are extensively metabolized by non-CYP450 enzymes. There are no major human metabolites of eribulin. CYP3A4 negligibly metabolizes it in vitro, and it's eliminated primarily in feces as unchanged drug (HALAVEN® USPI).

Vinorelbine undergoes substantial hepatic elimination in humans with large amounts recovered in feces. About 18% and 46% is recovered in urine (mostly unchanged drug) and in feces, respectively. Vinca alkaloid metabolism is mediated by the CYP3A subfamily. Two vinorelbine metabolites are found in human blood, plasma, and urine: vinorelbine N-oxide and deacetylvinorelbine. The latter is the primary human metabolite and has antitumor activity similar to vinorelbine. Therapeutic vinorelbine doses (30 mg/m<sup>2</sup>) yield small, if any, quantifiable levels of either metabolite in blood or urine (NAVELBINE® USPI). Even if margetuximab leads to cytokine-mediated CYP3A enzyme modulation, total vinorelbine biologically active moieties

(parent + active metabolite) in systemic circulation would remain more or less unchanged, compared with vinorelbine used as a single agent.

In summary, margetuximab is not expected to cause PK drug-drug interactions by cytokine-mediated secondary modulation of CYP/transporter levels. No consistent pattern of cytokine production was revealed after margetuximab administration in monkeys or humans. PPK analysis supports that margetuximab exposure is unaffected when the biologic was coadministered with either capecitabine, gemcitabine, eribulin, or vinorelbine. Safety and efficacy of these combinations have been demonstrated (**Section 8**).

Margetuximab has not been studied in combination with anthracyclines. Based on margetuximab washout and clinical data from other HER2-targeted antibodies, patients receiving anthracyclines for up to 4 months after stopping margetuximab may be at increased risk of cardiac dysfunction. The proposed label includes text in the Drug Interactions section to inform of this potential interaction.

#### The Applicant's Position:

Margetuximab is a mAb administered via IV infusion, so food-drug interaction is not expected. Margetuximab metabolism is presumed to occur via catabolic degradation into small peptides and amino acids. Drug-drug interactions involving CYPs, other metabolizing enzymes, or transporters are not expected. Thus, no management strategy is needed for food-drug or drug-drug interactions.

#### The FDA's Assessment:

FDA agrees that no drug-drug interactions involving CYP enzymes or transporters requiring clinical management are expected with margetuximab.

No formal in vitro or in vivo CYP450 or transporter-mediated drug-drug interaction studies have been conducted with margetuximab as a victim or a perpetrator. No DDIs are expected with concurrent chemotherapies (capecitabine, gemcitabine, eribulin and vinorelbine) and population PK supports that these concurrent chemotherapies do not have a meaningful impact on margetuximab exposure.

In the 15m/kg Q3W cohort in Study 01, transient increases in serum cytokines TNF $\alpha$ , IFN $\gamma$ , IL-6 and IL-10 were observed in individual patients. These elevations were generally resolved within 72 hr post the first dose (sampling after subsequent doses was largely restricted to pre-dose trough samples and no elevations were observed). The impact of these margetuximab-mediated elevations on the PK of sensitive CYP substrates via indirect modulation of CYP activity has not been clinically evaluated. However, the transient nature of these elevations makes them unlikely to be clinically significant with regard to suppression of CYP enzyme or

transporter activity. The safety of vinorelbine (CYP3A substrate) in combination with margetuximab has been established in Study 04.

The clinical pharmacology review team agrees with the Applicant's proposed washout period of 4 months after terminating margetuximab dosing for avoidance of concomitant anthracycline use. Based on population PK predictions, margetuximab concentrations decline to a concentration of 3.5 µg/mL (~3% of steady-state Ctrough) within 110 days (16 weeks) for 95% of subjects following discontinuation of 15 mg/kg Q3W dosing regimen.

FDA also has the following clarification regarding the Applicant's position:

- The clinical relevance of cytokine elevations with regard to infusion reactions has not been systematically evaluated in Study 04 or the infusion sub-study.

X

X

---

Krithika Arun Shetty  
Junshan Qui  
Jeffrey Kraft  
Primary Reviewer

Pengfei Song  
Jingyu Yu  
Rosane Charlab Orbach  
Team Leader

## 7 Sources of Clinical Data

---

### 7.1. Table of Clinical Studies

Data:

Studies pertinent to margetuximab efficacy and safety evaluation are summarized in **Table 7**. This submission incorporates the following data.

- Study 04 safety and efficacy data at the planned primary analysis after 257 PFS events (data cutoff 10-Oct-2018).
- Supplementary Study 04 safety and updated efficacy data:
  - AE data from a supplementary data cutoff of 10-Apr-2019
  - OS data from second interim analysis after 270 deaths (data cutoff 10-Sep-2019)
  - Investigator-assessed PFS, as of 10-Sep-2019, the top secondary endpoint
- Supportive Study 01 efficacy data (main CSR data cutoff of 01-Oct-2015 and CSR Addendum data cutoff of 23-Feb-2019).
- Supportive Study 01 and Study 02 safety data within pooled safety analyses, as well as ongoing Study 04 Infusion Substudy (data cutoff 17-Jun-2019).
- PPK and immunogenicity data from Studies 01, 02, and 04, as well as E-R analysis from Study 04 (data cutoff 10-Oct-2018).

**Table 7: Listing of Clinical Trials Relevant to this BLA**

| Trial Identity/<br>NCT No.                           | Trial Design                                                                           | Regimen/<br>Schedule/Route                                                                                                                                                                       | Study<br>Endpoints                                                                                                                                                                     | Treatment<br>Duration/<br>Follow Up                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | No. of Patients<br>Enrolled                                                                                       | Study<br>Population                                                                                                                                                                                                               | No. of<br>Centers and<br>Countries                      |
|------------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| <b><i>Studies to Support Efficacy and Safety</i></b> |                                                                                        |                                                                                                                                                                                                  |                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                   |                                                                                                                                                                                                                                   |                                                         |
| CP-MGAH22-04<br>NCT02492711                          | Phase 3,<br>randomized,<br>open-label,<br>active<br>comparator-<br>controlled<br>study | <u>Margetuximab</u><br>15 mg/kg IV Q3W plus<br>chemotherapy<br><br>versus<br><br><u>Trastuzumab</u><br>8 mg/kg loading dose<br>(Cycle 1) then 6 mg/kg<br>IV Q3W thereafter,<br>plus chemotherapy | <u>Primary:</u><br>Sequentially<br>measured,<br>independent<br>blinded PFS<br>and OS.<br><u>Secondary:</u><br>PFS by<br>Investigator<br>assessment;<br>ORR by<br>independent<br>review | Study therapy until<br>disease progression,<br>unacceptable toxicity,<br>consent withdrawal,<br>physician decision, or<br>death.<br><br><u>Enrollment:</u> 38 months<br>from 26-Aug-2015<br><u>Treatment + follow up:</u><br>24 months<br>PFS cutoff:<br>10-Oct-2018<br>Safety cutoff:<br>10-Apr-2019<br><br><u>Median duration of<br/>follow-up for OS<br/>analysis (as of<br/>10-Sep-2019): Overall:</u><br>15.6 months (range:<br>0.1-43.0)<br>M: 15.8 months<br>(range: 0.7-41.4)<br>T: 15.4 months (range:<br>0.1-43.0) | <u>Margetuximab:</u><br>Enrolled: 266<br>Treated: 264<br><br><u>Trastuzumab:</u><br>Enrolled: 270<br>Treated: 266 | Subjects with<br>advanced<br>treatment-<br>resistant HER2+<br>breast cancer<br>after at least 2<br>prior anti-HER2<br>regimens,<br>including<br>pertuzumab, and<br>1-3 regimens for<br>metastatic<br>disease therapy.<br>ECOG ≤ 1 | Global,<br>multicenter:<br>166 sites in<br>17 countries |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

| Trial Identity/<br>NCT No.                            | Trial Design                                                                                           | Regimen/<br>Schedule/Route                                                                                                                                                                                                                                                                                                                                                                                                | Study<br>Endpoints                                                                                                                                 | Treatment<br>Duration/<br>Follow Up                                                                                                                                                                                       | No. of Patients<br>Enrolled                                              | Study<br>Population                                                                                                                         | No. of<br>Centers and<br>Countries                    |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| CP-MGAH22-04<br>(Infusion<br>Substudy)<br>NCT02492711 | Nonrandomized<br>cohort of<br>CP-MGAH22-04                                                             | Margetuximab<br>15 mg/kg IV Q3W,<br>single agent or with<br>chemotherapy.<br><u>Stage A1 infusion:</u><br>120 min Cycle 1,<br>60 min Cycle 2+<br><u>Stage A2/B infusion:</u><br>120 min Cycle 1,<br>30 min Cycle 2+                                                                                                                                                                                                       | <u>Primary:</u><br>≥ Grade 3<br>infusion related<br>reaction (IRR)<br><br><u>Secondary:</u><br>Any grade IRR                                       | Study therapy until<br>disease progression,<br>unacceptable toxicity,<br>consent withdrawal,<br>physician decision, or<br>death.<br><br>24-Apr-2018 to data<br>cutoff on 17-Jun-2019                                      | Enrolled: 88<br>Treated: 88                                              | Subjects had<br>prior<br>trastuzumab,<br>pertuzumab, and<br>T-DM1, as well as<br>at least 4 prior<br>regimens for<br>metastatic<br>disease. | Global,<br>multicenter:<br>57 sites in 9<br>countries |
| CP-MGAH22-01<br>NCT01148849                           | Phase 1, open-<br>label, multi-<br>dose, single-<br>arm, multi-<br>center, dose<br>escalation<br>study | <u>Dose Escalation and<br/>MTD Dose Expansion:</u><br>margetuximab 0.1, 0.3,<br>1, 3, and 6 mg/kg IV<br>QW<br>Cycle 1: QW Days 1, 8,<br>15, 22 of 50-day cycle<br>Subsequent Cycles:<br>QW Days 1, 8, 15 of<br>28-day cycle<br><u>Intermittent Dosing<br/>Segment:</u><br>margetuximab 10, 15,<br>and 18 mg/kg IV Q3W<br>Cycle 1: Q3W Days 1,<br>22 of 50-day cycle<br>Subsequent cycles:<br>Q3W Day 1 of 21-day<br>cycle | <u>Primary:</u><br>Safety (AEs,<br>SAEs)<br><br><u>Secondary:</u><br>MTD; PK, ADAs;<br>preliminary<br>efficacy (OR<br>per RECIST<br>v1.1, PFS, OS) | Treatment to continue<br>until disease<br>progression, death,<br>withdrawal of consent,<br>Investigator or subject<br>request<br><br>30-Aug-2010 to data<br>cutoff on 10-Oct-2015<br>Addendum data cutoff:<br>23-Feb-2019 | Enrolled: 66<br>Treated: 66<br><br>HER2+ breast<br>cancer: 27<br>treated | HER2+ carcinoma<br>with no standard<br>therapy. ECOG ≤1                                                                                     | United States:<br>2 sites<br>South Korea:<br>1 site   |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

| Trial Identity/<br>NCT No.                                                                                  | Trial Design                                                       | Regimen/<br>Schedule/Route                                                                                                                                                                                       | Study<br>Endpoints                                                                                                       | Treatment<br>Duration/<br>Follow Up                                                                                                                                                                      | No. of Patients<br>Enrolled           | Study<br>Population                                                                                                      | No. of<br>Centers and<br>Countries           |
|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| <b>Studies to Support Safety</b>                                                                            |                                                                    |                                                                                                                                                                                                                  |                                                                                                                          |                                                                                                                                                                                                          |                                       |                                                                                                                          |                                              |
| CP-MGAH22-02<br>NCT01828021                                                                                 | Phase 2, single arm, open-label, study                             | <u>Original Protocol:</u><br>Margetuximab 6.0 mg/kg IV on Days 1, 8, and 15 of each 28-day cycle.<br><u>Protocol Amendment 2:</u><br>15 mg/kg IV on Day 1 of 21-day cycle                                        | <u>Primary:</u><br>OR per RECIST v1.1<br><br><u>Secondary:</u><br>ORR, DoR, PFS, OS, Safety (AEs, SAEs, labs, ECG, ADAs) | Continued until disease progression, unacceptable toxicity, consent withdrawal, or death<br><br>Duration: 43 months<br>Date first subject dosed: 16-May-2013<br>Date of last data collection: 7-Dec-2016 | Enrolled: 28<br>Treated: 25           | HER2 low expressing (IHC 1+/2+, FISH non-amplified) with relapsed or refractory advanced breast cancer. ECOG ≤1          | United States: 6 sites                       |
| <b>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</b> |                                                                    |                                                                                                                                                                                                                  |                                                                                                                          |                                                                                                                                                                                                          |                                       |                                                                                                                          |                                              |
| CP-MGAH22-05<br>NCT02689284<br><br><b>NOTE:</b><br>(b) (4)                                                  | Phase 1b/2, open-label, dose escalation and cohort expansion study | <u>Part A: Part 1:</u><br>Margetuximab: 10 mg/kg then 15 mg/kg IV;<br>Pembrolizumab: 200 mg IV<br><u>Part 2:</u> Margetuximab: 15 mg/kg IV;<br>Pembrolizumab: 200 mg IV<br><u>Part B-C:</u> Dose found in Part A | <u>Primary:</u><br>MTD/MAD; ORR and DoR per RECIST and irRC.<br><br><u>Secondary:</u><br>OS, PFS, pharmacodynamics, PK   | <u>Treatment:</u> ≤ 2 years dual therapy, then ≤ 2 years margetuximab alone, or until discontinuation criteria met.<br><u>Follow-up:</u><br>2 years after end of dual therapy                            | 95 (as of 23-Feb-2019; ongoing study) | Adult patients with relapsed/refractory unresectable locally advanced or metastatic HER2+ GEJ or gastric cancer. ECOG ≤1 | Global, multicenter: 24 sites in 5 countries |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

| <b>Trial Identity/<br/>NCT No.</b> | <b>Trial Design</b>                                         | <b>Regimen/<br/>Schedule/Route</b> | <b>Study<br/>Endpoints</b> | <b>Treatment<br/>Duration/<br/>Follow Up</b>                                             | <b>No. of Patients<br/>Enrolled</b> | <b>Study<br/>Population</b>                                                                                                                                            | <b>No. of<br/>Centers and<br/>Countries</b> |
|------------------------------------|-------------------------------------------------------------|------------------------------------|----------------------------|------------------------------------------------------------------------------------------|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| EA-MGAH22<br>NCT03133988           | Individually approved, Expanded Access, single-subject INDs | Margetuximab<br>15 mg/kg IV Q3W    | Safety                     | Continued until disease progression, unacceptable toxicity, consent withdrawal, or death | Treated: 5                          | Subjects with breast cancer and other HER2+ carcinomas who are not otherwise eligible for a MacroGenics sponsored study and potential benefit justifies potential risk | 5 sites in 1 country (USA)                  |

The Applicant's Position:

Primary evidence to support clinical efficacy and safety of margetuximab in patients with advanced pretreated HER2+ breast cancer derives from Study 04. This adequate and well-controlled clinical trial randomized 536 subjects (M: 266, T: 270). Pooled analysis of 355 subjects in Studies 04, 01, and 02 supports safety review. Study 04 provides primary safety data for the proposed label as it included the largest number of subjects and an active comparator group. All margetuximab recipients in Study 04 received the proposed regimen of 15 mg/kg Q3W.

Safety data from 88 subjects enrolled in the Infusion Substudy support use of 30-minute margetuximab infusions from Cycle 2 onward.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the studies listed in Table 7 above.

The FDA's evaluation of efficacy and safety is primarily based on data from Study 04. CP-MGAH22-01 (Study 01) and CP-MGAH22-02 (Study 02) supplied secondary data to support safety. Data from these 2 studies were not used for clinical efficacy due to the heterogeneity of the patient populations enrolled. The FDA's evaluation did not use data from CP-MGAH22-05 (Study 05) for efficacy or safety because Study 05 used a different treatment regimen than the indication being evaluated for approval.

## 8 Statistical and Clinical Evaluation

### 8.1. Review of Relevant Individual Trials Used to Support Efficacy

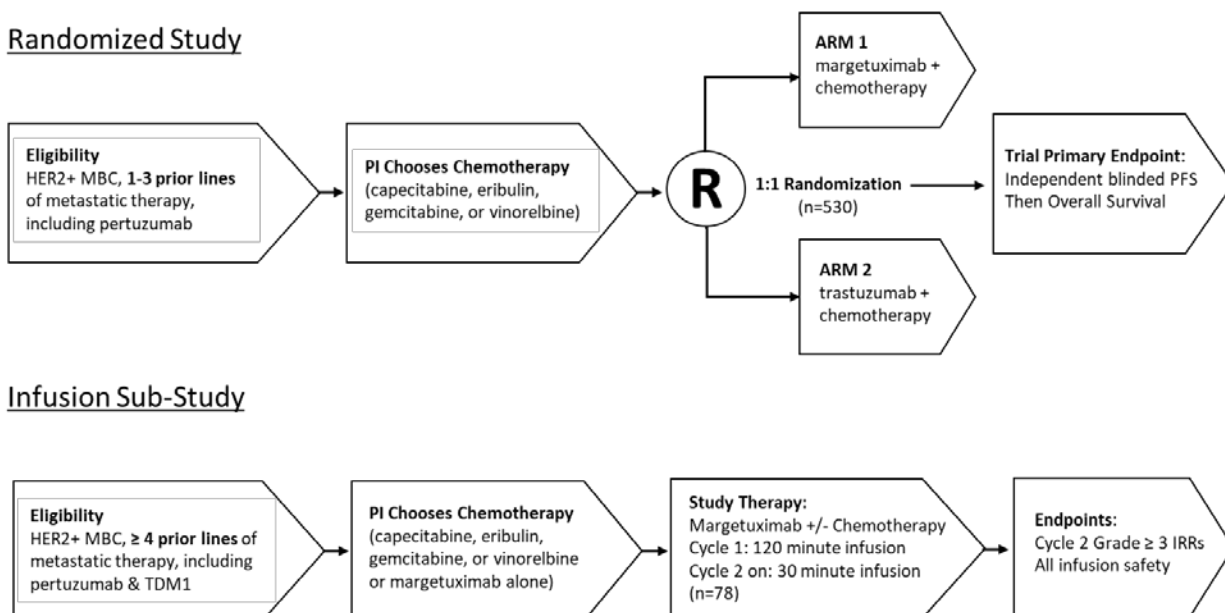
#### 8.1.1. CP-MGAH22-04 (SOPHIA, Study 04)

##### Trial Design

###### The Applicant's Description:

This Phase 3, randomized, open-label, study compared margetuximab to trastuzumab, each with chemotherapy, in subjects with advanced, pre-treated HER2+ metastatic breast cancer (**Figure 1**). Subjects must have progressed on or after the most recent therapy. Before randomization, Investigators selected 1 of 4 chemotherapy agents to administer with anti-HER2 study therapy. Options included capecitabine, eribulin, gemcitabine, or vinorelbine. Subjects were then randomized 1:1 to receive either margetuximab or trastuzumab with the selected chemotherapy. Randomization was stratified for chosen chemotherapy, number of prior therapies, and number of metastatic sites of disease. A separate, non-randomized substudy cohort evaluates safety and tolerability of sequential reductions in margetuximab infusion duration from 120 minutes in Cycle 1 to 30 minutes in Cycle 2 and beyond (see **Section 8.2.8**).

**Figure 1: Schematic of Study Design (CP-MGAH22-04)**



Abbreviations: HER2: human epidermal growth factor receptor 2; IRR: infusion-related reaction; MBC: metastatic breast cancer; PFS: progression-free survival; PI: principal investigator; T-DM1: ado-trastuzumab emtansine.

Subjects received margetuximab or trastuzumab on Day 1 of a 3-week cycle. Chemotherapy was given on each agent's schedule, consistent with local practice, beginning on Day 1. On days when both chemotherapy and study therapy were given, chemotherapy was given first. Subject treatment decisions were based on local (Investigator) reviews of available assessments.

Subjects were evaluated regularly for disease progression. Computed tomography (CT) and/or magnetic resonance imaging (MRI) scans were performed before treatment (baseline) and every 2 cycles for the first 24 weeks on study therapy. Starting from Cycle 9, tumor evaluations occurred every 4 cycles on treatment, or every 3 months post-treatment. Bone scans were performed at baseline, then as clinically indicated for assessment of bone metastasis. Disease response was determined both locally and by central review using Response Evaluation Criteria for Solid Tumors (RECIST) version (v) 1.1. Independent central reviews were blinded to study therapy.

A Data Safety Monitoring Committee (DSMC) monitored unblinded safety data throughout the study. The DSMC also reviewed efficacy data at interim analyses for PFS and OS. Interim futility analysis occurred after about 100 PFS events, followed by primary PFS analysis after at least 257 PFS events. Primary PFS analysis was to occur after the later of 257 confirmed PFS events or completion of randomization. Interim OS analyses were performed at the time of primary PFS analysis, then after 270 deaths (70% of target OS events). Final OS analysis will occur after about 385 deaths.

Randomization completed on 10-Oct-2018, generating an Intent-to-Treat (ITT) population of 536 subjects. Dual primary endpoints of PFS and OS were analyzed sequentially. In this hierarchical analysis, the primary PFS endpoint by central review was analyzed first by the stratified log-rank test. If PFS achieved statistical significance at a 2-sided alpha level of 0.05, the trial was considered positive. If positive, OS would be analyzed by a stratified log-rank test on occasions described above. O'Brien-Fleming type alpha spending was used to control overall type I error at a 2-sided alpha of 0.05.

*Trial Location:*

This study randomized subjects at 166 sites in 17 countries: Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Israel, Italy, South Korea, Netherlands, Poland, Portugal, Spain, United Kingdom, and USA, including Puerto Rico.

*Choice of Control Group:*

Trastuzumab is an appropriate anti-HER2 comparator for 3 reasons. First, evidence suggests that ongoing trastuzumab remains clinically active after progression on trastuzumab (39, 40), making placebo comparison unethical. In a Phase 3 study, continuation of trastuzumab plus

capecitabine improved ORR and time to progression (HR: 0.69, 95% CI: 0.48, 0.97) versus capecitabine alone in HER2-positive breast cancer progressing during trastuzumab treatment. Second, margetuximab has the same anti-HER2 specificity as trastuzumab. Hence, randomization against trastuzumab as an active comparator tests directly the immune activation potential of margetuximab. Finally, trastuzumab may be better tolerated than lapatinib, a HER2-targeted tyrosine kinase inhibitor. Q3W trastuzumab dosing was more convenient than weekly for patients and physicians, presented no known compromise in efficacy or safety, and was consistent with current NCCN guidelines in breast cancer.

Inclusion of backbone chemotherapies aligned with NCCN guidelines. Investigators chose 1 of 4 options commonly combined with trastuzumab in this population. Randomization after chemotherapy selection avoided any influence of group assignment on chemotherapy choice.

*Dose Selection:*

The margetuximab dose and schedule selected was 15 mg/kg Q3W by IV infusion. This regimen was based on prior safety, clinical activity, and PK of margetuximab at all dose levels tested to date, including Study 01 population PK analysis. Dose justification is in **Section 6.2.2.1**.

The approved clinical dose of trastuzumab for treatment of HER2+ MBC is a 4 mg/kg loading dose followed by 2 mg/kg QW (**Table 3**). In the adjuvant or neoadjuvant setting, trastuzumab is approved on a schedule of 8 mg/kg loading dose followed by 6 mg/kg Q3W. The trastuzumab dose and schedule selected for this study was 8 mg/kg loading dose then 6 mg/kg given Q3W as an IV infusion, consistent with the labeled regimen for adjuvant therapy. A Q3W schedule provided greater convenience to subjects and physicians with no known compromise in efficacy or safety. Treating subjects in the comparator arm at a Q3W schedule was consistent with current practice guidelines and was acceptable to regulators.

*Number of Subjects (Planned and Analyzed):*

About 530 subjects were planned, and 536 enrolled. The ITT Population comprised all 536 randomized subjects (M: 266, T: 270). The Safety Population comprised all randomized subjects that received any study therapy (M: 264, T: 266). The Response Evaluable Population comprised randomized subjects with baseline measurable disease by central blinded analysis (M: 262, T: 262).

*Diagnosis and Main Eligibility Criteria:*

Main inclusion criteria included subjects 18 years of age or older with histologically proven, advanced, relapsed/refractory HER2+ (3+ by IHC or in situ hybridization [ISH]-amplified as per ASCO and College of American Pathologists [CAP] Guidelines) breast cancer, measurable or non-measurable disease per RECIST 1.1, life expectancy  $\geq$  12 weeks, and ECOG Performance Status of 0 or 1. Subjects must have received at least 2 prior lines of anti-HER2 directed therapy,

including pertuzumab, and 1 to  $\leq$  3 lines of therapy overall in the metastatic setting. Main exclusion criteria were known, untreated brain metastasis, history of uncontrolled seizures within 6 months of randomization, history of prior allogeneic bone marrow, stem-cell, or solid organ transplantation, and history of clinically significant cardiovascular disease or pulmonary compromise.

*Duration of Treatment:*

Subjects were treated with margetuximab or trastuzumab, both in combination with chemotherapy, in 3-week (21-day) cycles. Study treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, physician recommendation to discontinue therapy, or death.

After study therapy discontinuation, subjects were followed for survival. The study will continue until after the last patient visit or one year after the final survival analysis. Final OS analysis is to occur after 385 survival events.

*Procedures and Schedule:*

**Table 8** presents frequency and timing of study measurements. Assessments were performed by the Investigator or designee.

**Table 8: Schedule of Events (CP-MGAH22-04)**

| DAY                                                                                 | Screening      |           | Cycle 1        |                | Cycle 2 and Even Cycles |                | Cycle 3 and Odd Cycles |                | End of Treatment | Post-Treatment |
|-------------------------------------------------------------------------------------|----------------|-----------|----------------|----------------|-------------------------|----------------|------------------------|----------------|------------------|----------------|
|                                                                                     | -28 to -1      | -14 to -1 | 1 <sup>r</sup> | 8 <sup>s</sup> | 1                       | 8 <sup>s</sup> | 1                      | 8 <sup>s</sup> |                  |                |
| <b>CLINICAL ASSESSMENTS</b>                                                         |                |           |                |                |                         |                |                        |                |                  |                |
| Informed consent, HER2 status <sup>g</sup> or tissue sample <sup>h</sup>            | X              |           |                |                |                         |                |                        |                |                  |                |
| Medical history <sup>b</sup>                                                        |                | X         | X              |                |                         |                |                        |                |                  |                |
| Physical examination <sup>c</sup> , vital signs <sup>d</sup> , and ECG <sup>e</sup> |                | X         | X              |                | X                       |                | X                      |                | X                |                |
| Weight                                                                              |                | X         | X              |                |                         |                | X                      |                | X                |                |
| ECOG performance status                                                             |                | X         |                |                |                         |                |                        |                | X                |                |
| MUGA or echocardiography <sup>f</sup>                                               | X              |           |                |                |                         |                | X                      |                | X                |                |
| NFBSI-16 and EQ-5D-5L surveys                                                       |                |           | X              |                |                         |                | X                      |                | X                |                |
| Review of AEs and concomitant medications                                           |                | X         | X              | X              | X                       | X              | X                      | X              | X                |                |
| <b>LABORATORY EVALUATIONS</b>                                                       |                |           |                |                |                         |                |                        |                |                  |                |
| Fc receptor genotyping                                                              |                |           | X              |                |                         |                |                        |                |                  |                |
| Serum or urine pregnancy test <sup>i</sup>                                          |                | X         | X              |                | X                       |                | X                      |                | X                | X <sup>t</sup> |
| Hematology and chemistry <sup>j</sup>                                               |                | X         | X              |                | X                       |                | X                      |                | X                |                |
| Prothrombin time, aPTT, urinalysis                                                  |                |           | X              |                | X                       |                | X                      |                | X                |                |
| <b>PK/ADA</b>                                                                       |                |           |                |                |                         |                |                        |                |                  |                |
| Margetuximab PK (margetuximab group only) <sup>k</sup>                              |                |           | X              |                | X                       |                | X                      |                | X                | X              |
| ADA sampling (margetuximab group only) <sup>l</sup>                                 |                |           | X              |                |                         |                | X                      |                | X                | X              |
| <b>THERAPEUTIC ACTIVITY</b>                                                         |                |           |                |                |                         |                |                        |                |                  |                |
| Tumor evaluations <sup>m</sup> , vital status <sup>n</sup>                          | X <sup>u</sup> |           |                |                |                         |                | X                      |                |                  | X              |
| <b>STUDY DRUG ADMINISTRATION</b>                                                    |                |           |                |                |                         |                |                        |                |                  |                |
| Chemotherapy administration <sup>o</sup>                                            |                |           | X              | X              | X                       | X              | X                      | X              |                  |                |
| Margetuximab or trastuzumab administration <sup>p</sup>                             |                |           | X              |                | X                       |                | X                      |                |                  |                |

All procedures were to be performed on the scheduled study day, except central laboratory assessments (within 3 days pre-therapy) and MUGA/ECHO/radiology assessments (within 14 days pre-therapy). Day 8 procedures were performed only if subjects were to return for Day 8 chemotherapy. Refer to **Study 04 CSR - Section 9.5.1** for a description of footnotes and abbreviations.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the Study 04 protocol with the following clarifications and additions:

- Confirmatory central HER2 testing was not required for study entry, unless the patients original HER2 status was documented from a laboratory that does not conform to standards set for accreditation by CAP or an equivalent accreditation authority.
- Patients with known, untreated brain metastasis were excluded from the study.
- Patients with known, treated brain metastases were eligible provided they were on a stable dose of steroids ( $\leq 10$  mg/day of prednisone or equivalent) and/or all therapy for brain metastases concluded at least 4 weeks prior to randomization and are asymptomatic.
- Patients with signs/symptoms of brain metastasis were required to have a CT or MRI within 4 weeks prior to randomization to specifically exclude the presence of radiographically detectable brain metastases.
- Patients received IV trastuzumab as per standard of care. Subcutaneous trastuzumab or trastuzumab biosimilars were not used in the study.
- Infusion related reactions (IRR) may occur with monoclonal antibodies. There was no protocol specified premedication for administration of trastuzumab. Premedication for margetuximab was not required, but were not specifically prohibited prior to a patient experiencing an IRR. When margetuximab is not preceded by a chemotherapeutic agent requiring premedication, the protocol specified drugs for premedication should be given within 30 minutes of margetuximab administration. Premedication recommendations may be modified per investigator's discretion.
- No crossover from trastuzumab to margetuximab was permitted at progression.

**Study Endpoints**

The Applicant's Description:

This study evaluated efficacy of margetuximab plus chemotherapy versus trastuzumab plus chemotherapy in subjects with advanced HER2+ breast cancer. The primary endpoints were PFS, assessed by independent review, and OS, analyzed sequentially.

Independently assessed PFS is an appropriate clinical endpoint in this disease setting. PFS may predict OS benefit (10, 20, 31) and has supported anti-HER2-directed therapy approvals. Clinically meaningful improvement in PFS provides evidence for clinical benefit (per FDA guidance "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" and EMA guidance "Evaluation of Anticancer Medicinal Products in Man – Revision 5"). Also, FDA agreed on Study 04 study design elements, including use of PFS as a sequential primary endpoint, followed by OS.

Secondary endpoints include Investigator-assessed PFS and independent blinded ORR. Tertiary endpoints include margetuximab safety, CBR, Investigator assessed ORR, duration of response (DoR), PPK and E-R analyses, immunogenicity, and health related quality of life. Exploratory endpoints investigate effects of allelic variation in CD16A, CD32A, and CD32B receptors on the efficacy of margetuximab in all subjects receiving study treatments.

**The FDA’s Assessment:**

FDA agrees with the appropriateness of PFS and OS as primary endpoints in this disease setting, and their sequential analysis for efficacy assessment. FDA also agrees that investigator-assessed PFS and confirmed ORR were two key secondary endpoints in this study. These two endpoints could only be tested after OS passes the statistical significance testing in the hierarchy. In general, exploratory analyses without alpha allocation are considered hypothesis generating only.

**Statistical Analysis Plan and Amendments**

**The Applicant’s Description:**

The SAP was amended 3 times to reflect changes in protocol design (see *Protocol Amendments* and **Table 9**). The SAP was finalized before database lock or any efficacy analysis.

**Table 9: Summary of Key SAP Amendments**

|                        |                                                                                                                                                                                                                                                               |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>SAP Version 2.0</b> | Changed stratification factor of line of prior therapy from 1 vs 2 to $\leq 2$ vs $> 2$ . Thus, in all stratified analysis, subjects enrolled under Protocol Amendment 1 with line of prior therapy 1 or 2 were categorized as line of prior therapy $\leq 2$ |
|                        | Implemented grouping of FF and FV in models to assess treatment effect differences between VV vs (FF and FV)                                                                                                                                                  |
|                        | Added sensitivity analyses and further subgroup analyses (including CD16A) for PFS and OS                                                                                                                                                                     |
| <b>SAP Version 3.0</b> | Further clarified the procedure for strata pooling strategy for stratified PFS and OS analyses                                                                                                                                                                |
| <b>SAP Version 4.0</b> | Added planned analyses throughout the SAP for the Infusion Substudy                                                                                                                                                                                           |

In Study 04, PFS and OS were prespecified sequential primary efficacy endpoints. To control for multiplicity, primary endpoints were tested in sequential, hierarchical order. Study 04 assessed differences in PFS (and OS) between treatment groups. It is powered to demonstrate a 2-month median PFS prolongation from 4 to 6 months (HR = 0.67) in patients treated with margetuximab plus chemotherapy. For exponentially distributed PFS, 257 events provide 90% power at a 2-sided  $\alpha = 0.05$  to achieve HR = 0.67. Sample size was also calculated to ensure 80% power for OS analysis. A 12-month median OS was presumed for the active comparator group, trastuzumab plus chemotherapy. Study 04 is powered to show an increase in median OS from 12 to 16 months in patients treated with margetuximab plus chemotherapy (HR = 0.75). For

exponentially distributed OS, 385 events provide 80% power at a 2-sided  $\alpha = 0.05$  to achieve HR = 0.75. Final database lock and OS analysis are to be done after 385 deaths have occurred.

Exploratory sensitivity analyses were performed for PFS and OS, as well as subgroup analyses, as specified in the SAP. PFS sensitivity analyses are consistent with FDA Guidance. Data from the second interim analysis, after 270 OS events accrued, provide supplemental information. Study 04 will continue at least until the minimum number of 385 protocol-specified deaths have been observed to initiate final OS analysis.

#### The FDA's Assessment:

FDA agrees with the Applicant's description of the SAP implemented for data analysis in this study. The major amendments in the three revisions of the SAP prior to data unblinding are not likely to have substantial impact on the primary and secondary analysis results. Strata pooling strategy was discussed and agreed upon with FDA prior to the amendment. Further subgroups added in the later version of SAP are exploratory and are intended to provide auxiliary information.

This study was designed to demonstrate superiority of margetuximab over an active control trastuzumab in combination with chemotherapy. This feature of the study has an implication in the interpretability and applicability of the study findings in this review.

#### **Protocol Amendments**

##### The Applicant's Description:

Three protocol amendments were implemented. Key changes are summarized below. All amendments were reviewed and approved by the sponsor, jurisdictional regulatory agencies, and IECs/IRBs. The original study protocol of 20-Feb-2015 was modified after review by regulatory agencies, IRBs/IECs, and Investigators.

Protocol Amendment 1, 21-Jan-2016, increased the number of allowable prior lines of therapy from 2 to 3; modified efficacy evaluation timing; and clarified eligibility.

Protocol Amendment 2, 09-Feb-2017, liberalized the requirement for 3 prior anti-HER2 targeted therapies (trastuzumab, pertuzumab, and T-DM1). After this amendment, subjects were required to have at least 2 prior lines of anti-HER2 targeted therapies in the MBC setting before study entry, 1 of which must have been pertuzumab.

Protocol Amendment 3, 26-Jan-2018, added an additional non-randomized cohort to demonstrate tolerability of lowering infusion duration from 120 minutes in Cycle 1 to 30 minutes in Cycle 2 and thereafter. To ensure non-overlapping eligibility for randomized versus infusion sub-study populations, sub-study eligibility included at least 4 prior lines of non-

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
{MARGENZA, margetuximab-cmkb}

hormonal metastatic therapy. Randomized subjects received 1 to 3 lines of prior therapy. Up to 78 subjects were to enroll.

Overall, none of the implemented changes were expected to compromise study integrity or interpretation of results.

The FDA's Assessment:

FDA agrees with the Applicant's description of the protocol amendments. The Applicant submitted a new version of the protocol with each amendments, which the FDA reviewed and agreed with the proposed major amendments in each revision leading up to the final version of the study protocol.

### 8.1.2. Study Results

#### Compliance with Good Clinical Practices

The Applicant's Position:

This study was conducted in compliance with current Good Clinical Practice and other applicable regulations, and in accordance with ethical principles from the Declaration of Helsinki. At each trial site, an institutional review board (IRB) or independent ethics committee (IEC) reviewed and approved this clinical trial protocol, the current Investigator's Brochure, and informed consent (IC). The IRB/IEC subsequently approved protocol amendments and revisions.

Written IC was obtained for all subjects before performance of any protocol specified procedures or interventions. Consents were amended, as needed, for protocol amendments. The Sponsor approved significant changes to site-specific sample consent documents.

The FDA's Assessment:

FDA agrees there is no evidence that compliance with good clinical practices was violated during conduct of Study 04.

#### Financial Disclosure

The Applicant's Position:

Financial disclosure information is provided in **Appendix 19.2**. There were no clinical investigators with disclosable financial arrangements.

The FDA's Assessment:

FDA agrees with the Applicant's position.

## Patient Disposition

### Data:

Subject disposition as of the 10-Oct-2018 cutoff for primary PFS analysis is presented in **Table 10**. Overall, treatment groups were well balanced with regards to subject disposition. No major differences in subject disposition were noted between treatment groups from the 10-Oct-2018 data cutoff of the Study 04 CSR and the 10-Apr-2019 data cutoff for CSR Addendum 1.

As of 10-Oct-2018, 137 subjects (25.6%) were receiving ongoing study therapy, with a higher proportion in the margetuximab group (M: 29.7%; T: 21.5%). Most discontinued subjects had progressive disease per RECIST (M: 78.4%; T: 73.9%).

**Table 10: Subject Disposition (ITT Population; Data Cutoff 10-Oct-2018)**

| Number (%) of Subjects                                 | Margetuximab plus<br>Chemotherapy<br>(N = 266) | Trastuzumab plus<br>Chemotherapy<br>(N = 270) | Total<br>(N = 536) |
|--------------------------------------------------------|------------------------------------------------|-----------------------------------------------|--------------------|
| <b>Overall</b>                                         |                                                |                                               |                    |
| Treated with Any Study Treatment                       | 264 (99.2)                                     | 265 (98.1)                                    | 529 (98.7)         |
| Randomized and Not Yet Treated                         | 0                                              | 1 (0.4)                                       | 1 (0.2)            |
| Never Treated                                          | 2 (0.8)                                        | 4 (1.5)                                       | 6 (1.1)            |
| Physician Decision                                     | 1 (50.0)                                       | 0                                             | 1 (16.7)           |
| Subject Decided to Discontinue Treatment               | 0                                              | 1 (25.0)                                      | 1 (16.7)           |
| Subject Withdrew Consent from Study                    | 1 (50.0)                                       | 3 (75.0)                                      | 4 (66.7)           |
| <b>Study Treatment</b>                                 |                                                |                                               |                    |
| On Any Study Treatment <sup>a</sup>                    | 79 (29.7)                                      | 58 (21.5)                                     | 137 (25.6)         |
| On Margetuximab/Trastuzumab Exclusively                | 13 (4.9)                                       | 5 (1.9)                                       | 18 (3.4)           |
| Off Any Study Treatment <sup>b</sup>                   | 187 (70.3)                                     | 211 (78.1)                                    | 398 (74.3)         |
| <b>Study Treatment Discontinuation</b>                 |                                                |                                               |                    |
| Adverse Event                                          | 185 (69.5)                                     | 207 (76.7)                                    | 392 (73.1)         |
| Death                                                  | 8 (4.3)                                        | 9 (4.3)                                       | 17 (4.3)           |
| Progressive Disease per RECIST                         | 2 (1.1)                                        | 3 (1.4)                                       | 5 (1.3)            |
| Non-Radiological Progressive Disease                   | 145 (78.4)                                     | 153 (73.9)                                    | 298 (76.0)         |
| Subject Withdrew Consent from Study                    | 12 (6.5)                                       | 19 (9.2)                                      | 31 (7.9)           |
| Physician Decision                                     | 6 (3.2)                                        | 10 (4.8)                                      | 16 (4.1)           |
| Subject Decided to Discontinue Treatment               | 7 (3.8)                                        | 5 (2.4)                                       | 12 (3.1)           |
| Other <sup>c</sup>                                     | 3 (1.6)                                        | 5 (2.4)                                       | 8 (2.0)            |
| Other <sup>c</sup>                                     | 2 (1.1)                                        | 3 (1.4)                                       | 5 (1.3)            |
| <b>Survival Follow-up</b>                              |                                                |                                               |                    |
| Alive <sup>d</sup>                                     | 266                                            | 270                                           |                    |
| Dead <sup>e</sup>                                      | 104 (39.1)                                     | 123 (45.6)                                    | 227 (42.4)         |
| Ongoing on Study Treatment                             | 78 (29.3)                                      | 80 (29.6)                                     | 158 (29.5)         |
| Withdrew Consent                                       | 74 (27.8)                                      | 55 (20.4)                                     | 129 (24.1)         |
| Off Treatment Missing End of Study Status <sup>f</sup> | 4 (1.5)                                        | 6 (2.2)                                       | 10 (1.9)           |
| Lost to Follow-up                                      | 4 (1.5)                                        | 5 (1.9)                                       | 9 (1.7)            |
|                                                        | 2 (0.8)                                        | 0                                             | 2 (0.4)            |

| Number (%) of Subjects | Margetuximab plus<br>Chemotherapy<br>(N = 266) | Trastuzumab plus<br>Chemotherapy<br>(N = 270) | Total<br>(N = 536) |
|------------------------|------------------------------------------------|-----------------------------------------------|--------------------|
| Never Treated          | 0                                              | 1 (0.4)                                       | 1 (0.2)            |

- a Study Treatment refers to any study therapy (margetuximab or trastuzumab), with or without chemotherapy.
- b Off Treatment is defined by discontinuation from study treatment, death, lost to follow-up, subject decided to discontinue treatment, subject withdrew consent from study, or never treated.
- c Comments indicate delays of study therapy longer than allowed, non-RECIST progressive disease, and change in backbone chemotherapy.
- d Alive on Survival Follow-up Form may be on or off study therapy. Details in ADAM dataset review guide.
- e Deaths as of the 10-Oct-2018 data cutoff date. Deaths at data cutoff for OS analysis (10-Sep-2019) are presented in **Study 04 CSR Addendum 1 – Table 4**.
- f Off Treatment Missing End of Study Status refers to subjects who discontinued study treatment and do not yet have any post-study treatment survival follow-up form data collected.

Source: ADSL dataset; **Study 04 CSR - Table 14.1.2**

#### The Applicant’s Position:

As anticipated in this advanced metastatic disease setting, the most common cause of study treatment discontinuation was clinical or radiological progression. In response to information request, the Applicant clarified that 1 never-treated subject in margetuximab arm and 3 never-treated subjects in trastuzumab arm were not included in ‘Subject Withdrew Consent from Study’ category in table 10 under ‘Study Treatment Discontinuation’. If these subjects are included, a total cumulative value for this discontinuation reason is 20. Similarly, 1 never-treated subject in trastuzumab arm was not included in ‘Subject Decided to Discontinue Treatment’ category, 1 never-treated subject was not included in ‘Physician Decision’ category, and 4 subjects (1 in margetuximab and 3 in trastuzumab) who withdrew consent and 1 subject for whom a physician decided to discontinue treatment were not included in the ‘never treated’ category under the ‘Survival Follow-up’ in table 10.

#### The FDA’s Assessment:

FDA agrees with the Applicant’s position of patient disposition. There were fewer patients who discontinued in the margetuximab plus chemotherapy arm (185 [70%]) compared to the trastuzumab plus chemotherapy arm (207 [77%]) vs ). The most common reason for treatment discontinuation was progressive disease per RECIST 1.1 criteria.

#### **Protocol Violations/Deviations**

##### Data:

Most subjects (96.3%) had at least 1 protocol deviation (**Table 11**). Most deviations were minor with the most frequent being tests and procedures, followed by schedule adherence. Major protocol deviations were balanced between groups (M: 12.8%; T: 11.1%). The most frequent

major deviations were visit schedule adherence (M: 44.1%; T: 33.3%) and tests and procedures (M: 29.4%; T: 36.7%).

**Table 11: Major Protocol Deviations (ITT Population; Data Cutoff 10-Oct-2018)**

| Number (%) of Subjects                       | Margetuximab plus<br>Chemotherapy<br>(N = 266) | Trastuzumab plus<br>Chemotherapy<br>(N = 270) | Total<br>(N = 536) |
|----------------------------------------------|------------------------------------------------|-----------------------------------------------|--------------------|
| <b>At Least One Major Protocol Deviation</b> | <b>34 (12.8)</b>                               | <b>30 (11.1)</b>                              | <b>64 (11.9)</b>   |
| AE/SAE                                       | 3 (1.1)                                        | 5 (1.9)                                       | 8 (1.5)            |
| Inclusion/Exclusion Criteria                 | 5 (1.9)                                        | 4 (1.5)                                       | 9 (1.7)            |
| Study Therapy Admin/Study Treatment          | 3 (1.1)                                        | 2 (0.7)                                       | 5 (0.9)            |
| Procedures/Tests                             | 10 (3.8)                                       | 11 (4.1)                                      | 21 (3.9)           |
| Visit Schedule                               | 15 (5.6)                                       | 10 (3.7)                                      | 25 (4.7)           |
| <b>At Least One Minor Protocol Deviation</b> | <b>259 (97.4)</b>                              | <b>257 (95.2)</b>                             | <b>516 (96.3)</b>  |
| AE/SAE                                       | 1 (0.4)                                        | 0                                             | 1 (0.2)            |
| Disallowed Medications                       | 0                                              | 2 (0.7)                                       | 2 (0.4)            |
| Inclusion/Exclusion Criteria                 | 1 (0.4)                                        | 0                                             | 1 (0.2)            |
| Informed Consent                             | 52 (19.5)                                      | 45 (16.7)                                     | 97 (18.1)          |
| Study Therapy Admin/Study Treatment          | 104 (39.1)                                     | 122 (45.2)                                    | 226 (42.2)         |
| Other                                        | 10 (3.8)                                       | 12 (4.4)                                      | 22 (4.1)           |
| Procedures/Tests                             | 244 (91.7)                                     | 228 (84.4)                                    | 472 (88.1)         |
| Visit Schedule                               | 178 (66.9)                                     | 179 (66.3)                                    | 357 (66.6)         |
| Withdrawal Criteria                          | 13 (4.9)                                       | 10 (3.7)                                      | 23 (4.3)           |
| <b>No Protocol Deviation</b>                 | <b>7 (2.6)</b>                                 | <b>13 (4.8)</b>                               | <b>20 (3.7)</b>    |

Abbreviations: AE: adverse event; ITT: intent-to-treat; N: number of subjects in dataset; SAE: serious adverse event.  
 Source: ADDV and ADSL datasets; *Study 04 CSR - Table 14.1.4*

The Applicant’s Position:

Overall, incidence of major protocol deviations in this study were low and balanced between treatment groups. Also, sensitivity analysis of independent PFS with major protocol deviations excluded from analysis was consistent with the statistically significant primary analysis (see *Sensitivity Analysis* below).

The FDA’s Assessment:

FDA agrees that the most common cause of protocol deviations were test procedures and visit schedule adherence. Test procedure violation was approximately 7% higher in the margetuximab treatment arm, while study therapy administration related violations were slightly higher in the trastuzumab treatment arm; visit schedule deviations were similar between the two treatment arms. Overall, these were minor protocol deviations and did not appear to have a significant impact on the conduct or outcome of the study. FDA agrees with the Applicant’s position that PFS per BIRC with major protocol deviations excluded from analysis was consistent with the primary analysis.

**Demographic and Baseline Characteristics**

Data:

Overall, treatment groups had well balanced demographics and baseline characteristics (**Table 12**). Of 536 ITT subjects, a majority were female (99.4%) and not of childbearing potential (73.7%). Most subjects were White (79.7%) and not Hispanic or Latino (80.4%). Median age and BSA were 56 years and 1.70 m<sup>2</sup>, respectively.

**Table 12: Demographic and Baseline Characteristics (ITT Population; Data Cutoff 10-Oct-2018)**

| Number (%) of Subjects                    | Margetuximab plus Chemotherapy (N = 266) | Trastuzumab plus Chemotherapy (N = 270) | Total (N = 536) |
|-------------------------------------------|------------------------------------------|-----------------------------------------|-----------------|
| <b>Age (years)</b>                        |                                          |                                         |                 |
| Mean (SD)                                 | 54.4 (11.4)                              | 55.7 (11.5)                             | 55.1 (11.5)     |
| Median                                    | 55.0                                     | 56.0                                    | 56.0            |
| Min – Max                                 | 29 – 83                                  | 27 – 86                                 | 27 – 86         |
| <b>Sex, n (%)</b>                         |                                          |                                         |                 |
| Female                                    | 266 (100.0)                              | 267 (98.9)                              | 533 (99.4)      |
| Male                                      | 0                                        | 3 (1.1)                                 | 3 (0.6)         |
| <b>Race, n (%)</b>                        |                                          |                                         |                 |
| American Indian or Alaska Native          | 0                                        | 0                                       | 0               |
| Asian                                     | 20 (7.5)                                 | 14 (5.2)                                | 34 (6.3)        |
| Black or African American                 | 16 (6.0)                                 | 12 (4.4)                                | 28 (5.2)        |
| Native Hawaiian or Other Pacific Islander | 1 (0.4)                                  | 2 (0.7)                                 | 3 (0.6)         |
| White                                     | 205 (77.1)                               | 222 (82.2)                              | 427 (79.7)      |
| Other                                     | 24 (9.0)                                 | 20 (7.4)                                | 44 (8.2)        |
| <b>Weight (kg) at Screening</b>           |                                          |                                         |                 |
| n                                         | 266                                      | 268                                     | 534             |
| Mean (SD)                                 | 68.15 (15.97)                            | 67.38 (15.74)                           | 67.76 (15.84)   |
| Median                                    | 65.20                                    | 64.00                                   | 65.00           |
| Min – Max                                 | 34.0 – 151.0                             | 42.0 – 122.7                            | 34.0 – 151.0    |
| <b>ECOG Performance Status, n (%)</b>     |                                          |                                         |                 |
| 0                                         | 149 (56.0)                               | 161 (59.6)                              | 310 (57.8)      |
| 1                                         | 117 (44.0)                               | 109 (40.4)                              | 226 (42.2)      |

Source: ADSL dataset; **Study 04 CSR - Table 14.1.5**

The Applicant’s Position:

Treatment groups were generally well balanced and represented the intended subject population with respect to demographic and baseline characteristics.

The FDA’s Assessment:

The FDA agrees with the demographic and baseline characteristics presented in this section. Most variables were well-balanced across the arms with no imbalance likely to have affected the results.

Only 20% of patients enrolled in Study 04 were 65 years of age or older. Three male patients

enrolled on Study 04, all received trastuzumab plus chemotherapy. Only patients with an ECOG performance status of 0 or 1 were eligible for Study 04; ECOG PS were similar in the two treatment arms.

Majority of the ITT population were from Europe (290/536 [54%]), but over a third of patients (186/536 [35%]) were treated in North America; the rest (59/536 [11%]) were from other geographic regions. Other than under representation of racial/ethnic minorities, the study population of Study 04 was generally consistent with a US population.

### Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

#### Data:

#### Baseline Cancer Status

Cancer disease history is summarized by treatment group in **Table 13**. Overall, treatment groups were balanced with regards to baseline cancer status and characteristics.

Most subjects (97.8%) had metastatic disease at study entry. Common metastatic sites included bone (57.5%), lymph nodes (54.3%), lungs (46.6%), and liver (35.1%). Groups were balanced for bone, lung, and liver metastasis. All subjects had documented HER2+ status including 54.3% IHC 3+ and 45.7% ISH amplification, and 62.3% were hormone receptor positive. Median number of target and non-target lesions was 2.

**Table 13: Cancer Disease History (ITT Population; Data Cutoff 10-Oct-2018)**

| Number (%) of Subjects                      | Margetuximab plus<br>Chemotherapy<br>(N = 266) | Trastuzumab plus<br>Chemotherapy<br>(N = 270) | Total<br>(N = 536) |
|---------------------------------------------|------------------------------------------------|-----------------------------------------------|--------------------|
| <b>HER2 Result <sup>a</sup></b>             |                                                |                                               |                    |
| ISH amplified                               | 117 (44.0)                                     | 128 (47.4)                                    | 245 (45.7)         |
| IHC3+                                       | 149 (56.0)                                     | 142 (52.6)                                    | 291 (54.3)         |
| <b>Hormone Receptor Status</b>              |                                                |                                               |                    |
| Positive (ER+ &/or PgR+)                    | 164 (61.7)                                     | 170 (63.0)                                    | 334 (62.3)         |
| Negative (ER- and PgR-)                     | 102 (38.3)                                     | 98 (36.3)                                     | 200 (37.3)         |
| Unknown                                     | 0                                              | 2 (0.7)                                       | 2 (0.4)            |
| <b>Disease Status at Study Entry</b>        |                                                |                                               |                    |
| Local, Resectable                           | 0                                              | 0                                             | 0                  |
| Locally Advanced, Unresectable              | 6 (2.3)                                        | 6 (2.2)                                       | 12 (2.2)           |
| Metastatic                                  | 260 (97.7)                                     | 264 (97.8)                                    | 524 (97.8)         |
| <b>Site(s) of Metastases at Study Entry</b> |                                                |                                               |                    |
| Bone                                        | 153 (57.5)                                     | 155 (57.4)                                    | 308 (57.5)         |
| Lymph Node                                  | 140 (52.6)                                     | 151 (55.9)                                    | 291 (54.3)         |
| Lung                                        | 124 (46.6)                                     | 126 (46.7)                                    | 250 (46.6)         |
| Liver                                       | 93 (35.0)                                      | 95 (35.2)                                     | 188 (35.1)         |

| Number (%) of Subjects                                                            | Margetuximab plus<br>Chemotherapy<br>(N = 266) | Trastuzumab plus<br>Chemotherapy<br>(N = 270) | Total<br>(N = 536) |
|-----------------------------------------------------------------------------------|------------------------------------------------|-----------------------------------------------|--------------------|
| Breast                                                                            | 44 (16.5)                                      | 37 (13.7)                                     | 81 (15.1)          |
| Skin                                                                              | 41 (15.4)                                      | 32 (11.9)                                     | 73 (13.6)          |
| Brain                                                                             | 37 (13.9)                                      | 34 (12.6)                                     | 71 (13.2)          |
| Pleura                                                                            | 22 (8.3)                                       | 17 (6.3)                                      | 39 (7.3)           |
| Other Visceral                                                                    | 21 (7.9)                                       | 15 (5.6)                                      | 36 (6.7)           |
| Other non-Visceral                                                                | 15 (5.6)                                       | 16 (5.9)                                      | 31 (5.8)           |
| Peritoneum                                                                        | 9 (3.4)                                        | 9 (3.3)                                       | 18 (3.4)           |
| Adrenal Medulla                                                                   | 4 (1.5)                                        | 2 (0.7)                                       | 6 (1.1)            |
| Ovary                                                                             | 4 (1.5)                                        | 0                                             | 4 (0.7)            |
| <b>Total Target Lesions per Subject at<br/>Screening (Independent Assessment)</b> |                                                |                                               |                    |
| Mean (SD)                                                                         | 1.6 (1.04)                                     | 1.6 (1.15)                                    | 1.6 (1.09)         |
| Median                                                                            | 2.0                                            | 2.0                                           | 2.0                |
| Min – Max                                                                         | 0 – 5                                          | 0 – 5                                         | 0 – 5              |

a Four subjects in each group did not have reference laboratory assessments but were confirmed HER2+ on central laboratory testing.

Source: ADSL, ADYF, and ADTU datasets; **Study 04 CSR - Table 12**

#### CD16A, CD32A, and CD32B Genotype

FcyR genotyping was done retrospectively by a validated assay in a central lab. Of the 536 subject ITT population, 5.6% had missing or unknown genotype data (M: 3.0%; T: 8.1%) (**Table 14**). Treatment groups were balanced for genotype variants. Most (81.5%) were carriers of the low affinity (-158F) allele of activating receptor CD16A, including 45.7% heterozygous CD16A-158F/V and 35.8% homozygous CD16A-158F/F.

**Table 14: Baseline CD16A, CD32A and CD32B Status (ITT Population; Data Cutoff 10-Oct-2018)**

| Number (%) of Subjects       | Margetuximab plus<br>Chemotherapy<br>(N = 266) | Trastuzumab plus<br>Chemotherapy<br>(N = 270) | Total<br>(N = 536) |
|------------------------------|------------------------------------------------|-----------------------------------------------|--------------------|
| <b>CD16A-158</b>             |                                                |                                               |                    |
| VV                           | 37 (13.9)                                      | 32 (11.9)                                     | 69 (12.9)          |
| FV                           | 119 (44.7)                                     | 126 (46.7)                                    | 245 (45.7)         |
| FF                           | 102 (38.3)                                     | 90 (33.3)                                     | 192 (35.8)         |
| F carrier (FF or FV)         | 221 (83.1)                                     | 216 (80.0)                                    | 437 (81.5)         |
| Missing/Unknown <sup>a</sup> | 8 (3.0)                                        | 22 (8.1)                                      | 30 (5.6)           |
| <b>CD32A-131</b>             |                                                |                                               |                    |
| HH                           | 78 (29.3)                                      | 59 (21.9)                                     | 137 (25.6)         |
| HR                           | 121 (45.5)                                     | 126 (46.7)                                    | 247 (46.1)         |
| RR                           | 59 (22.2)                                      | 63 (23.3)                                     | 122 (22.8)         |
| Missing/Unknown <sup>a</sup> | 8 (3.0)                                        | 22 (8.1)                                      | 30 (5.6)           |

| Number (%) of Subjects       | Margetuximab plus<br>Chemotherapy<br>(N = 266) | Trastuzumab plus<br>Chemotherapy<br>(N = 270) | Total<br>(N = 536) |
|------------------------------|------------------------------------------------|-----------------------------------------------|--------------------|
| <b>CD32B-232</b>             |                                                |                                               |                    |
| II                           | 200 (75.2)                                     | 180 (66.7)                                    | 380 (70.9)         |
| IT                           | 53 (19.9)                                      | 64 (23.7)                                     | 117 (21.8)         |
| TT                           | 5 (1.9)                                        | 4 (1.5)                                       | 9 (1.7)            |
| Missing/Unknown <sup>a</sup> | 8 (3.0)                                        | 22 (8.1)                                      | 30 (5.6)           |

a Of 30 subjects with missing or unknown FcyR allele information, 18 declined consent. The remaining 12 had a missing or incorrect sample then early death, loss to follow up, or refusal of re-draw.

Source: ADSL dataset; **Study 04 CSR - Table 14.1.9**

### Prior Systemic/Hormonal Therapy

About one-half received prior adjuvant therapy (M: 51.1%; T: 45.2%), and about one-quarter received neoadjuvant therapy (M: 30.5%; T: 24.1%), both in slightly higher proportions on margetuximab (**Table 15**). Most subjects received at least 2 prior lines of metastatic therapy (M: 91.4%; T: 95.6%), and about one-third received 3 prior lines (M: 34.6%; T: 32.2%). One subject with an eligibility violation (margetuximab group) received 4 prior lines of metastatic therapy. Treatment groups were balanced for prior anti-HER2 therapies. All subjects received prior trastuzumab, all but 1 subject on trastuzumab received prior pertuzumab, and most received T-DM1 (M: 91.0%; T: 91.5%). Relatively few had received lapatinib or other anti-HER2 therapies. Prior treatment with taxanes (M: 94.7%; T: 92.2%) was common in both groups.

**Table 15: Prior Systemic/Hormonal Therapy (ITT Population; Data Cutoff 10-Oct-2018)**

| Number (%) of Subjects              | Margetuximab plus<br>Chemotherapy<br>(N = 266) | Trastuzumab plus<br>Chemotherapy<br>(N = 270) | Total<br>(N = 536) |
|-------------------------------------|------------------------------------------------|-----------------------------------------------|--------------------|
| <b>Setting of Regimen</b>           |                                                |                                               |                    |
| Adjuvant                            | 136 (51.1)                                     | 122 (45.2)                                    | 258 (48.1)         |
| Neoadjuvant                         | 81 (30.5)                                      | 65 (24.1)                                     | 146 (27.2)         |
| Metastatic – First Line             | 264 (99.2)                                     | 269 (99.6)                                    | 533 (99.4)         |
| Metastatic – Second Line            | 243 (91.4)                                     | 258 (95.6)                                    | 501 (93.5)         |
| Metastatic – Third Line             | 92 (34.6)                                      | 87 (32.2)                                     | 179 (33.4)         |
| Metastatic – Fourth or Greater Line | 1 (0.4)                                        | 0                                             | 1 (0.2)            |
| <b>Category of Regimen</b>          |                                                |                                               |                    |
| Taxane                              | 252 (94.7)                                     | 249 (92.2)                                    | 501 (93.5)         |
| Anthracycline                       | 118 (44.4)                                     | 110 (40.7)                                    | 228 (42.5)         |
| Platinum                            | 34 (12.8)                                      | 40 (14.8)                                     | 74 (13.8)          |
| Hormone                             | 126 (47.4)                                     | 133 (49.3)                                    | 259 (48.3)         |
| Other                               | 168 (63.2)                                     | 155 (57.4)                                    | 323 (60.3)         |
| Trastuzumab                         | 266 (100.0)                                    | 270 (100.0)                                   | 536 (100.0)        |
| Pertuzumab                          | 266 (100.0)                                    | 269 (99.6)                                    | 535 (99.8)         |
| T-DM1                               | 242 (91.0)                                     | 247 (91.5)                                    | 489 (91.2)         |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

| Number (%) of Subjects                       | Margetuximab plus<br>Chemotherapy<br>(N = 266) | Trastuzumab plus<br>Chemotherapy<br>(N = 270) | Total<br>(N = 536) |
|----------------------------------------------|------------------------------------------------|-----------------------------------------------|--------------------|
| Lapatinib                                    | 41 (15.4)                                      | 39 (14.4)                                     | 80 (14.9)          |
| Other HER2                                   | 6 (2.3)                                        | 6 (2.2)                                       | 12 (2.2)           |
| <b>Overall lines of anti-HER2 therapy</b>    |                                                |                                               |                    |
| 1                                            | 7 (2.6)                                        | 3 (1.1)                                       | 10 (1.9)           |
| 2                                            | 112 (42.1)                                     | 130 (48.1)                                    | 242 (45.1)         |
| 3                                            | 124 (46.6)                                     | 109 (40.4)                                    | 233 (43.5)         |
| 4                                            | 23 (8.6)                                       | 28 (10.4)                                     | 51 (9.5)           |
| <b>Metastatic lines of anti-HER2 therapy</b> |                                                |                                               |                    |
| 0                                            | 2 (0.8)                                        | 0                                             | 2 (0.4)            |
| 1                                            | 24 (9.0)                                       | 14 (5.2)                                      | 38 (7.1)           |
| 2                                            | 159 (59.8)                                     | 183 (67.8)                                    | 342 (63.8)         |
| 3                                            | 79 (29.7)                                      | 71 (26.3)                                     | 150 (28.0)         |
| 4 <sup>a</sup>                               | 2 (0.8)                                        | 2 (0.7)                                       | 4 (0.7)            |
| <b>Category of Pertuzumab<sup>b</sup></b>    |                                                |                                               |                    |
| (Neo)Adjuvant                                | 21 (7.9)                                       | 11 (4.1)                                      | 32 (6.0)           |
| Metastatic                                   | 237 (89.1)                                     | 249 (92.2)                                    | 486 (90.7)         |
| Both Settings                                | 8 (3.0)                                        | 9 (3.3)                                       | 17 (3.2)           |

a **Study 04 CSR - Table 14.1.10** collects site-reported prior regimen counts, including for 1 subject with a protocol violation due to 4 prior lines of therapy in the metastatic setting. By contrast, **Study 04 CSR - Table 14.1.10.1** presents a programmed tabulation of number of prior therapies.

b One subject in the trastuzumab group had an eligibility violation of no prior pertuzumab.

Source: ADCM and ADSL datasets; **Study 04 CSR - Table 14.1.10, Table 14.1.10.1, and Table 14.2.5.3.3**

### Stratification Factors

Treatment groups were balanced for all 3 stratification factors in IVRS (**Table 16**).

**Table 16: Randomization Stratification Factors (ITT Population; Data Cutoff 10-Oct-2018)**

| Number (%) of Subjects                        | Margetuximab plus<br>Chemotherapy<br>(N = 266) | Trastuzumab plus<br>Chemotherapy<br>(N = 270) | Total<br>(N = 536) |
|-----------------------------------------------|------------------------------------------------|-----------------------------------------------|--------------------|
| <b>Backbone Chemotherapy</b>                  |                                                |                                               |                    |
| Capecitabine                                  | 71 (26.7)                                      | 72 (26.7)                                     | 143 (26.7)         |
| Eribulin                                      | 66 (24.8)                                      | 70 (25.9)                                     | 136 (25.4)         |
| Gemcitabine                                   | 33 (12.4)                                      | 33 (12.2)                                     | 66 (12.3)          |
| Vinorelbine                                   | 96 (36.1)                                      | 95 (35.2)                                     | 191 (35.6)         |
| <b>Number of Metastatic Sites</b>             |                                                |                                               |                    |
| ≤ 2                                           | 138 (51.9)                                     | 144 (53.3)                                    | 282 (52.6)         |
| > 2                                           | 128 (48.1)                                     | 126 (46.7)                                    | 254 (47.4)         |
| <b>Lines of Therapy in Metastatic Setting</b> |                                                |                                               |                    |
| ≤ 2                                           | 175 (65.8)                                     | 180 (66.7)                                    | 355 (66.2)         |

| Number (%) of Subjects | Margetuximab plus<br>Chemotherapy<br>(N = 266) | Trastuzumab plus<br>Chemotherapy<br>(N = 270) | Total<br>(N = 536) |
|------------------------|------------------------------------------------|-----------------------------------------------|--------------------|
| > 2                    | 91 (34.2)                                      | 90 (33.3)                                     | 181 (33.8)         |

Source: ADSL dataset; **Study 04 CSR - Table 14.1.16**

#### The Applicant's Position:

Overall, the subject population enrolled was representative of the pretreated patient population with metastatic HER2-positive breast cancer. Treatment groups were well balanced for baseline characteristics.

#### The FDA's Assessment:

FDA agrees with the Applicant's description of cancer disease history, baseline CD16A, CD32A and CD32B status, lines of anti-HER2 therapy, setting of regimens, and stratification factors. Distribution of these baseline characteristics were similar between treatment groups.

The addition of multiple agents to the treatment armamentarium for early-stage HER2-positive breast cancer means that at the time of diagnosis of metastatic disease, patients may have already received anywhere from 0 to 3 prior anti-HER2 therapies. Treatment decisions must therefore consider the history of treatment exposure rather than simply "line of therapy". Given all subjects in Study 04 received prior trastuzumab, all but 1 received prior pertuzumab, and 91% received T-DM1 means it is highly representative of the U.S. patient population for margetuximab's intended indication.

### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

#### The Applicant's Position:

##### *Treatment Compliance*

This study followed ICH Guideline E6 on GCP to monitor compliance with dose calculation, administration, and dosing regimen. Study treatment was administered at each study site by qualified personnel. Based on comparison of planned and actual doses of study treatment administered, compliance was not an issue in this trial (**Study 04 CSR - Section 12.1**).

##### *Concomitant Medications*

Nearly all subjects received concomitant medications on study (M: 99.2%; T: 98.54% **Study 04 CSR – Section 11.2.4**). Few protocol deviations were due to disallowed medications (M: 0%; T: 0.7%); all of which were minor in nature. Overall, differences in concomitant medications received during the study are not expected to affect interpretation of efficacy results.

*Rescue Medication Use*

Not applicable.

**The FDA's Assessment:**

FDA agrees overall with the Applicant's position.

**Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)**

The Applicant's Position:

*Primary Endpoint: Progression-Free Survival by Independent Review*

Study 04 met its primary endpoint of independently reviewed PFS prolongation in the ITT population of all subjects randomized. Stratified analysis showed that margetuximab plus chemotherapy led to a 24% risk reduction in PFS over trastuzumab plus chemotherapy (stratified HR: 0.76; 95% confidence interval [CI]: 0.593, 0.979;  $p = 0.0334$ ; **Table 17** and **Figure 2**). Median (95% CI) PFS was 5.8 months (5.52, 6.97) on margetuximab plus chemotherapy versus 4.9 months (4.17, 5.59) on active control (trastuzumab plus chemotherapy).

The HR (0.76) summarizes treatment effect over the entire duration of observation. By contrast, median PFS difference (0.9 months) describes the horizontal difference in PFS curves at only one point, when half have progressed. The HR of 0.76 represents 24% risk reduction and is more reflective of overall PFS benefit than median difference. The Sponsor believes that a 24% risk reduction is clinically meaningful in this population. Study 04 measured margetuximab benefit not against placebo but rather versus an active control of trastuzumab. Thus, margetuximab showed improvement over trastuzumab regimens routinely used in this advanced-stage patient population.

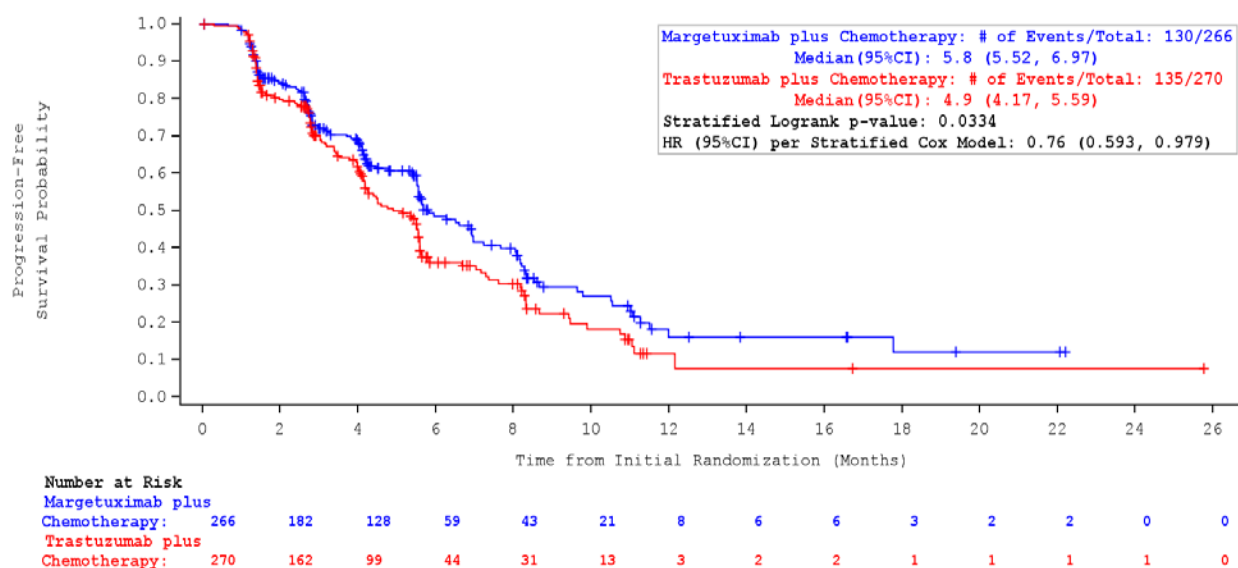
**Table 17: Study 04 Independently Assessed PFS (ITT Population; Data Cutoff 10-Oct-2018)**

|                                                   | <b>Margetuximab plus<br/>Chemotherapy<br/>(N = 266)</b> | <b>Trastuzumab plus<br/>Chemotherapy<br/>(N = 270)</b> |
|---------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------|
| Number of Events, n (%)                           | 130 (48.9)                                              | 135 (50.0)                                             |
| Progressive Disease                               | 118 (44.4)                                              | 125 (46.3)                                             |
| Death without Progressive Disease                 | 12 (4.5)                                                | 10 (3.7)                                               |
| Median PFS (Months)                               | 5.8                                                     | 4.9                                                    |
| (95% CI)                                          | (5.52–6.97)                                             | (4.17–5.59)                                            |
| Min–Max                                           | 0.03–22.21                                              | 0.03–25.76                                             |
| Stratified Log-Rank Test <i>p-value</i> (2-sided) | 0.0334                                                  |                                                        |
| HR per Stratified Cox Model (95% CI)              | 0.76 (0.593–0.979)                                      |                                                        |

|                               | Margetuximab plus<br>Chemotherapy<br>(N = 266) | Trastuzumab plus<br>Chemotherapy<br>(N = 270) |
|-------------------------------|------------------------------------------------|-----------------------------------------------|
| PFS Rate at 3 Months (95% CI) | 0.72 (0.65–0.77)                               | 0.70 (0.63–0.76)                              |
| PFS Rate at 6 Months (95% CI) | 0.48 (0.41–0.56)                               | 0.36 (0.28–0.44)                              |
| PFS Rate at 9 Months (95% CI) | 0.30 (0.22–0.38)                               | 0.22 (0.15–0.30)                              |

Source: ADTTEFF and ADSL datasets; *Study 04 CSR - Table 14.2.2.1*

**Figure 2: Study 04 Independently Assessed PFS (ITT Population; Data Cutoff 10-Oct-2018)**



Source: ADTTEFF dataset; *Study 04 CSR - Figure 14.2.2.2*

### Sensitivity Analysis

The following PFS sensitivity analyses were performed:

- Sensitivity Analysis 1 included PFS events regardless of when they occurred during the study. This analysis recovers PFS events that may have been censored at an earlier date due either to 2 consecutive missed tumor assessments or receipt of a subsequent anticancer treatment.
- Sensitivity Analysis 2 considered clinical disease progressions as PFS events, even if they could not be confirmed by central blinded analysis.
- Sensitivity Analysis 3 censored last tumor assessment before treatment discontinuation for subjects who stopped study therapy for reasons other than documented progressive disease or death. This analysis serves to assess the impact on PFS of treatment discontinuation due to toxicity or other non–progressive-disease reasons.

- Sensitivity Analysis 4 excluded subjects with major protocol deviations to assess the impact of major protocol deviations on primary PFS analysis.

Benefit of margetuximab remained statistically significant over trastuzumab for all 4 sensitivity analyses, with HRs from 0.74 to 0.78 for primary PFS analysis (**Study 04 CSR – Section 11.4.1.1.4**). These data support that the PFS advantage for margetuximab versus active comparator trastuzumab is robust against diverse censoring rules.

*Primary Endpoint: Overall Survival*

At data cutoff for primary PFS analysis (10-Oct-2018), 158 deaths had occurred (margetuximab [M]: 78 [29.3%]; trastuzumab [T]: 80 [29.6%]) (ITT Population). Median OS was 18.9 months on margetuximab and 17.2 months on trastuzumab (stratified Cox model HR: 0.95; 95% CI: 0.691, 1.309; stratified log-rank p = 0.7584) (**Study 04 CSR – Section 11.4.1.2**).

A second interim analysis of OS after 270 deaths occurred had data cutoff 10-Sep-2019 (M: 131 [49.2%]; T: 139 [51.5%]; **Table 18**). Median OS was 21.6 months on margetuximab and 19.8 months on trastuzumab (stratified Cox model HR: 0.885; 95% CI: 0.693, 1.130; stratified log-rank p = 0.3264). The stopping threshold was not reached, and the study is powered for final analysis at 385 events. No formal conclusions can be drawn from available data. OS data continue to mature and support clinically meaningful benefit of margetuximab plus chemotherapy in this population.

**Table 18: Study 04 Overall Survival (ITT Population; Data Cutoff 10-Sep-2019)**

|                                                   | <b>Margetuximab plus<br/>Chemotherapy<br/>(N = 266)</b> | <b>Trastuzumab plus<br/>Chemotherapy<br/>(N = 270)</b> |
|---------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------|
| Number of Events, n (%)                           | 131 (49.2)                                              | 139 (51.5)                                             |
| Median OS (Months)                                | 21.6                                                    | 19.8                                                   |
| (95% CI)                                          | (18.86–24.05)                                           | (17.54–22.28)                                          |
| Min–Max                                           | 0.66–41.43                                              | 0.07–43.01                                             |
| Stratified Log-Rank Test <i>p-value</i> (2-sided) | 0.3264                                                  |                                                        |
| HR per Stratified Cox Model (95% CI)              | 0.885 (0.693–1.130)                                     |                                                        |
| OS Rate at 12 Months (95% CI)                     | 0.75 (0.70–0.80)                                        | 0.75 (0.70–0.80)                                       |
| OS Rate at 18 Months (95% CI)                     | 0.60 (0.53–0.66)                                        | 0.56 (0.49–0.62)                                       |
| OS Rate at 24 Months (95% CI)                     | 0.44 (0.36–0.51)                                        | 0.40 (0.33–0.48)                                       |

Source: ADTTEFF and ADSL dataset; **Study 04 CSR Addendum 1 - Table 14.2.2.3**

*Subgroup Analysis*

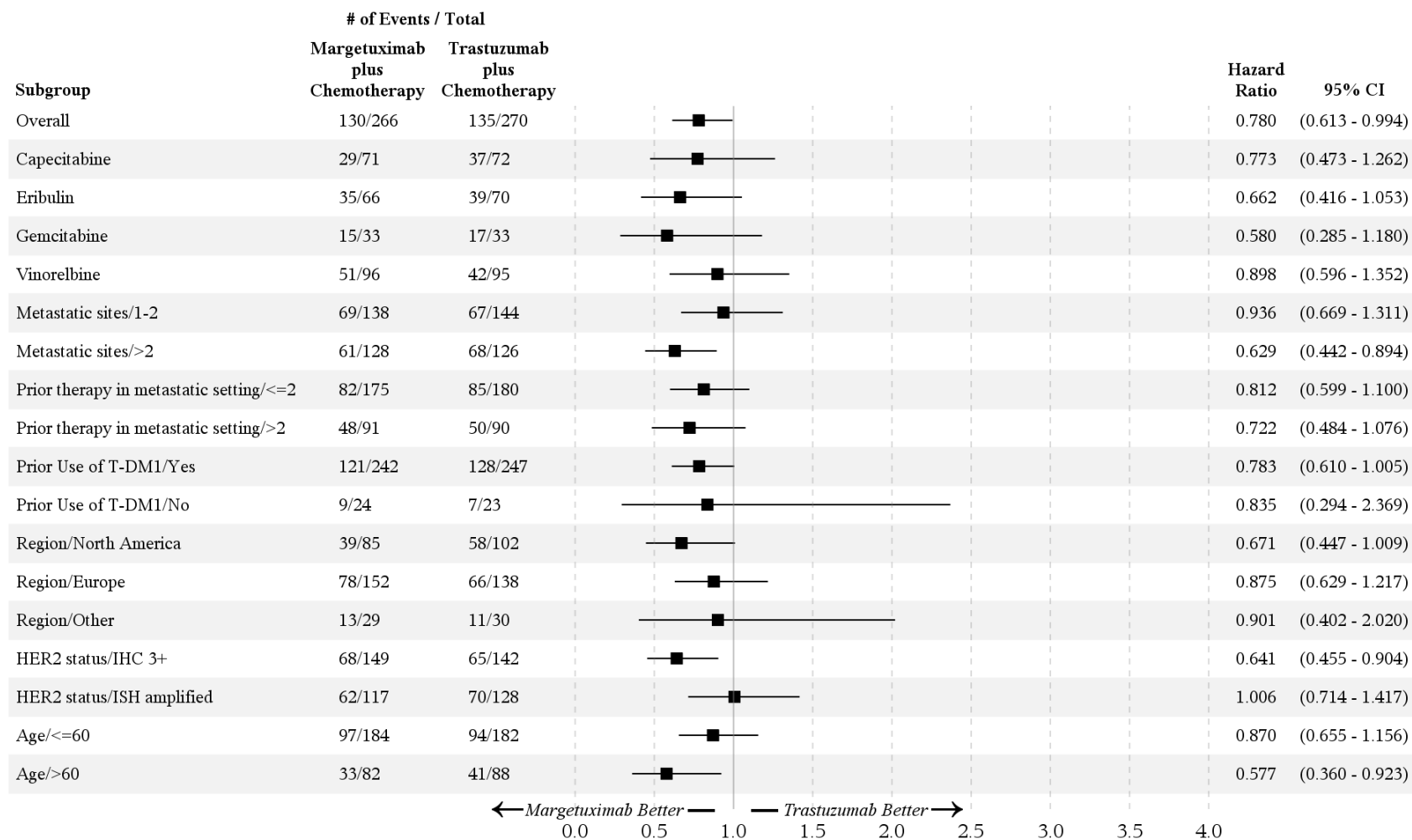
Margetuximab prolonged PFS over trastuzumab across most subgroups analyzed (**Figure 3**). IHC 3+ and hormone receptor negative status were associated with margetuximab benefit. Other

notable subgroups suggestive of margetuximab benefit included > 2 metastatic sites, age at least 60 years, and Black race. At second interim OS analysis, similar consistency of treatment effect was evident across major subgroups (**Figure 4**). IHC3+ status predicted for longer survival on anti-HER2 therapy, consistent with the idea that HER2 expression level may be predictive of immune activation by margetuximab.

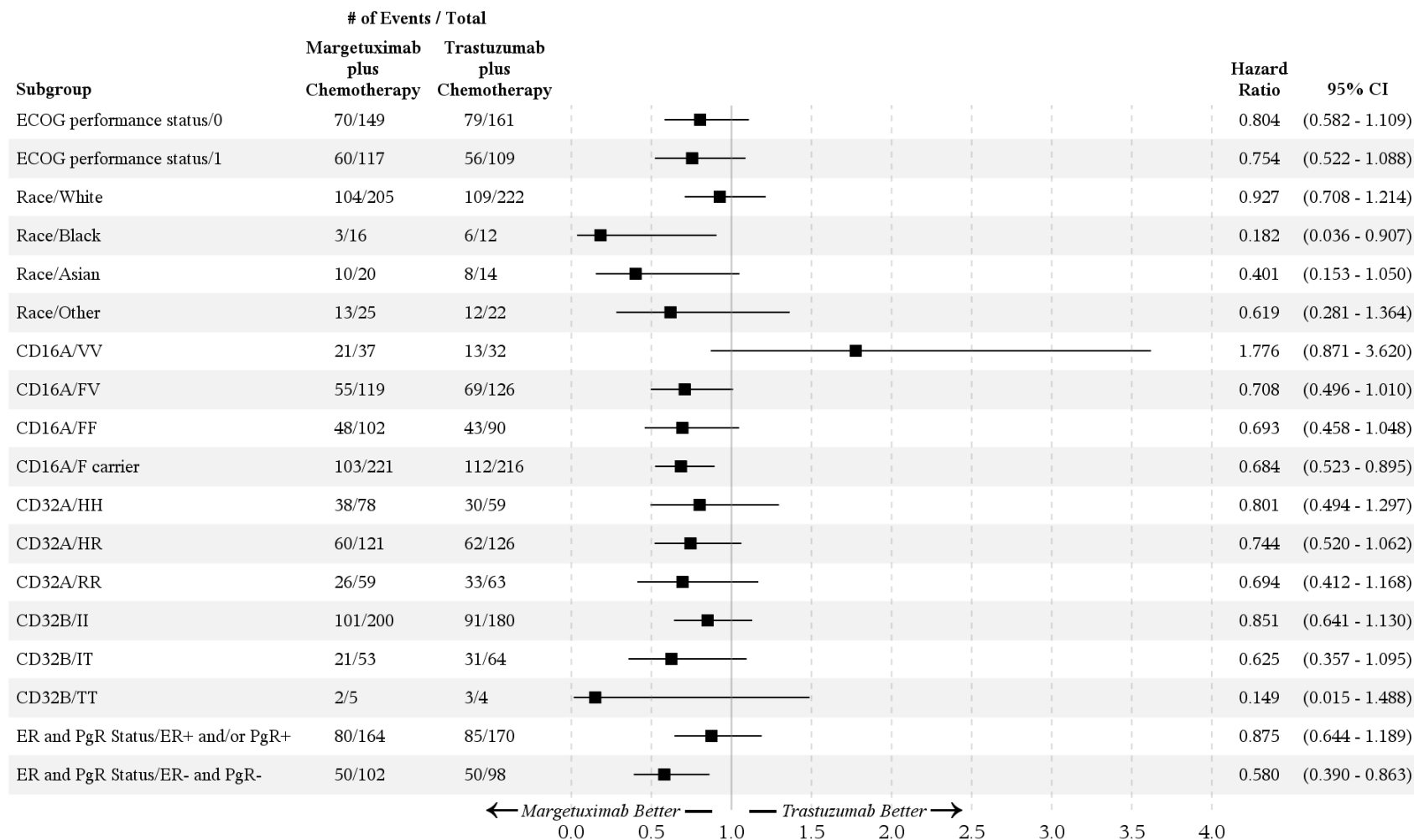
In Study 04, a CD16A by treatment interaction effect on primary PFS was observed (interaction  $p = 0.0121$ ). CD16A-158V/F or F/F genotypes predicted increased PFS advantage of margetuximab over trastuzumab (HR: 0.68; 95% CI: 0.523, 0.895). Conversely, there was no apparent margetuximab benefit in CD16A-158V/V homozygotes. Feasible explanations include small sample size ( $n = 69$ ), baseline patient characteristics, and influence of CD16A genetics on trastuzumab clinical outcomes. Margetuximab's Fc domain binds with increased affinity to both CD16A allotypes, resulting in greater ADCC potency than trastuzumab, irrespective of genotype (**27**). Because margetuximab Fc engineering increases affinity for both CD16A allotypes, the sponsor's expectation at the time of Study 04 design was that all CD16A genotypes could benefit, with greater relative improvement expected to accrue to 158F allele carriers (FF or FV). In Study 04, 158F allele carriers appear to benefit most from margetuximab relative to trastuzumab. Subsequent analysis of the NSABP-B31 trial (**11**) complements prior work in MBC (**25**) showing that best clinical outcomes of trastuzumab therapy are in V/V homozygotes. Study 04 results mirror this pattern of best trastuzumab clinical outcomes in V/V homozygotes.

For OS as of 10-Sep-2019, a similar CD16A by interaction treatment effect was observed (interaction  $p = 0.0709$ ). There was an OS trend favoring margetuximab for CD16A 158V/F or F/F genotypes (HR: 0.79; 95% CI: 0.607, 1.035). Conversely, margetuximab appeared no better than trastuzumab in the small subgroup of 69 (12.9%) CD16A-158V/V homozygotes (HR: 1.65; 95% CI: 0.819, 3.317).

**Figure 3: Study 04 Independently Assessed PFS - Pre-specified Subgroup Analyses (ITT Population; Data Cutoff 10-Oct-2018)**



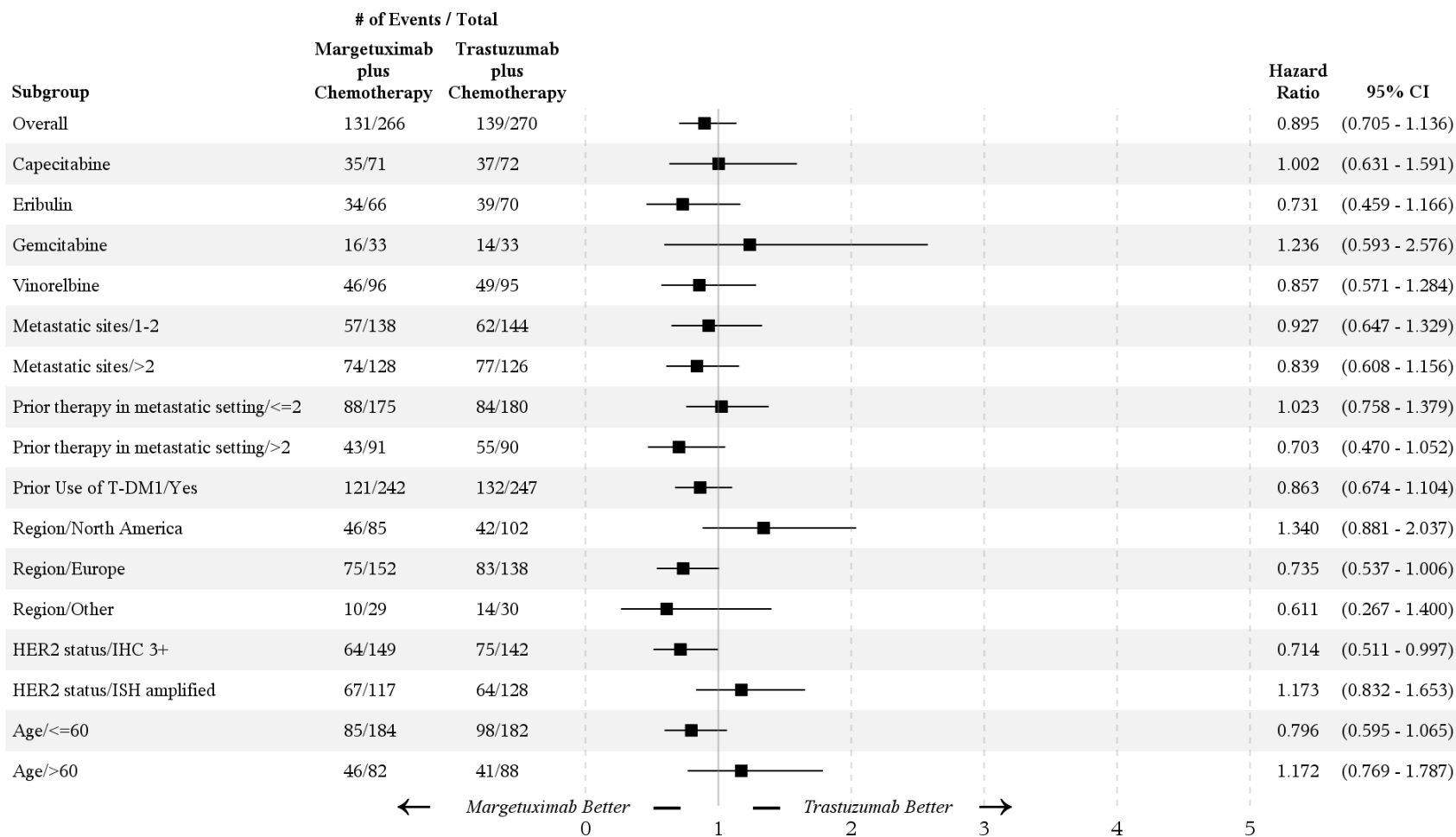
NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}



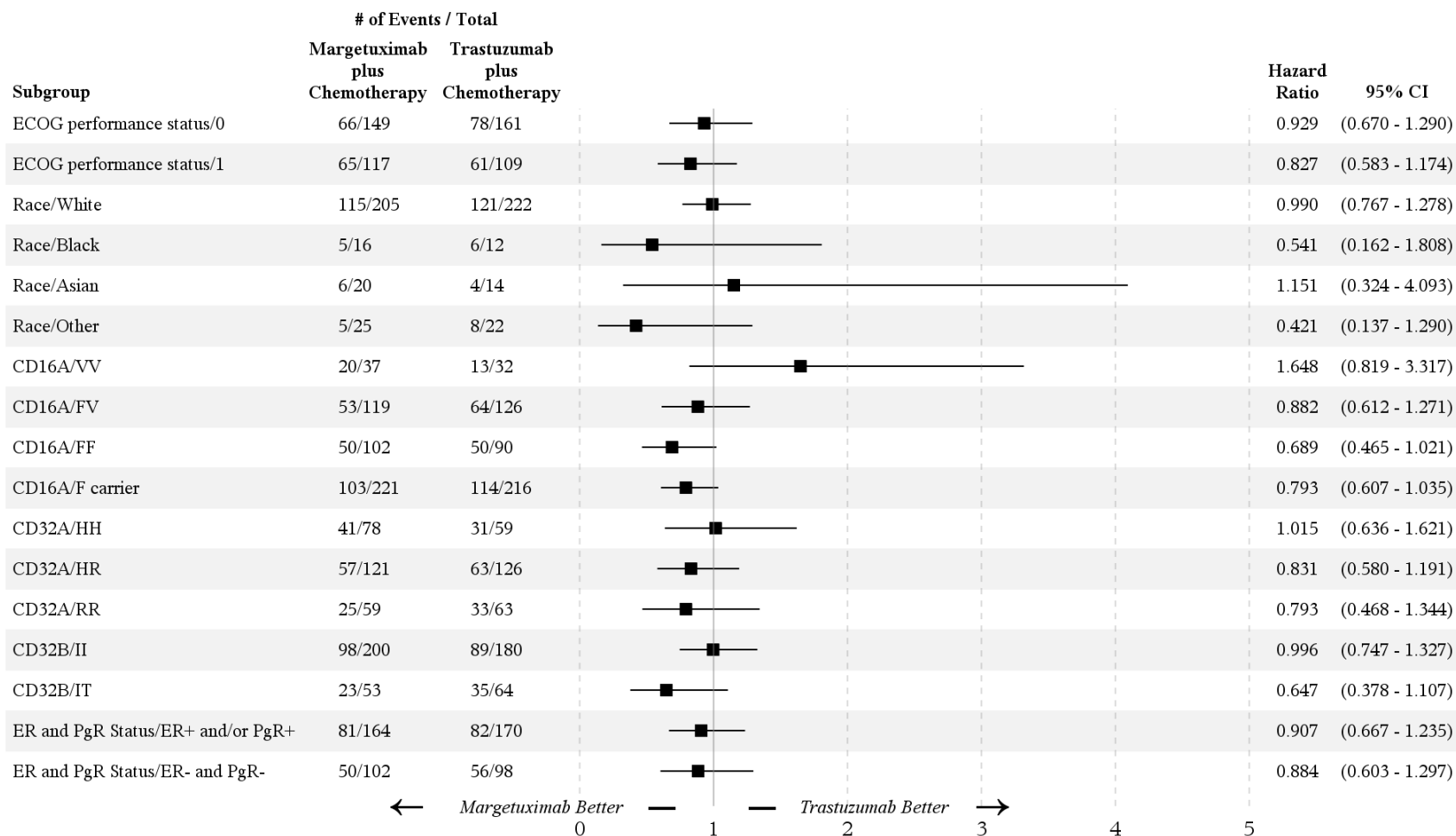
Abbreviations: CD: cluster of differentiation; ECOG: Eastern Cooperative Oncology Group; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization; PgR: progesterone receptor; T-DM1: ado-trastuzumab emtansine.

Source: ADTTEFF and ADSL datasets; **Study 04 CSR - Figure 14.2.5.2**

**Figure 4: Study 04 Overall Survival - Pre-specified Subgroup Analyses (ITT Population; Data Cutoff 10-Sep-2019)**



NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}



Abbreviations: CD: cluster of differentiation; ECOG: Eastern Cooperative Oncology Group; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization; PgR: progesterone receptor; T-DM1: ado-trastuzumab emtansine.  
 Source: ADTTEFF and ADSL datasets; **Study 04 CSR Addendum 1 - Figure 14.2.5.4**

### *Summary of Efficacy*

Overall, margetuximab led to treatment benefit beyond active comparator trastuzumab in patients receiving chemotherapy for pretreated HER2+ advanced breast cancer. In Study 04, margetuximab demonstrated statistically significant, clinically meaningful superiority in PFS that is robust to sensitivity analyses. Primary PFS, sensitivity analyses, interim OS, Investigator-assessed PFS, response-based data (see below), and Study 04 exposure-response observations provide complementary, internally consistent evidence of clinical benefit. Finally, emerging information on low-affinity FcγRs suggests that CD16A genetics may be predictive of benefit for margetuximab relative to trastuzumab in the F carrier population.

#### The FDA's Assessment:

The FDA agrees that the study met its primary endpoint of PFS by BICR. The OS data is immature (70% of targeted OS events) to provide a conclusive result.

Although, the improvement in median PFS is modest with margetuximab plus chemotherapy over the trastuzumab plus chemotherapy, the latter treatment regimen is an active control and margetuximab is a replacement therapy to trastuzumab (not an add on). Trastuzumab plus chemotherapy is included in guideline recommendations such as ASCO, NCCN and ESMO,) and its treatment effect is likely better than a placebo.

The FDA requested the Applicant to conduct a post-hoc interval censored analysis of PFS to assess sensitivity of primary analysis results with respect to imaging interval. The median PFS estimated with this approach in margetuximab was 5.6 months (95% CI: 5.62-5.82). It is shorter but close to primary analysis estimate. The median PFS diminished more in trastuzumab arm to 4.4 months (95% CI: 3.52-4.76 ). These results provide further assurance of robustness of primary analysis results. See Additional Analyses Conducted on the Individual Trial section for additional details.

The PFS benefit with margetuximab plus chemotherapy treatment is consistent across most of the subgroups with different demographic, disease, and treatment characteristics. These subgroup analyses were generally supportive of primary analysis results except for the subgroup of patients with CD16A-158V/V homozygotes. These subgroup results should be interpreted with caution because the sample size in each subgroup was not planned to power such analyses.

The Applicant also presented PFS and OS rates by arm, which are considered exploratory. The point estimate of event rates at a fixed time point for a time-to-event endpoint should be interpreted with caution because it does not represent the entire effect size of the treatment and the chosen landmark time is arbitrary.

Note, the FDA considers all subgroup analyses without alpha allocation to be exploratory and the results useful only for hypothesis generation. All the reported p-values associated with subgroup and exploratory analyses should be considered nominal only.

### Data Quality and Integrity

#### Data:

The Sponsor implemented a strategy to assure data quality and integrity (**Study 04 CSR – Section 9.6**), including investigational site monitoring, appropriate training, and data management procedures. Each electronic case report form was verified for completeness and accuracy against data sources. Independent site, vendor, and sponsor system audits were performed throughout the conduct of the study.

#### The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of submitted datasets, which are sufficiently complete to allow for a thorough review of efficacy. Furthermore, no data integrity concerns were identified during investigator site audits conducted for this study.

#### The FDA's Assessment:

The FDA agrees with the Applicant's position.

### Efficacy Results – Secondary and Other Relevant Endpoints

#### The Applicant's Position:

*Secondary Endpoint: Progression-Free Survival by Investigator Assessment*

The top secondary endpoint of Study 04, Investigator-assessed PFS, comprised 337 events as of the 10-Oct-2018 data cutoff date for primary PFS analysis (**Study 04 CSR – Section 11.4.1.1.2**). In that analysis, median Investigator-assessed PFS (95% CI) was 5.6 months (5.06, 6.67) on margetuximab plus chemotherapy versus 4.2 months (3.98, 5.39) on the active control of trastuzumab plus chemotherapy. In stratified analysis margetuximab plus chemotherapy led to 30% risk reduction in PFS over trastuzumab plus chemotherapy (stratified Cox model HR: 0.70; 95% CI: 0.556, 0.870; stratified log-rank nominal p = 0.0014).

An updated analysis of Investigator-assessed PFS was performed based on 430 PFS events as of 10-Sep-2019 data cutoff for interim OS analysis (**Study 04 CSR Addendum 1 – Section 2.2.2**). With continued data maturation, a greater number of observed events led to increased statistical significance in PFS by Investigator assessment. In stratified analysis margetuximab plus chemotherapy led to a 29% risk reduction in PFS over trastuzumab plus chemotherapy (HR: 0.707; 95% CI: 0.580, 0.862; stratified log-rank nominal p = 0.0006). Median (95% CI) PFS

was 5.7 months (5.22, 6.97) on margetuximab plus chemotherapy versus 4.4 months (4.14, 5.45) on the active control of trastuzumab plus chemotherapy.

Concordance between Investigator and independent assessments of PFS was acceptable (**Study 04 CSR – Table 14.2.6.6**). Of 266 subjects in the margetuximab group, 209 (78.6%) had agreement by Investigator and independent review in overall PD assessment, irrespective of timing. A similar concordance rate was observed in the trastuzumab group (205 of 270 subjects; 75.9%). These concordance rates appear consistent with those of other similar trials.

Central review censoring led to fewer PFS events counted for independent, as opposed to Investigator, assessments of PFS (**Study 04 CSR – Section 11.4.1.1.3**). Nonetheless, differences between independent and Investigator assessment of progressive disease appear balanced across treatment groups. The strong Investigator-assessed PFS results based on additional PFS events and the consistent results between Investigator-assessed and independent blinded analysis, further support margetuximab benefit.

#### *Secondary and Tertiary Endpoints*

Response-based secondary and tertiary endpoints, including blinded assessment of ORR and CBR, also demonstrate margetuximab disease activity, relative to trastuzumab (**Study 04 CSR – Section 11.4.1.3**). Nominal benefit of margetuximab over trastuzumab for confirmed ORR approached statistical significance (M: 22.1% [95% CI: 17.11, 27.16] vs T: 16.0% [95% CI: 11.59, 20.47]; nominal p = 0.0597). Also, a higher CBR was observed with margetuximab than trastuzumab (M: 36.6% [95% CI: 30.81, 42.48] vs T: 24.8% [95% CI: 19.58, 30.04]; nominal p = 0.0026).

Given timing of primary PFS analysis on completion of randomization, ORR in both arms may have been underestimated in this study. At completion of randomization, 8.4% of the population had less than the minimum 12 weeks on study therapy needed to confirm an objective response, and 21.8% had less than the 6 months of stable disease needed for a clinical benefit response.

#### The FDA's Assessment:

The FDA agrees that key secondary endpoint results are supportive of the primary analysis. Investigator-assessed PFS has acceptable concordance with the blinded independent review. Confirmed overall response rate (ORR) assessed by blinded independent review per RECIST 1.1 was evaluated in the response evaluable population (i.e., only those randomized subjects who had measurable disease at baseline). There were 7 complete and 51 partial responses in the margetuximab arm and there were 4 complete and 38 partial responses in the trastuzumab arm. The ORR was 22.1% with 95% CI (17.11-27.16) in the margetuximab arm and 16% with

95% CI (11.59-20.47) in the trastuzumab arm. Fifteen subjects in the margetuximab arm were not evaluable, 5 were not available and 14 subjects in the trastuzumab arm were not available and 13 were not evaluable. This slight discrepancy in the number of subjects with 'not available' tumor status is not likely to impact the overall conclusion that response rate is fairly similar in both treatment arms, with may be couple of percentage points improvement in the margetuximab arm. However, observed improvement in investigator assessed PFS and ORR are not conclusive because these endpoints are below OS in testing hierarchy, which has not reached the statistical significance. Therefore, all the reported p-values associated with secondary endpoints should be considered nominal only.

### **Dose/Dose Response**

#### The Applicant's Position:

**Section 6** discusses exposure-response data.

#### The FDA's Assessment:

Refer to Section 6.3.2.3 of the assessment aid for an assessment of dose response.

### **Durability of Response**

#### Data:

As of the 10-Oct-2018 cutoff date for the Study 04 CSR, independently assessed ORR was higher for the margetuximab group at 22.1% (95% CI: 17.11, 27.16) versus 16.0% (95% CI: 11.59, 20.47) for the trastuzumab group (2-sided nominal p = 0.0597 from stratified Mantel-Haenszel test). Median DoR for responding subjects was similar for the 2 groups (M: 6.1 months; T: 6.0 months).

#### The Applicant's Position:

Study 01 provides supportive evidence that single-agent margetuximab is durably active in HER2+ advanced breast cancer after prior anti-HER2 therapy (**Section 8.1.3**).

#### The FDA's Assessment:

The FDA agrees that the median duration of response with margetuximab plus chemotherapy is 6.1 months with 95% CI (4.1, 0.1), which is similar to the duration of response with trastuzumab plus chemotherapy treatment ( 6.0 months with 95% CI [4.0, 6.9]). The comparative advantage in ORR for patients on margetuximab over trastuzumab treatment is inconclusive. As indicated by the Applicant, the reported p-value should be considered nominal.

### **Persistence of Effect**

#### Data:

No long-term efficacy data are available for margetuximab in combination with chemotherapy at the time of this application, with the exception of those presented in the preceding sections.

The Applicant's Position:

In Study 04, currently ongoing, subjects were followed for a median 16.2 months (10-Sep-2019 cutoff; **Study 04 CSR Addendum 1 – Table 14.2.1.2**). Primary PFS data (10-Oct-2018 cutoff) demonstrated margetuximab benefit over trastuzumab. OS at a later data cutoff (after 270 deaths; 10-Sep-2019) nominally favor margetuximab, although these OS data remain immature and are not statistically significant.

In 355 subjects that received margetuximab study therapy, no treatment-emergent neutralizing antibodies have yet been detected. ADA newly developed after margetuximab in 4 (1.5%) of 264 margetuximab recipients in Study 04. No conclusions can be drawn regarding potential effects of neutralizing antibodies on effectiveness of margetuximab therapy.

Translational analysis of blood samples from subjects on Study 01 demonstrated that margetuximab activates HER2-specific B-cell antibody and T-cell mediated cellular immune responses (**Study 01 TCR Report** and **HER2 Immunity Report**). In 3 instances, immune responses were durable for at least 4 years, coincident with clinical stability on single-agent margetuximab (see **Section 8.1.3**). These data indicate potential for long term benefit from margetuximab.

The FDA's Assessment:

There is insufficient data to assess the long-term efficacy of margetuximab.

**Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints**

The Applicant's Position:

Patient-reported outcomes (PRO) are discussed in **Section 8.2.6**. The Applicant is not seeking to include PRO data in proposed labeling.

The FDA's Assessment:

Refer to Section 8.2.6 for details of FDA's review of COA endpoints.

**Additional Analyses Conducted on the Individual Trial**

The Applicant's Position:

No additional efficacy analyses were conducted.

The FDA's Assessment:

Two post-hoc analyses were conducted, one by the applicant per the FDA's request and the other by the FDA. The noteworthy issues were:

1. The FDA noted a modest median PFS benefit with margetuximab which is less than the imaging assessment frequency. The FDA requested the Applicant to conduct interval censored analysis to explore robustness of the primary analysis result. The Applicant conducted interval censored analysis of PFS by BIRC. In this analysis the stratified HR was 0.73 (0.57, 0.94) and median PFS was 5.6 months (5.5, 5.8) and 4.4 months (3.5, 4.8) for the margetuximab and trastuzumab treatment arms, respectively. These results were close to the investigator assessed PFS.
2. The FDA noted inconsistent results in subgroup of subjects with a CD16A-158V/V genotype. From a mechanistic standpoint margetuximab treatment is expected to exhibit similar or better treatment effect compared to trastuzumab. However, PFS and OS results from Study 04 are suggestive of unfavorable outcome with margetuximab treatment in the subgroup of patients with CD16A-158V/V genotype. The FDA conducted post-hoc analyses of PFS by BIRC (data-cutoff date: October 10, 2018) and OS (data-cutoff date: September 10, 2019) within this subgroup of subjects (n=69). The purpose was to explore imbalance in prognostic factors that may explain observed inconsistency between the findings in the ITT population and this subgroup of subjects. To this end, the FDA performed Cox PH regression analyses adjusting for age, ECOG performance status (0 vs. 1), lines of prior therapy in metastatic setting ( $\leq 2$  vs.  $> 2$ ) and metastasis sites at study entry (Lymph Node, Lung, Liver, and Brain). Based on these analyses, factors included in the analysis do not appear to completely account for better performance of trastuzumab in CD16A-158V/V genotype subgroup. These post-hoc analysis results do not provide confirmatory evidence that imbalance in prognostic factors account for the observed inconsistency in PFS and OS between the ITT and subgroup population. Further studies are needed to validate these inconsistent results in this important genotype subgroup.
3. Additional information pertinent to CD16A genotype and patient outcome from clinical trials that correlate CD16A genotype with trial efficacy endpoints to further characterize the clinical benefit of margetuximab will be provided as part of an agreed upon PMC.

### 8.1.3. Supportive Study for Efficacy: CP-MGAH22-01 (Study 01)

#### Data:

#### **Overview of Study Design**

Study 01 was an open label, multidose, single-arm, multicenter, Phase 1 dose escalation study to evaluate safety, including toxicity and MTD, PK, immunogenicity, pharmacodynamics, and antitumor activity of margetuximab in subjects with pretreated HER2+ overexpressing carcinomas for whom no standard therapy is available (**Table 7**). Three sequential segments evaluated 2 margetuximab dosing regimens, including once weekly (QW) and every 3 week (Q3W) administration. Weekly dose levels were 0.1, 0.3, 1.0, 3.0, and 6.0 mg/kg. Q3W dose

levels were 10.0, 15.0, and 18.0 mg/kg. For each regimen, margetuximab was given IV as a 120-minute infusion until disease progression, death, withdrawal of consent, Investigator or subject request.

### Study Population

Study 01 was in subjects with HER2+ carcinomas of diverse histology. Of 66 subjects enrolled, 43 subjects (65.2%) had HER2 status of IHC 3+ or IHC 2+, FISH amplified. Among 27 subjects with breast cancer, 23 were IHC 3+, 2 were FISH amplified, and 2 were neither IHC 3+ nor FISH amplified. Subjects received a median of 3 prior chemotherapy regimens. Of 27 subjects with breast cancer, 26 received prior trastuzumab. Of 20 subjects that received margetuximab monotherapy at 15 mg/kg Q3W, 12 had breast cancer.

### Antitumor Response Results

Study 01 best response of CR or PR was observed in 7/60 evaluable subjects (11.7%) receiving single-agent margetuximab study therapy, including 4 (16.7%) PRs among 24 evaluable subjects with breast cancer. CR, PR, or SD was observed in 38 subjects (63.3%), in 14/19 subjects (73.7%) at the 15 mg/kg Q3W dose level, and in 19/24 evaluable subjects (79.2%) with breast cancer (**Study 01 CSR – Table 14** and **Table 15**). Five of 60 evaluable subjects were stopped at Day 43 based on lack of radiographic response (PR or CR) or SD with  $\geq 25\%$  decrease in an elevated baseline tumor marker (**Study 01 CSR – Listing 16.2.1-1**). For 27 subjects with advanced breast cancer, median PFS was 18.1 weeks (4.2 months) and median OS was 89 weeks (20.5 months). No analysis of PFS or OS by margetuximab dose level was performed.

In summary, the ORR was 16.7%. Three patients, including 2 responders, continued single-agent margetuximab after at least 4.6, 5.2, and 5.8 years on study therapy, as of 23-Feb-2019 (**Study 01 CSR Addendum**).

#### The Applicant's Position:

The Study 01 population includes 27 subjects with pretreated HER2+ breast cancer that received margetuximab monotherapy. With this small number of subjects with breast cancer, response rate estimates are imprecise. Yet the progressive nature of advanced HER2+ breast cancer, extent of prior therapy, and Study 01 margetuximab monotherapy mean that any durable clinical responses on this trial are notable. As of 23-Feb-2019, 3 subjects continued Q3W margetuximab study therapy. Their cumulative exposure days (years) at that time were 1,696 (4.6), 1,920 (5.3), and 2,144 (5.9). These data provide proof of concept for margetuximab.

#### 8.1.4. Integrated Review of Effectiveness

#### The FDA's Assessment:

The FDA agrees that margetuximab plus chemotherapy led to a statistically significant benefit over trastuzumab plus chemotherapy. Although, the improvement in median PFS is modest with margetuximab plus chemotherapy over the trastuzumab plus chemotherapy, the latter treatment regimen is an active control and margetuximab replaces (does not add on) to trastuzumab. Trastuzumab plus chemotherapy treatment effect is included in guideline recommendations such as ASCO, NCCN and ESMO and is likely better than placebo.

The FDA agrees with the applicant's description of OS results and emphasizes that the OS data is immature for definitive conclusion. The efficacy results from Study 04 are supported by two key secondary endpoints: PFS per investigator assessment and ORR. These endpoints are lower in hierarchy from OS. Therefore, FDA considers results from these secondary endpoints to be exploratory and non-conclusive. Pre-specified subgroups (including CD16A genotype) without alpha allocation are also considered exploratory only. Additional, considerations and the FDA's summary of efficacy are addressed in detail in Section 8.1.6.

#### 8.1.5. Assessment of Efficacy Across Trials

##### The Applicant's Position:

Not applicable. Study 04 provides primary evidence of efficacy for this application (**Section 8.1.1**). Study 01 was submitted as a supportive study (**Section 8.1.3**) and includes 27 subjects with pretreated HER2+ breast cancer that received margetuximab monotherapy. As of 23-Feb-2019, 3 long-term (at least 4 years) clinical responders among 27 subjects with pretreated HER2+ MBC continued single-agent margetuximab. These 3 long-term responders indicate that single-agent margetuximab is clinically active in the intended indication.

##### The FDA's Assessment:

The FDA agrees that the assessment of efficacy across trials is not applicable because the application is supported by a single study.

#### Additional Efficacy Considerations

##### The FDA's Assessment:

Not applicable.

#### 8.1.6. Integrated Assessment of Effectiveness

##### The Applicant's Position:

Evidence of margetuximab plus chemotherapy efficacy in MBC is derived from a single adequate and well-controlled clinical trial. Study 04 was a multicenter, multinational, randomized study. The first sequential primary endpoint was independently assessed PFS,

independently assessed by blinded, third party review. This study enrolled a pretreated population representative of real-world patients with unmet medical need.

Study 04 showed the following benefits:

- Margetuximab plus chemotherapy led to a statistically significant, clinically meaningful PFS benefit over trastuzumab plus chemotherapy, with a 24% reduction in the risk of progression (stratified HR: 0.76; 95% CI: 0.593, 0.979; p = 0.0334). Estimated median PFS on margetuximab was 5.8 months compared to 4.9 months on trastuzumab. Sensitivity analyses support statistical robustness of this result.
- Investigator-assessed PFS, the top secondary endpoint, complemented primary PFS with 29% risk reduction. In addition, Investigator-assessed PFS increased in significance from 10-Oct-2018 (stratified HR: 0.70; 95% CI: 0.556, 0.870; nominal p = 0.0014) to 10-Sep-2019 (stratified HR: 0.71; 95% CI: 0.580, 0.862; p = 0.0006).
- The response-based endpoint ORR provides additional supportive clinical evidence of benefit of margetuximab over trastuzumab (M: 22.1% [95% CI: 17.11, 27.16] vs T: 16.0% [95% CI: 11.59, 20.47]; nominal p = 0.0597).
- In the second interim OS analysis after 270 deaths (70% of target OS events), median OS was 21.6 months on margetuximab vs 19.8 months on trastuzumab (p = 0.3264). Although these data remain immature, the OS trend favoring margetuximab has developed from a 5% risk reduction (stratified HR: 0.95; 95% CI: 0.691, 1.309; p = 0.7584) to an 11% risk reduction (stratified HR: 0.89; 95% CI: 0.693, 1.130; p = 0.3264).
- Margetuximab benefit was observed broadly across prespecified subgroups, including backbone chemotherapy, prior anti-HER2-directed therapies, HER2 and hormone receptor status, and presence of MBC at diagnosis.
- Exploratory analysis of independently assessed PFS by CD16A genotype suggests that margetuximab has greatest benefit over trastuzumab for subjects with CD16A-158F (V/F or F/F) genotypes (HR: 0.68; 95% CI: 0.523, 0.895). CD16A-158F carriers comprise about 85% of the treated population (**Table 1**). A similar trend was observed for OS results. Trastuzumab recipients may have a diminished clinical response in patients carrying low-affinity F alleles (**11, 34**).

Study 04 demonstrated statistically significant, clinically meaningful PFS benefit of margetuximab over active comparator trastuzumab in pretreated patients with HER2+ MBC.

Clinical benefit was observed despite progression on 2 prior anti-HER2 agents. In this setting, unmet medical need persists.

Phase 1 Study 01 (monotherapy setting) provides supportive evidence of efficacy based on response rate, including 3 non-progressing subjects with MBC who appear still to be deriving benefit from margetuximab after over 4 years of therapy.

**The FDA's Assessment:**

This application is primarily supported by results from Study-04 (SOPHIA), a multicenter, multinational, randomized comparing margetuximab plus chemotherapy (n=262) to trastuzumab plus chemotherapy (N=262) in patients with advanced, HER2+ metastatic breast cancer who had received at least one prior lines of therapy, which demonstrated a statistically significant improvement in PFS (HR: 0.76; 95% CI: 0.593, 0.979; p = 0.0334). Estimated median PFS on the margetuximab plus chemotherapy arm was 5.8 months compared to 4.9 months on trastuzumab plus chemotherapy arm as assessed by BICR per RECIST 1.1. The unstratified cox analysis result of PFS was consistent with the stratified primary analysis (PFS HR: 0.78; 95% CI: 0.61, 0.99). Sensitivity analyses demonstrated the robustness of the primary PFS results while subgroup analyses demonstrated the consistency of the results across various prespecified subgroups except for the CD16A-V/V genotype. The PFS results were further supported by a clinically meaningful confirmed ORR of 22.1% (95% CI: 17.1-27.2) in the margetuximab plus chemotherapy arm with a median DOR of 6.1 months (95% CI: 4.1-9.1 months). The ORR was 16% (95% CI: 11.6-20.5) in the trastuzumab plus chemotherapy arm with median DOR of 6.0 months (95% CI: 4.0-6.9). Investigator-assessed PFS is also supportive of the primary analysis results. These results represent a slight improvement over trastuzumab plus chemotherapy treatment. Of note, trastuzumab plus chemotherapy is active in this disease setting and provides a meaningful benefit over placebo.

Although, immature at the time of this BLA submission (70% of targeted OS events), the OS result in the ITT population is trending favorably toward the margetuximab treatment arm; HR = 0.95 (0.69, 1.31) in the first interim analysis and HR = 0.88 (0.71, 1.13) in the second interim analysis. Further demonstration of non-detrimental effect on OS with margetuximab treatment from the planned final analysis will be needed to confirm that there is no detriment to overall survival with margetuximab plus chemotherapy.

Margetuximab treatment effect in subgroups of patients defined by Fc-gamma receptor genotypes are of special interest because margetuximab was specifically Fc-engineered to enhance affinity to these genotypes. Study 04 results by this genotype suggest that patients with a CD16A-158F genotype treated with margetuximab plus chemotherapy has improved PFS and OS compared to those treated with trastuzumab plus chemotherapy. However, patients with a CD16A-158V/V homozygote genotype treated with margetuximab plus chemotherapy

showed a detriment in both PFS and OS compared to those treated with trastuzumab plus chemotherapy. These subgroup results must be interpreted with caution because sample sizes for CD16A-158V/V subgroup is small (13% of the entire study population), balance in baseline characteristics is not assured due to a lack of stratification by this factor, and mechanistic basis for this anomalous finding is unclear. Additional CD16A F158V genotyping and patient outcome data from ongoing margetuximab clinical studies may help to further understand and characterize the possible impact of CD16A genotype on the clinical benefit of margetuximab.

Overall, given the similar efficacy observed between margetuximab plus chemotherapy and trastuzumab plus chemotherapy in Study 04, treatment with margetuximab 15 mg/kg Q3W by IV infusion plus chemotherapy will provide an additional treatment option for patients previously treated with HER2+ metastatic breast cancer.

## 8.2. Review of Safety

### The Applicant's Position:

This safety evaluation is based on data from 355 subjects treated in 3 clinical studies (Studies 04, 01, and 02). Each study enrolled distinct populations (**Table 7**). The primary focus is data from Study 04, a randomized, open-label, active-controlled Phase 3 study in subjects with pretreated HER2+ metastatic breast cancer. The Study 04 Safety Population comprises 264 subjects that received margetuximab plus chemotherapy and 266 that received trastuzumab plus chemotherapy. Data from 355 subjects treated with various dose levels of margetuximab in Studies 04, 01, 02 are assessed in a pooled analysis.

The Study 04 Infusion Substudy provides data for 88 margetuximab-treated subjects to support safety and tolerability of 30-minute infusions from Cycle 2 onwards (**Section 8.2.8**). Note that Infusion Substudy subjects were not included in pooled analyses.

See **Section 7** for a summary of data used in the safety analysis. Study 04 in pooled analysis is from the 10-Oct-2018 data cutoff for primary PFS analysis. A second data cutoff performed on 10-Apr-2019 provides updated safety data in Study 04 CSR Addendum 1 but is not included in pooled analysis.

Data from these studies allow for a comprehensive and adequate assessment of the margetuximab safety profile and evaluation of its overall benefit-risk in the intended patient population. The safety population of Study 04 is considered adequate for detection and characterization of common AEs and to provide guidance on toxicity management.

### The FDA's Assessment:

The FDA agrees with the Applicant that the safety population of Study 04 is adequate for both

detection and characterization of common AEs and for providing guidance on toxicity management.

The FDA review of safety is based primarily on data from Study 04. Although the FDA also reviewed the pooled safety analysis that included data from Study 01, a phase 1 dose ranging study of margetuximab in subjects with pretreated HER2+ carcinomas had breast cancer, and Study 02, a phase 2 study investigating margetuximab in subjects with HER2 low expressing advanced breast cancer. The pooled analysis did not meaningfully augment the safety information from Study 04 due to the relatively small contribution and disparate information from these other studies.

### 8.2.1. Safety Review Approach

#### Data:

Safety data for Study 04 alone and from pooled safety analyses are in the BLA submission. The proposed product label contains safety data from Study 04 only. Pooled data do not appreciably add to margetuximab safety information for 2 reasons: 1) Study 01 and Study 02 provide a relatively small amount of safety data; and 2) Study 01 and Study 02 patients received margetuximab monotherapy, which is not the treatment regimen proposed in this submission.

Supplemental analysis of Study 04 safety data to a 10-Apr-2019 data cutoff date confirm consistency of margetuximab safety over a longer treatment duration. Furthermore, safety data from the Study 04 Infusion Substudy support safety and tolerability of 30-minute infusion duration from Cycle 2 onwards.

Characteristic safety-related issues for therapeutic antibodies include IRRs, hypersensitivity reactions/anaphylaxis, and neutralizing ADA antibody development. Labelled warnings and precautions for approved US-approved anti-HER2-directed are in **Table 3**. Labelled warnings and precautions for backbone chemotherapy regimens administered in Study 04 (capecitabine, eribulin, gemcitabine, or vinorelbine) are in the Clinical Overview (**BLA – Table 2.5-9**). Study 04 specified adverse events of special interest (AESI) to be: Common Terminology Criteria for Adverse Events (CTCAE) Grade  $\geq$  3 IRR or cytokine release syndrome (CRS), and left ventricular dysfunction leading to dose delay or discontinuation.

Pooled safety analyses included data from Study 04, Study 01, and Study 02 and were performed only for margetuximab-treated subjects (see **ISS SAP**). The safety evaluation included all subjects who received any dose of margetuximab in Study 01 and Study 02, or any dose of margetuximab or chemotherapy in the margetuximab plus chemotherapy group of the randomized portion of Study 04. Standardized Medical Dictionary for Regulatory Activities

(MedDRA) queries (SMQs) were used to seek other potential safety signals in pooled safety analyses (**ISS SAP – Section 3.7**).

#### The Applicant's Position:

Available data support use of margetuximab in combination with chemotherapy for treatment of patients with metastatic HER2-positive breast cancer after prior HER2-targeted therapy. Margetuximab has acceptable safety that is consistent across studies and comparable to that of trastuzumab in Study 04. Most common Study 04 AEs on margetuximab were fatigue, nausea, neutropenia/neutrophil count decreased, and diarrhea. Backbone chemotherapy did not appear to influence the margetuximab safety profile.

#### The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment that safety data from Study 04 support the use of margetuximab plus chemotherapy for patients with previously treated HER2+ metastatic breast cancer. FDA also agrees that choice of chemotherapy did not significantly alter margetuximab's safety profile, especially in instances where toxicities clearly attributable to chemotherapy can be delineated.

The FDA's primary analysis of safety is based on 530 patients enrolled on Study 04 who received at least one dose of study treatment. These included a total of 264 patients on the margetuximab arm and 266 patients on the trastuzumab arm with a data cut off date of October 10, 2018. The Applicant provided a 120-day safety update with a data cut-off date of April 10, 2019 which did not identify any new safety signals or significantly different toxicity profile from the previously reported safety analysis.

FDA's safety analysis focused on deaths, treatment-emergent adverse events (TEAEs) including serious TEAEs, TEAEs leading to study drug discontinuation or interruption, and AEs of special interest (AESIs). Based on the known toxicities of antibody-based HER2/neu receptor antagonists, the Applicant-identified grade  $\geq 3$  IRR or cytokine release syndrome (CRS), and left ventricular dysfunction leading to dose delay or discontinuation as AESIs for Study 04

The infusion substudy of Study 04, which evaluated safety and tolerability of sequential reductions in margetuximab infusion duration among the 88 patients enrolled, provide support for shorter infusion duration from 120 minutes to 30 minutes for patients who tolerate their initial margetuximab treatment. FDA agrees that overall, the shorter infusion duration did not significantly alter the toxicity profile of margetuximab, including IRR's, from those observed in the main study.

### 8.2.2. Review of the Safety Database

## Overall Exposure

### Data:

In pooled safety analysis (Study 04, 01, and 02), 355 subjects received treatment with margetuximab (any dose, any tumor type), not including the Study 04 Infusion Substudy group. Of 295 subjects in pooled safety analysis that received the margetuximab 15 mg/kg Q3W regimen, 264 were from Study 04; 20 were from Study 01, and 11 were from Study 02 (**BLA – Section 2.7.4.1.2.1.1**).

As of 10-Oct-2018, Study 04 median (range) number of cycles was 6.0 (1-34) on margetuximab and 5.0 (1-37) on trastuzumab (**Table 19**). At that time, 137 subjects (25.6%) remained on study therapy (M: 79 [29.7%]; T: 58 [21.5%]). As of the 10-Apr-2019 data cutoff, 57 subjects (10.6%) remained on study therapy (M: 37 [13.9%]; T: 20 [7.4%]; **Study 04 CSR Addendum 1 – Table 2**).

**Table 19: Subject Exposure (Safety Population; Data Cutoff 10-Oct-2018)**

|                                                                                    | Margetuximab plus<br>Chemotherapy<br>(N = 264) | Trastuzumab plus<br>Chemotherapy<br>(N = 265) |
|------------------------------------------------------------------------------------|------------------------------------------------|-----------------------------------------------|
| <b>Total Number of 21-Day Cycles of Margetuximab/Trastuzumab Received</b>          |                                                |                                               |
| n                                                                                  | 262                                            | 265                                           |
| Mean (SD)                                                                          | 7.6 (5.9)                                      | 6.5 (5.2)                                     |
| Median                                                                             | 6.0                                            | 5.0                                           |
| Min - Max                                                                          | 1 - 34                                         | 1 - 37                                        |
| <b>Actual Total Dose (mg)</b>                                                      |                                                |                                               |
| n                                                                                  | 262                                            | 265                                           |
| Mean (SD)                                                                          | 7655.6 (6115.2)                                | 2687.5 (2127.6)                               |
| Median                                                                             | 5880.0                                         | 2048.0                                        |
| Min - Max                                                                          | 465.0 - 42058.0                                | 384.0 - 12552.0                               |
| <b>Chemotherapy<br/>Total Number of 21-Day Cycles of<br/>Chemotherapy Received</b> |                                                |                                               |
| n                                                                                  | 264                                            | 265                                           |
| Mean (SD)                                                                          | 7.0 (5.6)                                      | 6.1 (5.0)                                     |
| Median                                                                             | 6.0                                            | 5.0                                           |
| Min - Max                                                                          | 1 - 34                                         | 1 - 37                                        |

Source: ADEX dataset; **Study 04 CSR - Table 14.1.17** and **Table 14.1.18**

### The Applicant's Position:

The exposure to study drug was considered adequate to allow for a comprehensive assessment of safety in subjects who were representative of the intended target population.

### The FDA's Assessment:

The FDA agrees with the Applicant's assessment of durations of exposure as presented in Table 19.

### Relevant characteristics of the safety population:

#### Data:

Baseline characteristics for margetuximab recipients are summarized by dose for Study 04, Study 01, and Study 02, as well as for 15 mg/kg Q3W, all other doses, and for all doses across studies in **BLA – Table 2.7.4-12**. Pooled characteristics are similar to those of Study 04.

Baseline demographic characteristics for randomized subjects are described in **Section 8.1.2** and are summarized by treatment group in **Table 12**. Treatment groups had balanced demographics and baseline characteristics. Most subjects were female, White, and not Hispanic or Latino, with a median age of 56 years.

Subjects in Study 04 received at least 2 prior anti-HER2-directed therapies, including pertuzumab. All 536 ITT subjects had HER2 status of IHC 3+ or HER2 gene amplification by in situ hybridization (ISH). About half received prior adjuvant therapy, and over 90% received at least 2 prior regimens of therapy for metastatic disease (**Table 15**). All received prior trastuzumab, and all but one (assigned to trastuzumab) had prior pertuzumab. Of 536 subjects, 91% received prior T-DM1.

#### The Applicant's Position:

Study 04 eligibility criteria were clinically relevant for the target population of subjects that will receive margetuximab in the proposed indication after regulatory approval. The Study 04 subject population in Study 04 was a clearly defined and homogenous population of pretreated subjects with HER2-positive metastatic breast cancer. Demographic and baseline characteristics were balanced across treatment groups. The study population was generally representative of the broad population of patients with HER2-positive metastatic breast cancer seen in medical practice who had received at least 2 prior anti-HER2 therapies.

#### The FDA's Assessment:

FDA agrees with the demographic and baseline disease characteristics tables the Applicant has presented in Section 8.1.2, and that the two treatment arms of Study 04 were relatively well-balanced. FDA has the following additions/clarifications:

1. Of the 536 patients in Study 04, approximately 20% were ≥65 years of age; however, only 4% accounted for patients that were ≥75 years of age.
2. Male patients were also eligible for Study 04; as expected, a very small number of male patients (3 total) were enrolled, all were randomized to the trastuzumab arm.
3. Racial minorities were under represented in Study 04: Asians had the largest representation (~6%) followed closely by Black/African American (~5%). The higher

participation of Asians is likely a result of enrollment from Asian countries rather than of minorities from non-Asian sites.

4. Study 04 was predominantly comprised of patients with metastatic disease at study entry (~98%); a small minority had locally advanced, unresectable disease.
5. The most common site of metastasis is the bone (~58%), while the lung (~47%) followed by liver (~35%) are the most common sites of visceral metastasis at study entry. Approximately 13% of patients in Study 04 had treated and stable metastasis to the brain at study entry.
6. More than half of the patients (~62%) had tumors that were also hormone receptor positive; only 2 patients in Study 04 had unknown hormone receptor status.
7. Majority of the patients had prior treatment with the three most commonly used antibody-based HER2 receptor antagonists: trastuzumab (100%), pertuzumab (99.8%) and T-DM1 (~91%).
8. Vinorelbine was the most common physician choice chemotherapy to combine with either margetuximab or trastuzumab (~36%), followed by capecitabine and eribulin (~27% and 25%, respectively).

FDA agrees with the Applicant's assessment that the population characteristics of the 536 patients enrolled in Study 04 were generally representative of a US population for the intended indication.

### **Adequacy of the safety database:**

#### Data:

The Study 04 Safety Population consisted of all subjects who were randomized and received any amount of any study therapy, including 264 subjects in the margetuximab group and 266 subjects in the trastuzumab group. These subjects comprised the primary focus of the safety review.

Pooled safety analysis (Study 04, 01, and 02) included 355 subjects who received treatment with margetuximab (any dose, any tumor type). Of 295 subjects in pooled safety analysis that received margetuximab 15 mg/kg Q3W, 264 were from Study 04, 20 were from Study 01, and 11 were from Study 02.

#### The Applicant's Position:

The safety database was considered adequate to evaluate safety of margetuximab in the intended population at the target dose. By the statistical rule of three (13), 264 Study 04 margetuximab recipients suffice to detect uncommon adverse reactions occurring at an incidence of at least 1.1%.

#### The FDA's Assessment:

FDA agrees that the safety database is adequate to evaluate the safety profile of margetuximab.

### 8.2.3. Adequacy of Applicant's Clinical Safety Assessments

#### Issues Regarding Data Integrity and Submission Quality

##### The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were identified during investigator site audits conducted for margetuximab studies included in the submission; data in CRFs and AE databases were consistent.

##### The FDA's Assessment:

FDA agrees with the Applicant's assessment of data integrity and submission quality based on our own review and clinical inspections from the Office of Scientific Investigations (OSI). Please see Section 4.1 for additional information.

#### Categorization of Adverse Events

##### Data:

All AE summaries and analyses are for treatment-emergent AEs (TEAEs). TEAEs began or worsened on or after first study drug through an End of Treatment Visit or 28 days after last study treatment. AEs were coded to preferred terms of MedDRA version 21.1. CTCAE v4.03 was used for severity grading.

##### The Applicant's Position:

Categorization of AEs was appropriate for safety data evaluation.

##### The FDA's Assessment:

FDA agrees with the Applicant's categorization of adverse events (AEs) in Study 04.

#### Routine Clinical Tests

##### The Applicant's Position:

**Table 8** presents the Study 04 schedule of clinical assessments. Frequency and selection of clinical assessments is adequate for expected toxicities associated with margetuximab.

##### The FDA's Assessment:

FDA agrees with the Applicant's assessment.

### 8.2.4. Safety Results

## Deaths

### Data:

In Study 04, similar proportions on margetuximab (38.6%) and trastuzumab (43.6%) died, as expected for subjects with advanced cancer (**Table 20**). Most deaths were attributed to disease progression. Few subjects had fatal AEs: 3 (1.1%) on margetuximab and 2 (0.8%) on trastuzumab. These included 3 events of viral pneumonia (2 on margetuximab, 1 on trastuzumab), 1 aspiration pneumonia (margetuximab), and 1 acute kidney injury (trastuzumab). None of the fatal AEs were considered related to study therapy.

In Study 04, 9 subjects (3.4%) in each treatment group died within 30 days after last dose of margetuximab (**Table 20**). In margetuximab recipients, primary cause of death was disease progression (2.3%) and unrelated AEs (1.1%).

In pooled analyses, 2.3% of subjects in Study 04, Study 01, and Study 02 died within 30 days after last dose of margetuximab (**ISS – Table 2.7**). Primary cause of death was disease progression for 5 subjects (1.4%), unrelated AEs for 2 subjects (0.6%), and other reasons (acute renal failure) for 1 subject (0.3%). No deaths in Study 01 or Study 02 were due to AEs.

**Table 20: Summary of Deaths (Safety Population; Data Cutoff 10-Apr-2019)**

|                                                         | Margetuximab plus<br>Chemotherapy<br>(N = 264)<br>n (%) | Trastuzumab plus<br>Chemotherapy<br>(N = 266)<br>n (%) |
|---------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------|
| <b>Any Death</b>                                        | 102 (38.6)                                              | 116 (43.6)                                             |
| Reason: Disease progression                             | 87 (33.0)                                               | 102 (38.3)                                             |
| Reason: Adverse event                                   | 3 (1.1)                                                 | 2 (0.8)                                                |
| Reason: Other                                           | 12 (4.5)                                                | 12 (4.5)                                               |
| Acute respiratory distress syndrome                     | 0                                                       | 1 (0.4)                                                |
| Clinical deterioration/worsening of clinical conditions | 1 (0.4)                                                 | 2 (0.8)                                                |
| Complication new cancer therapy                         | 1 (0.4)                                                 | 0                                                      |
| Intestinal occlusion                                    | 0                                                       | 1 (0.4)                                                |
| Leukemia                                                | 0                                                       | 1 (0.4)                                                |
| Pleural effusion                                        | 1 (0.4)                                                 | 0                                                      |
| Pulmonary emboli or cerebral infarct                    | 0                                                       | 1 (0.4)                                                |
| Total failure of the organism                           | 0                                                       | 1 (0.4)                                                |
| Unknown/not specified                                   | 9 (3.4)                                                 | 5 (1.9)                                                |
| <b>Death Within 30 Days of First Study Dose</b>         | 2 (0.8)                                                 | 1 (0.4)                                                |
| <b>Death Within 30 Days after Last Study Dose</b>       | 9 (3.4)                                                 | 9 (3.4)                                                |
| Reason: Disease progression                             | 6 (2.3)                                                 | 6 (2.3)                                                |
| Reason: Adverse event                                   | 3 (1.1)                                                 | 2 (0.8)                                                |
| Reason: Unknown/not specified                           | 0                                                       | 1 (0.4)                                                |

Source: ADSL dataset

The Applicant's Position:

A review of deaths in Study 04 and across studies did not identify any pattern. Most subjects who died had underlying contributing comorbidities and complications associated with their disease. Most deaths were due to disease progression.

The FDA's Assessment:

The FDA generally agrees with Table 20 outlining the summary of deaths in the Study 04.

FDA performed an independent analysis of deaths in the Study 04 safety population. Approximately 41% of the safety population in Study 04 have died; ~87% of these 218 deaths are from disease progression. Few deaths were due to TEAEs.

FDA reviewed all death narratives submitted by the Applicant. A summary of all deaths potentially due to TEAEs are described below, listed by treatment arm.

Margetuximab arm:

- **Subject** (b) (6): This is a 44-year-old female who had 3 prior lines of therapy for metastatic HER2+ breast cancer. Her last dose of study drug, was administered on day 21 for margetuximab and on day 28 for vinorelbine. On day 43 (or 21 days from the last margetuximab dose), the subject died due to disease progression. An autopsy was not performed. The Investigator considered the event of death not-related to margetuximab or vinorelbine. FDA agrees that the patient's death was unlikely related to study medication; however, there is insufficient information to completely rule this out.
- **Subject** (b) (6): This is a 41-year-old female who had 2 prior lines of therapy for metastatic HR2+ breast cancer. On day 20 (19 days from the last margetuximab dose), she died of disease progression. An autopsy was not performed. The Investigator considered the event as not related to margetuximab and vinorelbine. Although it is likely that she died from metastatic disease, the FDA assigns her cause of death as unknown as there is insufficient information to rule out a relationship to study medication.
- **Subject** (b) (6): This is a 77-year-old female who had 3 prior lines of therapy, but only 2 contained anti-HER2 directed agent(s). On day 534 (18 days from most recent study dose), the patient was hospitalized with pneumonia (an SAE). She was afebrile at that time but required 35% oxygen by venti-mask. She was noted to be cachectic. On day 537, CT angiography showed extensive bilateral lung infection. She died on day 539 due to pneumonia. An autopsy was not performed. The Investigator and the Applicant considered the pneumonia unrelated to margetuximab or gemcitabine. FDA agrees with this assessment.
- **Subject** (b) (6): This is a 47-year-old female who had 3 prior lines of therapy for metastatic HER2+ breast cancer. On day 65, margetuximab was discontinued due to progressive disease per RECIST, and she died on day 91 (26 days from most recent dose)

due to disease progression. An autopsy was not performed. At the time of her death, the patient was experiencing dizziness and nausea and had ongoing abnormalities of increased alanine aminotransferase, alkaline phosphatase, bilirubin. The Investigator considered the patient's death as not related to margetuximab and vinorelbine. FDA agrees with this assessment.

- **Subject** (b) (6): This is a 71-year-old female who had 2 prior lines of therapy for metastatic HER2+ breast cancer. On day 20 (19 days from last recent study dose), the subject seen in clinic due to diarrhea, fatigue, nausea, and vomiting. She was hospitalized for observation. On the same day, the patient experienced septic shock and acute hypoxemic respiratory failure due to aspiration pneumonia (an SAE). After initial treatment for the pneumonia, her status was changed to DNR, and all medications were discontinued. The subject died 9 days later (day 29) due to aspiration pneumonia. An autopsy was performed indicating pre-mortem blood and BAL cultures positive for *Klebsiella pneumoniae* and hemorrhagic small and large bowel mucosa with possible ischemia. The Investigator and Applicant considered the event of aspiration pneumonia as unlikely related to both margetuximab and capecitabine. FDA agrees with this assessment.

Trastuzumab arm:

- **Subject** (b) (6): This is an 86-year-old female who had 2 prior lines of therapy for metastatic HER2+ breast cancer. On day 15 day, trastuzumab and capecitabine were discontinued due to stomatitis, diarrhea, and anorexia. She received her last trastuzumab and capecitabine doses on days 1 and 14, respectively. On day 22, her GI toxicities were upgraded to Grade 3, and were classified as SAEs due to hospitalization. During her hospitalization she was diagnosed with acute kidney injury. On day 24, colonoscopy showed diffuse pancolitis. The subject died on day 33 due to acute kidney injury. An autopsy was not performed. The Investigator attributed the events of gastrointestinal toxicity as well as acute kidney injury as unrelated trastuzumab and probably related to capecitabine. The FDA agrees with this assessment.
- **Subject** (b) (6): This is a 40-year-old female who had received 3 prior lines of therapy for metastatic HER2+ breast cancer, although her first -line treatment did not contain an anti-HER2 agent. On day 22 study therapy was discontinued due to non-radiological progressive disease. On day 47 (25 days from most recent study dose), she died due to disease progression. An autopsy was not performed. The Investigator considered the event of death not related to either trastuzumab or vinorelbine. The FDA agrees that the cause of death was likely due to disease progression; however, there is insufficient information to completely rule-out contribution of study medication.
- **Subject** (b) (6): This is a 49-year-old female who had 3 prior lines of therapy for metastatic HER2+ breast cancer. On day 211, trastuzumab was discontinued and on day 231 (20 days from most recent study dose), the subject died due to disease progression. An autopsy was not performed. The events of arthralgia, nausea, dyspnea, abdominal pain, paresthesia, muscular weakness, fatigue, abnormal loss of weight, constipation, and

musculoskeletal chest pain were ongoing at the time of subject's death. The Investigator considered the event of death as not related to trastuzumab and vinorelbine. FDA agrees with this assessment.

- **Subject** (b) (6): This is an 83-year-old female who had 2 prior lines of therapy for metastatic HER2+ breast cancer. On day 75 (4 days from most recent study dose), she presented with right leg swelling and erythema and was diagnosed with Grade 3 cellulitis (an SAE due to hospitalization). An ultrasound ruled out DVT. The cellulitis resolved on day 80 and she was discharged. On day 97 (5 days from most recent study dose), she was noted to have Grade 3 asthenia and was hospitalized for generalized weakness, fatigue, poor appetite and right groin pain. Inpatient, she was noted to have sacral ulcers, anemia and leukopenia. She was also diagnosed with acute kidney injury due to dehydration. While hospitalized, her metastatic disease and overall prognosis worsened. On day 102, she was transferred to hospice care. On day 105, she died due to disease progression. An autopsy was not performed. The Investigator considered cause of death unrelated to study treatment; asthenia not related to trastuzumab and probably related to gemcitabine. FDA generally agrees with these assessments, except trastuzumab's relationship to asthenia could not be completely ruled out.
- **Subject** (b) (6): This is a 67-year-old female who had 2 prior lines of therapy for metastatic HER2+ breast cancer. On day 22 (21 days from the most recent dose of trastuzumab), she was hospitalized for Grade 3 encephalopathy, presenting with altered mental status. Brain imaging showed no acute findings or intracranial metastasis. The patient had not been taking her methadone for the preceding 3 days; and the Investigator determined that the encephalopathy was related to methadone withdrawal and unrelated to study treatment. On day 24, she was discharged from the hospital, but encephalopathy did not resolve until day 30. The subject died approximately 2 months post discharge due to disease progression. It is unknown if an autopsy was performed. The Investigator considered the death not-related to both trastuzumab and capecitabine. FDA generally agrees with the cause of death but there is insufficient information to rule out any relationship to the study medication.
- **Subject** (b) (6): This is a 51-year-old female who had 3 prior lines of therapy for metastatic HER2+ breast cancer. On day 19 (18 days from most recent dose of trastuzumab), she presented with shortness of breath and chest pain and was hospitalized for Grade 3 pleural effusion (an SAE). Chest X-ray revealed a possible infectious process and CT showed bilateral pleural effusions which resolved on day 21 and she was discharged from the hospital. On day 29 (28 days from most recent dose of trastuzumab), the patient died due to an unknown cause. It is not known if an autopsy was performed. The Investigator and Sponsor considered the event of pleural effusion as well as her death to be unrelated to trastuzumab and capecitabine. FDA disagrees with this assessment; since cause of death is unknown, we cannot rule out the possibility of it being related to study medications. Furthermore, there is insufficient information to fully rule out relationship between the pleural effusion and study treatment.

- **Subject** <sup>(b) (6)</sup>: This is a 59-year-old female who had 3 prior lines of therapy for metastatic HER2+ breast cancer. On day 318 (24 days from most recent dose of trastuzumab), she was admitted to the intensive care unit for influenza pneumonia and secondary acute respiratory failure. An echocardiogram on the same day revealed pericardial tamponade. The subject died the following day from pneumonia. It is unknown if an autopsy was performed. The Investigator and the Sponsor considered the event of acute respiratory failure and pneumonia as unlikely related to trastuzumab and capecitabine. FDA agrees with this assessment.

### Serious Adverse Events

#### Data:

SAE incidence was low and similar between treatment groups (**Table 21**). Most commonly reported SAEs ( $\geq 1\%$  subjects) on margetuximab were febrile neutropenia, neutropenia/neutrophil count decreased, pneumonia, and IRR.

**Table 21: Serious Adverse Events (Regardless of Causality) in  $\geq 2$  Subjects (Safety Population; Data Cutoff 10-Apr-2019)**

| Preferred Term                                      | Margetuximab plus<br>Chemotherapy<br>(N = 264)<br>n (%) | Trastuzumab plus<br>Chemotherapy<br>(N = 266)<br>n (%) |
|-----------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------|
| Subjects with any serious TEAE                      | 43 (16.3)                                               | 49 (18.4)                                              |
| Febrile neutropenia                                 | 4 (1.5)                                                 | 10 (3.8)                                               |
| Pneumonia                                           | 4 (1.5)                                                 | 7 (2.6)                                                |
| Neutropenia/neutrophil count decreased <sup>a</sup> | 4 (1.5)                                                 | 2 (0.8)                                                |
| Infusion related reaction                           | 3 (1.1)                                                 | 0                                                      |
| Anaemia                                             | 2 (0.8)                                                 | 2 (0.8)                                                |
| Urinary tract infection                             | 2 (0.8)                                                 | 2 (0.8)                                                |
| Pleural effusion                                    | 1 (0.4)                                                 | 4 (1.5)                                                |
| Pyrexia                                             | 1 (0.4)                                                 | 3 (1.1)                                                |
| Cellulitis                                          | 1 (0.4)                                                 | 3 (1.1)                                                |
| Breast cellulitis                                   | 0                                                       | 2 (0.8)                                                |

a Preferred terms of “neutropenia” and “neutrophil count decreased” are combined for ease of review

Source: ADAE dataset; **Study 04 CSR Addendum 1 - Table 14.3.1.12**

#### The Applicant’s Position:

Observed SAEs in Study 04 were consistent with existing safety profiles of margetuximab and trastuzumab. These mainly include events of IRR and febrile neutropenia/neutrophil count decreased that can be managed by premedication, dose adjustments, and supportive strategies. IRRs and neutropenia are discussed in **Section 8.2.5**.

#### The FDA’s Assessment:

The FDA conducted an independent analysis of SAEs with an initial data cut off date of October 10, 2018 and confirmed that the April 10, 2019 data up date did not significantly change the incidence of SAEs represented in Table 21. Additionally FDA agrees with the Applicants analysis of SAEs presented in Table 21. SAEs occurred in 16% of the 264 patients in the margetuximab plus chemotherapy arm. No clinically meaningful differences in SAEs were observed between the margetuximab and trastuzumab treatment arms, except for IRRs (1.1% vs 0, respectively), febrile neutropenia (1.5% vs 3.8%, respectively) and pneumonia (1.5% vs 2.6%, respectively). SAEs that occurred in >1% of patients treated with margetuximab plus chemotherapy included febrile neutropenia, neutropenia/neutrophil count decrease, pneumonia and IRR. IRR was the only SAE of note when examined in the additional 31 patients in Study 01 and 02 treated with margetuximab (15 mg/kg Q3W) without chemotherapy.

### Dropouts and/or Discontinuations Due to Adverse Effects

#### Data:

In both groups, few subjects had AEs leading to permanent discontinuation of all study therapy (M: 3.0%; T: 2.6%; **Table 22**). Of these, the most common AE leading to discontinuation of all study therapy was left ventricular dysfunction: 3 (1.1%) margetuximab recipients and 1 (0.4%) trastuzumab recipient. One subject on margetuximab experienced an unrelated acute myocardial infarction that led to an unrelated event of left ventricular dysfunction leading to study treatment discontinuation. Two subjects discontinued margetuximab due to IRRs (**Section 8.2.5**).

**Table 22: Adverse Events Leading to Discontinuation from Whole Study Treatment (Regardless of Causality) (Safety Population; Data Cutoff 10-Apr-2019)**

| Preferred Term                                                               | Margetuximab plus<br>Chemotherapy<br>(N = 264)<br>n (%) | Trastuzumab plus<br>Chemotherapy<br>(N = 266)<br>n (%) |
|------------------------------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------|
| Subjects with any TEAE leading to Discontinuation from Whole Study Treatment | 8 (3.0)                                                 | 7 (2.6)                                                |
| Left ventricular dysfunction                                                 | 3 (1.1)                                                 | 1 (0.4)                                                |
| Colitis                                                                      | 1 (0.4)                                                 | 0                                                      |
| Gastrointestinal toxicity                                                    | 0                                                       | 1 (0.4)                                                |
| Pneumonia                                                                    | 0                                                       | 1 (0.4)                                                |
| Infusion related reaction                                                    | 1 (0.4)                                                 | 0                                                      |
| Seroma                                                                       | 1 (0.4)                                                 | 0                                                      |
| Blood bilirubin increased                                                    | 0                                                       | 1 (0.4)                                                |
| Leukaemia                                                                    | 0                                                       | 1 (0.4)                                                |
| Haemorrhage intracranial                                                     | 0                                                       | 1 (0.4)                                                |
| Hydronephrosis                                                               | 1 (0.4)                                                 | 0                                                      |
| Pleural effusion                                                             | 0                                                       | 1 (0.4)                                                |

| Preferred Term       | Margetuximab plus<br>Chemotherapy<br>(N = 264)<br>n (%) | Trastuzumab plus<br>Chemotherapy<br>(N = 266)<br>n (%) |
|----------------------|---------------------------------------------------------|--------------------------------------------------------|
| Pneumonia aspiration | 1 (0.4)                                                 | 0                                                      |

Source: ADAE dataset; **Study 04 CSR Addendum 1 - Table 14.3.1.14**

#### The Applicant's Position:

A similar proportion of subjects on margetuximab and trastuzumab experienced AEs leading to discontinuation. Observed AEs were consistent with existing safety profiles of margetuximab and trastuzumab.

#### The FDA's Assessment:

The FDA conducted an independent analysis of adverse events leading to discontinuations with an initial data cut off date of October 10, 2018 and confirmed that the April 10, 2019 data update did not significantly change the incidence of adverse events leading to discontinuations represented in Table 22. Additionally FDA agrees with the Applicants analysis of AEs leading to discontinuation presented in Table 22. Study drug discontinuations were low on Study 04, 3% on each arm. The most common TEAE leading to study drug discontinuation was left ventricular dysfunction, which caused more study drug discontinuation on the margetuximab (3 patients [1.1%]) versus the trastuzumab treatment arm (1 patient [0.4%]).

#### **Dose Interruption/Reduction Due to Adverse Effects**

##### Data:

AEs (regardless of relationship to study treatment) resulting in infusion interruption or modification of *study therapy* (margetuximab/trastuzumab) are summarized in **Study 04 CSR Addendum 1 – Table 14.3.1.16**. A greater proportion of subjects on margetuximab than trastuzumab had AEs leading to infusion interruption (M: 10.6%; T: 3.0%). This difference was predominantly due to IRRs (M: 8.7%; T: 1.1%; **Section 8.2.5**). No other AE leading to treatment interruption occurred in more than 1 subject (0.4%) in either group. A greater proportion of subjects had AEs leading to delay of trastuzumab compared to margetuximab (M: 20.1%; T: 28.9%). With the exception of neutropenia/neutrophil count decreased (M: 5.7%; T: 7.1%), no other AE leading to treatment delay occurred at a frequency of  $\geq 4\%$  subjects in either group. There were no other clinically meaningful differences between treatment groups.

AEs resulting in interruption or modification of *chemotherapy* are summarized in **Study 04 CSR Addendum 1 – Table 14.3.1.17**. A similar proportion of subjects in both treatment groups experienced AEs leading to chemotherapy interruption (M: 15.5%; T: 17.3%), dose delay (M: 37.1%; T: 36.5%), dose reduction (M: 26.1%; T: 23.7%), or dose delay and reduction (M: 8.7%; T: 9.0%). In both treatment groups, neutropenia together with decreased neutrophil count was the most common cause of these interruptions (M: 8.7%; T: 6.8%; **Study 04 CSR Addendum 1 –**

**Table 14.3.1.17.1**), including chemotherapy delays (M: 12.9% and 4.9%; T: 8.6% and 7.1%), dose reductions (M: 5.7% and 2.3%; T: 4.5% and 3.0%), and dose delays with reductions (M: 1.9% and 2.3%; T: 2.3% and 1.5%).

#### The Applicant's Position:

AEs leading to dose interruption were more frequent with margetuximab than trastuzumab in Study 04. This difference was predominantly due to IRRs. Delay of dosing was higher in the trastuzumab group, and interruption/modification of chemotherapy was similar in both groups. Observed AEs associated with dose interruption and/or reduction were as expected in this patient population and were similar to those of approved products in this class.

#### The FDA's Assessment:

The FDA conducted an independent analysis of adverse events leading to dose interruptions with an initial data cut off date of October 10, 2018 and confirmed that the April 10, 2019 data up date did not significantly change the incidence of adverse events leading to interruptions. Additionally FDA agrees with the Applicants analysis of AEs leading to interruptions. Dose interruptions occurred more frequently in the margetuximab plus chemotherapy arm (10.6%) compared to the trastuzumab plus chemotherapy arm (3.0%), predominantly due to IRRs (8.7% vs. 1.1%, respectively). Dose delay, typically of the chemotherapy backbone, occurred less frequently on the margetuximab plus chemotherapy compared to the trastuzumab plus chemotherapy arm (20.1% vs. 28.9%, respectively), with neutropenia/neutrophil count decreased as the predominant cause.

### Significant Adverse Events

#### Data:

##### *Maximum CTCAE Grade 3-5 AEs*

In Study 04, there were no notable differences in proportions of subjects with Grade  $\geq 3$  AEs. About one-half (53-54%) in both groups had Grade  $\geq 3$  AEs (**Table 23**). Grade 4 ( $\leq 11\%$ ) and Grade 5 ( $\leq 2\%$ ) AEs in each group had similar low frequencies. The most frequently reported Grade  $\geq 3$  AEs ( $\geq 4\%$  subjects) on margetuximab were neutropenia/neutrophil count decreased, anemia, fatigue, and febrile neutropenia; none of which were Grade 5.

Three subjects on margetuximab and 2 on trastuzumab had fatal AEs (see *Deaths* section). All were considered unrelated to study treatment (anti-HER2 or chemotherapy).

**Table 23: Adverse Events Grade ≥ 3 (Regardless of Causality) in ≥ 4 Subjects (Safety Population; Data Cutoff 10-Apr-2019)**

| Preferred Term                                       | Margetuximab plus<br>Chemotherapy<br>(N = 264)<br>n (%) | Trastuzumab plus<br>Chemotherapy<br>(N = 266)<br>n (%) |
|------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------|
| Subjects with any TEAE with CTCAE Severity Grade ≥ 3 | 142 (53.8)                                              | 140 (52.6)                                             |
| Neutropenia/neutrophil count decreased <sup>a</sup>  | 71 (26.9)                                               | 58 (21.8)                                              |
| Anaemia                                              | 13 (4.9)                                                | 17 (6.4)                                               |
| Febrile neutropenia                                  | 8 (3.0)                                                 | 13 (4.9)                                               |
| Leukopenia                                           | 4 (1.5)                                                 | 1 (0.4)                                                |
| Diarrhoea                                            | 6 (2.3)                                                 | 6 (2.3)                                                |
| Abdominal pain                                       | 4 (1.5)                                                 | 3 (1.1)                                                |
| Vomiting                                             | 2 (0.8)                                                 | 4 (1.5)                                                |
| Fatigue                                              | 13 (4.9)                                                | 8 (3.0)                                                |
| Asthenia                                             | 6 (2.3)                                                 | 5 (1.9)                                                |
| Pneumonia                                            | 5 (1.9)                                                 | 7 (2.6)                                                |
| Infusion related reaction                            | 4 (1.5)                                                 | 0                                                      |
| White blood cell count decreased                     | 5 (1.9)                                                 | 8 (3.0)                                                |
| Aspartate aminotransferase increased                 | 7 (2.7)                                                 | 3 (1.1)                                                |
| Alanine aminotransferase increased                   | 5 (1.9)                                                 | 4 (1.5)                                                |
| Hypokalaemia                                         | 4 (1.5)                                                 | 4 (1.5)                                                |
| Syncope                                              | 4 (1.5)                                                 | 0                                                      |
| Dyspnoea                                             | 3 (1.1)                                                 | 6 (2.3)                                                |
| Pleural effusion                                     | 2 (0.8)                                                 | 4 (1.5)                                                |
| Palmar-plantar erythrodysesthesia syndrome           | 1 (0.4)                                                 | 8 (3.0)                                                |
| Hypertension                                         | 5 (1.9)                                                 | 2 (0.8)                                                |

a Preferred terms of “neutropenia” and “neutrophil count decreased” are combined for ease of review.

Source: ADAE dataset; **Study 04 CSR Addendum 1 – Table 14.3.1.5** and **Table 14.3.1.5.1**

#### The Applicant’s Position:

Overall, there were no clinically meaningful differences in Grade 3-5 AEs between treatment groups (margetuximab or trastuzumab). IRR and neutropenia are discussed in **Section 8.2.5**.

#### The FDA’s Assessment:

The FDA conducted an independent analysis of Grade 3-4 adverse events with an initial data cut off date of October 10, 2018 and confirmed that the April 10, 2019 data up date did not significantly change the incidence of Grade 3-4 adverse events leading to discontinuations represented in Table 23. Additionally FDA agrees with the Applicants analysis of Grade 3-4 AEs presented in Table 23.

#### **Treatment Emergent Adverse Events and Adverse Reactions**

Data:

In Study 04 (data cutoff 10-Apr-2019), the most frequently reported AEs on margetuximab in combination with chemotherapy (incidence rate  $\geq 20\%$ ) were fatigue, nausea, neutropenia/neutrophil count decreased, diarrhea, and vomiting (**Table 24**). Similarly, on trastuzumab plus chemotherapy, fatigue, nausea, neutropenia/neutrophil count decreased, diarrhea, and anemia were most frequently reported. No AE was reported at a  $\geq 10\%$  higher or lower frequency on margetuximab than on trastuzumab. These data were consistent with pooled safety analyses from 10-Oct-2018 data cutoff, where the most frequently reported AEs ( $\geq 20\%$  subjects) on margetuximab were fatigue (34.9%), nausea (29.0%), diarrhea (21.1%), and neutropenia (21.1%; **ISS – Table 2.2**).

The most frequently reported Grade  $\geq 3$  AEs on margetuximab plus chemotherapy included neutropenia/neutrophil count decreased, anemia, and fatigue (**Study 04 CSR Addendum 1 – Table 14.3.1.5**). Events were most commonly in the system organ class (SOC) Blood and lymphatic system disorders, as might be expected for treatment with a regimen that included cytotoxic chemotherapy (including myelosuppressive eribulin, gemcitabine, and vinorelbine). A discussion of AESI, including IRR, neutropenia, and cardiac dysfunction, is provided in **Section 8.2.5**.

**Table 24: Adverse Events (Regardless of Causality) in  $\geq 5\%$  Subjects (Safety Population; Data Cutoff 10-Apr-2019)**

| System Organ Class<br>Preferred Term                   | Margetuximab plus<br>Chemotherapy<br>(N = 264)<br>n (%) | Trastuzumab plus<br>Chemotherapy<br>(N = 266)<br>n (%) |
|--------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------|
| Subjects with any TEAE with Incidence Rate $\geq 5\%$  | 256 (97.0)                                              | 254 (95.5)                                             |
| <b>Blood and lymphatic system disorders</b>            | <b>104 (39.4)</b>                                       | <b>104 (39.1)</b>                                      |
| Neutropenia/neutrophil count decreased <sup>a</sup>    | 101 (38.3)                                              | 89 (33.5)                                              |
| <i>Neutropenia</i>                                     | 75 (28.4)                                               | 55 (20.7)                                              |
| <i>Neutrophil count decreased<sup>a</sup></i>          | 33 (12.5)                                               | 39 (14.7)                                              |
| Anaemia                                                | 49 (18.6)                                               | 62 (23.3)                                              |
| Thrombocytopenia/platelet count decreased <sup>b</sup> | 30 (11.4)                                               | 30 (11.3)                                              |
| <i>Thrombocytopenia</i>                                | 22 (8.3)                                                | 13 (4.9)                                               |
| <i>Platelet count decreased<sup>b</sup></i>            | 8 (3.0)                                                 | 17 (6.4)                                               |
| Leukopenia                                             | 14 (5.3)                                                | 10 (3.8)                                               |
| <b>Gastrointestinal disorders</b>                      | <b>170 (64.4)</b>                                       | <b>172 (64.7)</b>                                      |
| Nausea                                                 | 86 (32.6)                                               | 86 (32.3)                                              |
| Diarrhoea                                              | 66 (25.0)                                               | 67 (25.2)                                              |
| Constipation                                           | 51 (19.3)                                               | 44 (16.5)                                              |
| Vomiting                                               | 54 (20.5)                                               | 38 (14.3)                                              |
| Abdominal pain                                         | 25 (9.5)                                                | 37 (13.9)                                              |
| Stomatitis                                             | 27 (10.2)                                               | 21 (7.9)                                               |
| Abdominal pain upper                                   | 20 (7.6)                                                | 21 (7.9)                                               |
| Dyspepsia                                              | 14 (5.3)                                                | 20 (7.5)                                               |

**Table 24: Adverse Events (Regardless of Causality) in ≥ 5% Subjects (Safety Population; Data Cutoff 10-Apr-2019)**

| System Organ Class<br>Preferred Term                        | Margetuximab plus<br>Chemotherapy<br>(N = 264)<br>n (%) | Trastuzumab plus<br>Chemotherapy<br>(N = 266)<br>n (%) |
|-------------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------|
| <b>General disorders and administration site conditions</b> | <b>180 (68.2)</b>                                       | <b>154 (57.9)</b>                                      |
| Fatigue                                                     | 111 (42.0)                                              | 94 (35.3)                                              |
| Pyrexia                                                     | 50 (18.9)                                               | 37 (13.9)                                              |
| Asthenia                                                    | 47 (17.8)                                               | 33 (12.4)                                              |
| Oedema peripheral                                           | 19 (7.2)                                                | 25 (9.4)                                               |
| Mucosal inflammation                                        | 26 (9.8)                                                | 8 (3.0)                                                |
| Influenza like illness                                      | 18 (6.8)                                                | 10 (3.8)                                               |
| <b>Infections and infestations</b>                          | <b>57 (21.6)</b>                                        | <b>61 (22.9)</b>                                       |
| Urinary tract infection                                     | 26 (9.8)                                                | 28 (10.5)                                              |
| Upper respiratory tract infection                           | 19 (7.2)                                                | 23 (8.6)                                               |
| Nasopharyngitis                                             | 19 (7.2)                                                | 18 (6.8)                                               |
| <b>Injury, poisoning and procedural complications</b>       | <b>35 (13.3)</b>                                        | <b>9 (3.4)</b>                                         |
| Infusion related reaction <sup>c</sup>                      | 35 (13.3)                                               | 9 (3.4)                                                |
| <b>Investigations</b>                                       | <b>74 (28.0)</b>                                        | <b>94 (35.3)</b>                                       |
| Neutrophil count decreased <sup>a</sup>                     | 33 (12.5)                                               | 39 (14.7)                                              |
| Aspartate aminotransferase increased                        | 22 (8.3)                                                | 34 (12.8)                                              |
| Alanine aminotransferase increased                          | 24 (9.1)                                                | 26 (9.8)                                               |
| White blood cell count decreased                            | 19 (7.2)                                                | 27 (10.2)                                              |
| Weight decreased                                            | 16 (6.1)                                                | 15 (5.6)                                               |
| Platelet count decreased <sup>b</sup>                       | 8 (3.0)                                                 | 17 (6.4)                                               |
| <b>Metabolism and nutrition disorders</b>                   | <b>51 (19.3)</b>                                        | <b>52 (19.5)</b>                                       |
| Decreased appetite                                          | 38 (14.4)                                               | 36 (13.5)                                              |
| Hypokalaemia                                                | 16 (6.1)                                                | 19 (7.1)                                               |
| <b>Musculoskeletal and connective tissue disorders</b>      | <b>87 (33.0)</b>                                        | <b>71 (26.7)</b>                                       |
| Pain in extremity                                           | 30 (11.4)                                               | 23 (8.6)                                               |
| Arthralgia                                                  | 27 (10.2)                                               | 23 (8.6)                                               |
| Back pain                                                   | 22 (8.3)                                                | 25 (9.4)                                               |
| Myalgia                                                     | 18 (6.8)                                                | 15 (5.6)                                               |
| Muscle spasms                                               | 16 (6.1)                                                | 10 (3.8)                                               |
| <b>Nervous system disorders</b>                             | <b>103 (39.0)</b>                                       | <b>87 (32.7)</b>                                       |
| Headache                                                    | 47 (17.8)                                               | 42 (15.8)                                              |
| Neuropathy peripheral                                       | 26 (9.8)                                                | 28 (10.5)                                              |
| Dizziness                                                   | 25 (9.5)                                                | 16 (6.0)                                               |
| Dysgeusia                                                   | 16 (6.1)                                                | 15 (5.6)                                               |
| Peripheral sensory neuropathy                               | 17 (6.4)                                                | 13 (4.9)                                               |
| <b>Psychiatric disorders</b>                                | <b>15 (5.7)</b>                                         | <b>15 (5.6)</b>                                        |
| Insomnia                                                    | 15 (5.7)                                                | 15 (5.6)                                               |
| <b>Respiratory, thoracic and mediastinal disorders</b>      | <b>85 (32.2)</b>                                        | <b>73 (27.4)</b>                                       |
| Cough                                                       | 37 (14.0)                                               | 31 (11.7)                                              |
| Dyspnoea                                                    | 34 (12.9)                                               | 28 (10.5)                                              |
| Epistaxis                                                   | 18 (6.8)                                                | 19 (7.1)                                               |
| Pleural effusion                                            | 8 (3.0)                                                 | 14 (5.3)                                               |

**Table 24: Adverse Events (Regardless of Causality) in ≥ 5% Subjects (Safety Population; Data Cutoff 10-Apr-2019)**

| System Organ Class<br>Preferred Term          | Margetuximab plus<br>Chemotherapy<br>(N = 264)<br>n (%) | Trastuzumab plus<br>Chemotherapy<br>(N = 266)<br>n (%) |
|-----------------------------------------------|---------------------------------------------------------|--------------------------------------------------------|
| <b>Skin and subcutaneous tissue disorders</b> | <b>87 (33.0)</b>                                        | <b>87 (32.7)</b>                                       |
| Alopecia                                      | 47 (17.8)                                               | 39 (14.7)                                              |
| Palmar-plantar erythrodysesthesia syndrome    | 33 (12.5)                                               | 41 (15.4)                                              |
| Rash                                          | 16 (6.1)                                                | 15 (5.6)                                               |
| <b>Vascular disorders</b>                     | <b>14 (5.3)</b>                                         | <b>6 (2.3)</b>                                         |
| Hypertension                                  | 14 (5.3)                                                | 6 (2.3)                                                |

- a Preferred terms “neutropenia” and “neutrophil count decreased” are combined for ease of review; neutrophil count decreased belongs in the Investigation SOC. Neutropenia is discussed in **Section 8.2.5**.
- b Preferred terms “thrombocytopenia” and “platelet count decreased” are combined for ease of review; platelet count decreased belongs in the Investigation SOC.
- c IRRs are discussed in **Section 8.2.5**.

Source: ADAE dataset; **Study 04 CSR Addendum 1 - Table 14.3.1.20, Table 14.3.1.2.1, and Table 14.3.1.2.2**

Consistent with the established safety profile of trastuzumab, the most frequently reported all grade treatment-related AEs in Study 04 were fatigue, IRR, and nausea (**Table 25**). These data were consistent with pooled safety analysis (**ISS – Table 2.6**). There were no clinically meaningful differences between treatment groups for treatment-related Grade ≥ 3 AEs (**Table 25**).

**Table 25: Adverse Reactions in ≥ 5% Subjects (Safety Population; Data Cutoff 10-Apr-2019)**

| System Organ Class<br>Preferred Term         | All Grades                                              |                                                        | Grade ≥ 3                                               |                                                        |
|----------------------------------------------|---------------------------------------------------------|--------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------|
|                                              | Margetuximab plus<br>Chemotherapy<br>(N = 264)<br>n (%) | Trastuzumab plus<br>Chemotherapy<br>(N = 266)<br>n (%) | Margetuximab plus<br>Chemotherapy<br>(N = 264)<br>n (%) | Trastuzumab plus<br>Chemotherapy<br>(N = 266)<br>n (%) |
| Subjects with any Study Therapy Related TEAE | 128 (48.5)                                              | 83 (31.2)                                              | 34 (12.9)                                               | 22 (8.3)                                               |
| <b>Blood and lymphatic system disorders</b>  | <b>25 (9.5)</b>                                         | <b>23 (8.6)</b>                                        | <b>14 (5.3)</b>                                         | <b>14 (5.3)</b>                                        |
| Anaemia                                      | 13 (4.9)                                                | 17 (6.4)                                               | 6 (2.3)                                                 | 6 (2.3)                                                |
| Neutropenia                                  | 17 (6.4)                                                | 9 (3.4)                                                | 9 (3.4)                                                 | 4 (1.5)                                                |
| <b>Gastrointestinal disorders</b>            | <b>51 (19.3)</b>                                        | <b>38 (14.3)</b>                                       | <b>2 (0.8)</b>                                          | <b>1 (0.4)</b>                                         |
| Nausea                                       | 26 (9.8)                                                | 20 (7.5)                                               | 0                                                       | 0                                                      |
| Diarrhoea                                    | 19 (7.2)                                                | 13 (4.9)                                               | 2 (0.8)                                                 | 1 (0.4)                                                |
| Constipation                                 | 18 (6.8)                                                | 11 (4.1)                                               | 0                                                       | 0                                                      |
| Vomiting                                     | 15 (5.7)                                                | 8 (3.0)                                                | 0                                                       | 0                                                      |

**Table 25: Adverse Reactions in ≥ 5% Subjects (Safety Population; Data Cutoff 10-Apr-2019)**

| System Organ Class<br>Preferred Term                            | All Grades                                                 |                                                           | Grade ≥ 3                                                  |                                                           |
|-----------------------------------------------------------------|------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------|-----------------------------------------------------------|
|                                                                 | Margetuximab<br>plus<br>Chemotherapy<br>(N = 264)<br>n (%) | Trastuzumab<br>plus<br>Chemotherapy<br>(N = 266)<br>n (%) | Margetuximab<br>plus<br>Chemotherapy<br>(N = 264)<br>n (%) | Trastuzumab<br>plus<br>Chemotherapy<br>(N = 266)<br>n (%) |
| <b>General disorders and<br/>administration site conditions</b> | <b>79 (29.9)</b>                                           | <b>41 (15.4)</b>                                          | <b>7 (2.7)</b>                                             | <b>1 (0.4)</b>                                            |
| Fatigue                                                         | 54 (20.5)                                                  | 27 (10.2)                                                 | 6 (2.3)                                                    | 1 (0.4)                                                   |
| Asthenia                                                        | 18 (6.8)                                                   | 10 (3.8)                                                  | 1 (0.4)                                                    | 0                                                         |
| Pyrexia                                                         | 17 (6.4)                                                   | 8 (3.0)                                                   | 0                                                          | 0                                                         |
| <b>Injury, poisoning and procedural<br/>complications</b>       | <b>34 (12.9)</b>                                           | <b>8 (3.0)</b>                                            | <b>5 (1.9)</b>                                             | <b>0</b>                                                  |
| Infusion related reaction                                       | 34 (12.9)                                                  | 8 (3.0)                                                   | 4 (1.5)                                                    | 0                                                         |

Source: ADAE dataset; *Study 04 CSR Addendum 1 - Table 14.3.1.21, Table 14.3.1.8, and Listing 16.2.7.2*

**The FDA's Assessment:**

The FDA conducted an independent analysis of treatment emergent adverse events (TEAE) with an initial data cut off date of October 10, 2018 and confirmed that the April 10, 2019 data up date did not significantly change the incidence of TEAEs represented in Table 24. In general FDA agrees the sponsor assessment of TEAEs presented in Table 24; however did use group PT terms in order to more accurately define adverse events. Additionally FDA excluded laboratory related adverse events. An evaluation of laboratory related adverse events can be found in Table 27. Table 26 displays FDA's analysis of TEAEs.

**Table 26: FDA Analysis of Treatment Emergent Adverse Events in ≥5% of Patients in Study 04 data cut off date October 10, 2018.**

| Adverse Reaction                                            | Margetuximab + Chemotherapy<br>(n = 264) |                       | Trastuzumab + Chemotherapy<br>(n = 266) |                       |
|-------------------------------------------------------------|------------------------------------------|-----------------------|-----------------------------------------|-----------------------|
|                                                             | All Grades<br>n (%)                      | Grade 3 or 4<br>n (%) | All Grades<br>n (%)                     | Grade 3 or 4<br>n (%) |
| <b>General disorders and administration site conditions</b> |                                          |                       |                                         |                       |
| Fatigue/Asthenia                                            | 140 (53)                                 | 18 (7)                | 117 (44)                                | 11 (4.1)              |
| Pyrexia                                                     | 50 (19)                                  | 1 (0.)                | 37 (14)                                 | 1 (0.4)               |
| Mucosal inflammation                                        | 26 (10)                                  | 0                     | 8 (3.0)                                 | 1 (0.4)               |
| Influenza like illness                                      | 18 (7)                                   | 1 (0.4)               | 10 (3.8)                                | 0                     |
| Peripheral edema <sup>a</sup>                               | 18 (7)                                   | 1 (0.4)               | 24 (9)                                  | 2 (0.8)               |
| <b>Gastrointestinal disorders</b>                           |                                          |                       |                                         |                       |
| Nausea                                                      | 81 (31)                                  | 3(1.1)                | 84 (32)                                 | 1 (0.4)               |
| Diarrhea                                                    | 59 (22)                                  | 6 (2.3)               | 62 (23)                                 | 5 (2.3)               |
| Vomiting                                                    | 49 (19)                                  | 2 (0.8)               | 36 (14)                                 | 4 (1.5)               |
| Constipation                                                | 48 (18)*                                 | 2 (0.8)               | 42 (16)                                 | 2 (0.8)               |
| Abdominal pain <sup>b</sup>                                 | 42 (16)                                  | 4 (1.5)               | 51 (19)                                 | 4 (1.5)               |
| Stomatitis                                                  | 26 (10)                                  | 2 (0.8)               | 18 (7)                                  | 0                     |
| Dyspepsia                                                   | 11 (4)                                   | 0                     | 18 (7)                                  | 0                     |
| <b>Skin and Subcutaneous tissue</b>                         |                                          |                       |                                         |                       |
| Alopecia                                                    | 45 (17)                                  | 0                     | 36 (14)                                 | 0                     |
| Palmar-plantar erythrodysasthesia                           | 33 (13)                                  | 0                     | 36 (14)                                 | 0                     |
| Rash <sup>c</sup>                                           | 19 (7)                                   | 1 (0.4)               | 17 (6)                                  | 1 (0.4)               |
| <b>Nervous System Disorders</b>                             |                                          |                       |                                         |                       |
| Headache <sup>d</sup>                                       | 48 (18)                                  | 0                     | 43 (16)                                 | 0                     |
| Peripheral neuropathy <sup>e</sup>                          | 40 (15)                                  | 3 (1.1)               | 29 (11)                                 | 5 (1.9)               |
| Dizziness                                                   | 22 (8)                                   | 1 (0.4)               | 14 (5)                                  | 0                     |
| Dysgeusia                                                   | 15 (6)                                   | 0                     | 15 (6)                                  | 0                     |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |                                          |                       |                                         |                       |
| Dyspnea                                                     | 31 (12)                                  | 3 (1.1)               | 26 (10)                                 | 5 (1.9)               |
| Cough                                                       | 29 (11)                                  | 1 (0.4)               | 26 (10)                                 | 0                     |
| Epistaxis                                                   | 17 (6)                                   | 0                     | 15 (6)                                  | 0                     |
| <b>Metabolism and nutrition disorders</b>                   |                                          |                       |                                         |                       |
| Decreased appetite                                          | 35 (13)                                  | 1 (0.4)               | 34 (13)                                 | 1 (0.4)               |
| <b>Musculoskeletal and connective tissue disorders</b>      |                                          |                       |                                         |                       |
| Arthralgia/myalgia                                          | 34 (13)                                  | 1 (0.4)               | 26 (10)                                 | 2 (0.8)               |
| Extremity pain                                              | 27 (10)                                  | 2 (0.8)               | 21 (8)                                  | 0                     |

|                                                       |        |         |         |         |
|-------------------------------------------------------|--------|---------|---------|---------|
| Back pain                                             | 18 (7) | 1 (0.4) | 23 (9)  | 3 (1.1) |
| Muscle spasms                                         | 14 (5) | 1 (0.4) | 8 (3.0) | 0       |
| <b>Injury, poisoning and procedural complications</b> |        |         |         |         |
| Infusion Related Reaction                             | 13     | 1.5     | 3       | 0       |
| <b>Infections and infestations</b>                    |        |         |         |         |
| Urinary tract infection                               | 19 (7) | 2 (0.8) | 26 (10) | 3 (1.1) |
| Nasopharyngitis                                       | 15 (6) | 0       | 16 (6)  | 0       |
| Upper respiratory tract infection                     | 14 (5) | 0       | 18 (7)  | 1 (0.4) |
| <b>Investigations</b>                                 |        |         |         |         |
| Weight decreased                                      | 13 (5) | 2 (0.8) | 14 (5)  | 1 (0.4) |
| <b>Psychiatric disorders</b>                          |        |         |         |         |
| Insomnia                                              | 15 (5) | 0       | 15 (6)  | 0       |

- a. Includes peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, neuropathy
- b. Includes abdominal pain, abdominal discomfort, lower abdominal pain and upper abdominal pain
- c. Includes rash, erythematous rash, and maculopapular rash
- d. Includes headache and migraine
- e. Includes peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, and neuropathy

## Laboratory Findings

### Data:

Results of clinical laboratory evaluations were classified based on CTCAE v4.03 toxicity grade. Clinically significant abnormal laboratory findings observed during the study were considered AEs and are therefore included in summary tables presented elsewhere.

As of 10-Oct-2018, there were no clinically meaningful differences between treatment groups in laboratory values over time or toxicity grade shifts for any hematology, chemistry, coagulation, or urinalysis parameter (**Study 04 CSR – Section 12.4.2**).

### The Applicant's Position:

Observed laboratory abnormalities were as expected for subjects with advanced cancers receiving chemotherapy. There were no clinically meaningful differences between treatment groups.

Analysis of laboratory findings supports the absence of a detectable liver, kidney, or urinalysis safety signal for margetuximab.

### The FDA's Assessment:

FDA agrees with the Applicant's assessment. Table 27 display the FDA conducted independent analysis of laboratory values in Study 04; the table below shows laboratory values worsening

from baseline in  $\geq 20\%$  of patients:

**Table 27: : FDA Analysis of Laboratory Abnormalities in  $\geq 20\%$  of Patients that worsened from baseline in Study 04 data cut off date October 10, 2018.**

**Select Laboratory Abnormalities ( $\geq 20\%$ ) that Worsened from Baseline in Study 04**

| Laboratory Abnormality         | Margetuximab + chemotherapy <sup>1</sup> |                  | Trastuzumab + chemotherapy <sup>1</sup> |                  |
|--------------------------------|------------------------------------------|------------------|-----------------------------------------|------------------|
|                                | All Grades (%)                           | Grade 3 or 4 (%) | All Grades (%)                          | Grade 3 or 4 (%) |
| <b>Hematology</b>              |                                          |                  |                                         |                  |
| Decreased hemoglobin           | 52                                       | 3.2              | 43                                      | 2.4              |
| Decreased leukocytes           | 40                                       | 5                | 36                                      | 3.2              |
| Decreased neutrophils          | 34                                       | 9                | 28                                      | 9                |
| Increased aPTT                 | 32                                       | 3.4              | 34                                      | 4.3              |
| Decreased lymphocytes          | 31                                       | 4.4              | 38                                      | 4.4              |
| Increased INR                  | 24                                       | 1.2              | 25                                      | 0.4              |
| <b>Chemistry</b>               |                                          |                  |                                         |                  |
| Increased creatinine           | 68                                       | 0.4              | 60                                      | 0                |
| Increased ALT                  | 32                                       | 2                | 30                                      | 0.8              |
| Increased lipase               | 30                                       | 6                | 24                                      | 3.2              |
| Increased AST                  | 23                                       | 2                | 22                                      | 0.8              |
| Increased alkaline Phosphatase | 21                                       | 0                | 23                                      | 0.8              |

<sup>1</sup> The denominator used to calculate the rate varied from 229 to 253 based on the number of patients with a baseline value and at least one post-treatment value.

### Vital Signs

Data:

In Study 04, vital sign evaluations include blood pressure, heart rate, respiratory rate, and temperature. Mean and median vital sign values did not reveal relevant differences between treatment groups at any cycle or at end of treatment. Clinically meaningful treatment-emergent abnormalities in physical exam assessments were reported as AEs.

The Applicant's Position:

There were no clinically meaningful differences in vital signs between treatment groups.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

### Electrocardiograms (ECGs)

Data:

Effects of margetuximab plus chemotherapy on ECG parameters were assessed in Study 04. There were no marked differences in ECG intervals between treatment groups. As of 10-Oct-2018 (Study 04 CSR cutoff date), more subjects on margetuximab than trastuzumab had heart rate > 100 bpm (M: 13.6%; T: 7.9%), largely due to Cycle 1 Day 1 IRR (**Section 8.2.5**). Few AEs related to ECG interval changes were observed, including no AEs related to QTc intervals.

The Applicant's Position:

Overall, effects were comparable for margetuximab versus trastuzumab on ECG parameters or cardiac safety. Also, margetuximab had no effect on ECG parameters in monkey safety studies.

The FDA's Assessment:

As margetuximab is a monoclonal antibody, it is not expected to cause QT prolongation (please see QT IRT review for additional information).

## QT

The Applicant's Position:

Refer to ECG section above. No dedicated clinical QT studies of margetuximab were conducted.

The FDA's Assessment:

As margetuximab is a monoclonal antibody, it is not expected to cause QT prolongation (please see QT IRT review for additional information).

## Immunogenicity

Data:

Four of 263 subjects (1.5%) treated with margetuximab in combination with chemotherapy in Study 04 tested positive for treatment-emergent ADA. No subjects had neutralizing antibodies. ADA induction in the Study 04 Infusion Substudy was similarly modest; 2 of 80 subjects (2.5%) developed ADAs, and no subjects had on-therapy neutralizing antibodies. Moreover, none of 66 subjects in Study 01 and 22 in Study 02 tested positive for treatment emergent ADA.

The Applicant's Position

Immunogenicity appears to have no clinically meaningful effect on PK, safety, or efficacy of margetuximab.

The FDA's Assessment:

Please refer to the FDA's assessment in section 6.3.1 for a detailed review of margetuximab ADA data. Overall, due the limited number of patients who were positive for anti-margetuximab antibodies during treatment with margetuximab, the impact of anti-margetuximab antibodies on the PK, safety and efficacy of margetuximab is not definitively known. A PMC will be issued to assess the development of neutralizing antibodies against

margetuximab in Study 04 and the infusion sub-study using an adequately validated assay.

## 8.2.5. Analysis of Submission-Specific Safety Issues

### 8.2.5.1 Infusion Related Reaction

#### The Applicant's Position:

IRRs (including CRS) are an important identified risk of margetuximab therapy and closely monitored in the margetuximab clinical development program. Subjects were to be premedicated with steroids, antihistamines, and antipyretics for the first infusion, with antihistamines and antipyretics for subsequent infusions, per Investigator discretion. If IRRs were still observed standard guidelines regarding treatment and prevention were provided as outlined in individual study protocols.

In Study 04, a higher proportion of subjects on margetuximab than trastuzumab reported IRRs (M: 13.3%; T: 3.4%; **Table 24**). Most IRRs were Grade 1 or 2, and no IRR was higher than Grade 3. Grade 3 IRRs occurred in 4 subjects (1.5%) on margetuximab. Of these 4 events, 3 were serious, and 2 led to margetuximab discontinuation. Nearly all such events occurred on Cycle 1 Day 1 (**Study 04 CSR Addendum 1 – Figure 14.3.1.31**), with complete resolution within 24 hours of onset, and were manageable with supportive care. These data were consistent with pooled safety analyses.

In Study 04, a higher incidence of IRRs leading to infusion interruption (M: 8.7%; T: 1.1%) or delay of study drug dosing (M: 0.8%; T: 0.4%) was observed in margetuximab than trastuzumab recipients (**Study 04 CSR Addendum 1 – Table 14.3.1.16**). Few discontinued due to IRRs (M: 0.8%; T: 0.0%). Of the 35 subjects (13.3%) with IRRs on margetuximab, 32 received additional infusions.

IRR symptoms were similar for margetuximab and trastuzumab, predominately chills and pyrexia with few events of hypertension and no hypotension (**Study 04 CSR Addendum 1 – Table 14.3.1.28**).

A higher incidence of IRRs on margetuximab than trastuzumab in Study 04 can be attributed, at least in part, to all subjects at baseline being margetuximab naïve yet trastuzumab experienced. Margetuximab IRR frequency appears similar to that described in the HERCEPTIN® (trastuzumab) USPI. Also, a retrospective chart review of 197 first-time trastuzumab recipients revealed that 32 (16.2%) experienced IRRs (**37**). Consistent with the experience for margetuximab in Study 04, these authors observed that trastuzumab IRRs generally occurred with the first infusion, were mild in severity, could be managed medically, and were characteristically without enduring consequence for safety or efficacy.

In the Study 04 Infusion Substudy, 88 subjects enrolled as of the 17-Jun-2019 data cutoff date and received margetuximab 15 mg/kg Q3W. IRRs occurred in 18 (20.5%) of these subjects, predominantly during the first (120 minute) administration, as seen in randomized Study 04. Of 88 enrolled subjects, 76 were assigned to receive margetuximab over 30 minutes from Cycle 2 onwards (8 in Stage A2 and 68 in Stage B; see **Section 8.2.8**). No subjects experienced Grade  $\geq 3$  IRR or IRRs meeting SAE criteria. From Cycle 2 onward, despite reduced infusion time, 1 subject only (1.1%) had Grade 1 IRR. Although the Infusion Substudy population was more heavily pretreated than the randomized Study 04 population, AE incidence, type, and severity are generally consistent with Study 04. Reduction of infusion duration to 30 minutes for Cycle 2 and beyond does not adversely affect margetuximab safety or increase IRR risk or severity.

#### The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment. FDA's independent analysis of IRR in Study 04, including the infusion substudy confirm that IRRs were reported in 13% of patients on the margetuximab plus chemotherapy treatment arm; most occurred during Cycle 1. Grade 3 IRRs were reported in 1.5% of patients treated on the margetuximab plus chemotherapy arm. All IRRs resolved within 24 hours, irrespective of severity. IRRs leading to dose interruption occurred more frequently on the margetuximab plus chemotherapy treatment arm (8.7%) compared to the trastuzumab plus chemotherapy arm (1.1%).

In the Study 04 Infusion Substudy, infusion times were shortened from 120 minutes to 30 minutes, this substudy did not show a significantly increased rate or severity of IRR. IRRs occurred in 18 (20.5%) of these subjects, predominantly during the first (120 minute) administration, as seen in randomized Study 04. From Cycle 2 onward, despite reduced infusion time, only 1 subject (1.1%) had Grade 1 IRR.

### **8.2.5.2 Left Ventricular Dysfunction**

#### The Applicant's Position:

Cardiac toxicity has been observed after anti-HER2 therapies, including trastuzumab. Thus, cardiac safety, ECG, and LVEF monitoring were included in all margetuximab clinical trials. Overall, there was no evidence of increased cardiotoxicity on margetuximab compared to trastuzumab.

Proportions of subjects in Study 04 with LVEF dysfunction events leading to dose delay or discontinuation were low and comparable across treatment groups (**Study 04 CSR Addendum 1 – Table 14.3.1.23**). None of these events met SAE criteria. In pooled safety analyses, 34 subjects (9.6%) on margetuximab across studies (Study 04: M: 5/264; T: 5/265) had  $\geq 15\%$  reduction in LVEF (**BLA – Section 2.7.4.4.3**). All such decreases in LVEF were clinically asymptomatic, without observation of treatment-related cardiomyopathy and/or cardiac failure. Cardiac events of left ventricular dysfunction, ejection fraction decreased, and cardiac failure, were reported in a combined total of 10 subjects (2.8%) on margetuximab (**ISS – Table 2.18, ISS – Listing 16.2.7.3**).

In Study 04, left ventricular dysfunction was reported in similar proportions between the margetuximab and trastuzumab groups (M: 2.7%; T: 2.6%; **Study 04 CSR Addendum 1 – Table 14.3.1.2**).

Left ventricular dysfunction was also assessed by SMQ analysis of AE terms. No cardiotoxicity SMQs revealed potential margetuximab safety issues. Cardiac failure and cardiomyopathy SMQs identified primarily dyspnea and peripheral edema. Events of dyspnea were isolated and did not appear to be of pulmonary or cardiac origin. SMQ analysis of Torsade/QTc prolongation did not identify potential safety issues for margetuximab. In Study 04, categorical analysis of cardiac intervals revealed no notable differences between baseline and end of treatment in either treatment group. There was no evidence that margetuximab induced cardiac conduction abnormalities.

In conclusion, LVEF measurements, TEAEs, and ECG intervals support a similar, acceptable cardiac safety profile for margetuximab and trastuzumab.

#### The FDA's Assessment:

FDA agrees with the Applicant's assessment. Less than 2% of patients treated in each arm of Study 04 experienced  $\geq 15\%$  reduction in LVEF; all were clinically asymptomatic and very few led to dose delay or discontinuation. FDA notes that margetuximab has not been studied in patients with a pretreatment LVEF value of  $< 50\%$ , a prior history of myocardial infarction or unstable angina within 6 months, or congestive heart failure NYHA class II-IV.

Left ventricular dysfunction is listed as a Black Boxed Warning and a Warning and Precaution in the USPI as decreases in LVEF and LV dysfunction is a known class effect of HER2-directed therapies. Dose management guidelines for decreases in LVEF and symptomatic congestive heart failure are also in the USPI.

### **8.2.5.3 Neutropenia**

#### The Applicant's Position:

In Study 04, 38.3% of subjects on margetuximab plus chemotherapy experienced all grade neutropenia/neutrophil count decreased compared to 33.5% of subjects on trastuzumab plus chemotherapy (**Table 24**). The proportion with Grade  $\geq 3$  neutropenia/neutrophil count decreased was also higher on margetuximab plus chemotherapy (M: 26.9%; T: 21.8%; **Table 23**). However, clinical sequelae of neutropenia were more frequent in the trastuzumab group, including febrile neutropenia (all events Grade  $\geq 3$ : M: 3.0%, T: 4.9%) and SOC Infections and infestations (all grades: M: 43.2%, T: 44.7%; Grade  $\geq 3$ : M: 5.3%, T: 9.0%). These data indicate no meaningful difference between groups for risk of infection, regardless of the ~5% difference between groups in proportions experiencing neutropenia.

Similar proportions in each group experienced neutropenia/neutrophil count leading to interruption (M: 0.4%; T: 0%) or delay (M: 5.7%; T: 7.1%) of study drug, or interruption of backbone chemotherapy (M: 8.7%; T: 6.8%).

Numerically higher incidence of neutropenia on margetuximab was restricted to randomized Study 04, coincident with administration of study drug (antibody) with a chemotherapy agent. No subjects treated with single-agent margetuximab in the Infusion Substudy experienced neutropenia. Similar results were seen in subjects in Study 01 and 02 who received single-agent margetuximab. In Study 01, only 2 subjects (3.0%), each treated with margetuximab 6 mg/kg QW, experienced transient Grade 2 neutropenia. No neutropenia events were reported in Study 02.

Overall, laboratory parameter values and changes over time were as expected for subjects with advanced cancers receiving chemotherapy.

In conclusion, there is no evidence of a clinically meaningful difference between margetuximab and trastuzumab in generation of neutropenia. No specific monitoring for neutropenia is included in the proposed margetuximab label.

#### The FDA's Assessment:

FDA agrees with the Applicant's assessment. FDA's independent analysis of neutropenia and neutrophil count decrease is consistent with the Applicant's finding of higher proportion of patients in the margetuximab plus chemotherapy arm experiencing neutropenia and decreased neutrophil counts. These did not result in clinically significant sequela such as higher rates of febrile neutropenia or infections.

### **8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability**

#### The Applicant's Position

A tertiary objective was to evaluate health-related quality of life by NFBSI-16 and EQ-5D-5L surveys. Most subjects completed baseline surveys; 1 of 266 (0.4%) margetuximab recipients and 3 of 270 (1.2%) trastuzumab recipients did not complete them.

Mean NFBSI-16 total scores were similar between treatment groups at baseline and end of treatment. Overall least square mean estimates (95% CIs) of change from baseline NFBSI-16 total scores were -1.99 (-3.395, -0.594) in the margetuximab group, and -2.13 (-3.794, -0.469) in the trastuzumab group. Mean EQ-5D-5L overall scores were similar between treatment groups at baseline and end of treatment. Overall least square mean estimates (95% CIs) of change from baseline in EQ-5D-5L total scores suggest subjects on margetuximab had less signs of deterioration than those on trastuzumab (M: -0.93 [-4.493, 2.637]; T: -3.93 [-8.253, 0.387]).

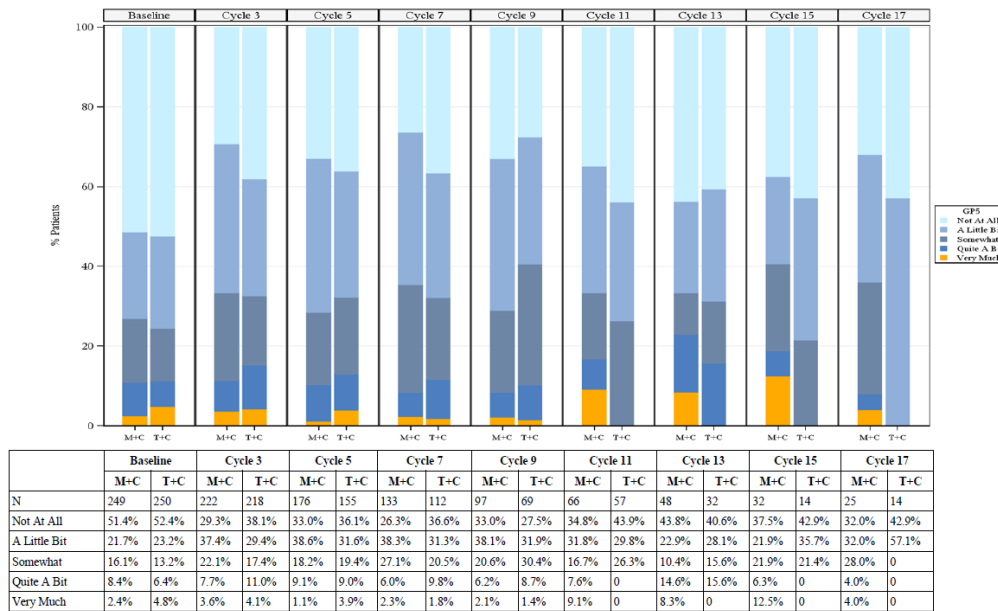
In Study 04 the effect of margetuximab on health-related quality of life was similar to that of trastuzumab. No safety concerns were identified, and there were no statistically significant differences between treatment groups for either PRO instrument. The Applicant is not seeking to include PRO data in proposed labeling.

**The FDA's Assessment:**

At baseline, completion rates for "answered all questions" was 87.1% for the margetuximab plus chemotherapy arm and 88.3% for the trastuzumab plus chemotherapy arm. On treatment, over the first 12 months, completion rates for all answered questions remained above 78% for margetuximab plus chemotherapy and 72% for trastuzumab plus chemotherapy.

The FDA does not consider mean difference in the total score and conclusions regarding quality of life to be appropriate because the total score combines disease symptoms, side effects, and impacts. For this reason, the sponsors analysis is difficult to interpret in regard to comparing the treatment arms; also these analysis were not included in the statistical hierarchy. Exploratory GP5 analysis that were requested by the FDA as part of an IR indicated that side effect bother did not appear to be different between the two study arms for patients who remained on treatment (see below; figure 3 provided by Applicant). Care should be taken in interpreting these results, especially from cycle 9 onward as less than half of the ITT population remained on treatment.

Figure 3 Summary of GP5 (Bothered by Side Effects) by Treatment for First Year of Treatment



8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

**Disclaimer:** In this document, sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect positions of FDA.

Subgroup analyses were conducted on the pooled safety population (**ISS SAP – Section 6** and **BLA – Section 2.7.4.5**). AE categories were selected based on trastuzumab’s known safety profile. Categories examined include AEs of Grade 3 or above, AEs related to margetuximab, SAEs, AESIs and laboratory parameters pertinent to anemia, neutropenia, and thrombocytopenia. In summarizing subgroup analyses below, the focus was on comparison of overall total and 15 mg/kg Q3W dose groups. The results are supplemented by those of the margetuximab population PK analysis (**Section 6.2.2.2**).

Subgroup analyses typically demonstrated a pattern of events consistent with that reported for the overall study populations.

#### *Demographic Characteristics*

Safety in elderly subjects ( $\geq 65$  years old) was generally consistent with that of younger subjects, although a higher proportion of elderly subjects experienced SAEs, Grade  $\geq 3$  AEs, and potential cardiotoxicity AEs (by SMQ). Given that elderly subjects generally have more comorbidities, a higher background incidence of AEs is expected. A majority of subjects in pooled safety analyses were female; no conclusions can be made regarding effect of gender on margetuximab safety. Safety in White subjects was generally consistent with that of non-White subjects and among geographic regions (North America, Europe, and Other regions). No notable differences were seen between subjects with ECOG 0 versus ECOG 1 performance status.

#### *Organ Dysfunction*

Subjects with significant renal impairment were excluded from margetuximab studies. Most subjects in pooled safety analyses (92.7%) had creatinine clearance  $\geq 60$  mL/min. In pooled safety analyses, a higher proportion with  $< 60$  mL/min than  $\geq 60$  mL/min had SAEs (30.8% of 26 subjects vs 15.2% of 328 subjects), but no other notable differences were observed. In Study 04, individual exposure values indicated no meaningful differences among subjects with mild or moderate renal impairment. Renal function does not appear to have a meaningful effect on margetuximab clearance or safety. Margetuximab dose adjustment does not appear warranted for patients with mild to moderate renal impairment.

Subjects with severe hepatic impairment were excluded from margetuximab studies. Median steady-state margetuximab exposure values for subjects with mild hepatic impairment were similar to those of subjects with normal hepatic function. Hepatic enzyme levels, AEs, and SMQ-derived events did not suggest a safety issue for subjects treated with margetuximab. Margetuximab dose adjustment does not appear warranted for patients with mild to moderate hepatic impairment.

### *CD16A Genotype*

In pooled safety analyses, CD16A genotype differences do not appear to have a clinically meaningful effect on margetuximab safety (**BLA – Section 2.7.4.5.1.7**).

#### The FDA's Assessment:

FDA agrees with the Applicant's assessment.

## 8.2.8. Specific Safety Studies/Clinical Trials

### Data:

Interim results are available from the non-randomized Infusion Substudy cohort of Study 04 (see schema **Figure 1**). This cohort evaluated safety and tolerability of reduced duration margetuximab infusions. Two sequential safety run-in groups enrolled first. In the safety run-in, margetuximab was given over 120 minutes in Cycle 1, then either 60 (Stage A1) or 30 minutes (Stage A2) from Cycle 2 onward. Infusion duration in subsequent cohort expansion (Stage B) was per Stage A2. The primary endpoint was incidence of  $\geq$  Grade 3 IRRs by end of Cycle 2. A secondary endpoint was incidence of IRRs of any grade.

Eligibility for Study 04 randomized versus infusion substudy patients differed in 2 ways: 1) substudy participants must have received at least 4 prior lines of non-hormonal therapy for metastatic disease, and 2) eligible subjects received all of prior trastuzumab, pertuzumab, and T-DM1. Investigators chose margetuximab study therapy as a single agent or in combination with any of 4 single-agent chemotherapies (capecitabine, eribulin, gemcitabine, or vinorelbine).

As of 17-Jun-2019, all 88 enrolled subjects had received Cycle 1 study treatment. Group assignments included 8 subjects in Stage A1, 9 in Stage A2, and 71 in Stage B. Eighty-three received Cycle 2 study treatment and were followed for at least 1 week post-treatment. Of these 83, 79 received accelerated infusion(s) at or after Cycle 2. Of 88 enrolled, 37 subjects remained on study therapy, 14 died, 13 had SAEs, and 3 discontinued due to AEs unrelated to infusion time. Eighteen had an IRR, none of which were  $\geq$  Grade 3. From Cycle 2 onward, despite reduced infusion time, only 1 subject had an IRR (Grade 1). This nonrandomized cohort study remains ongoing.

The 30-minute infusion resulted in comparable PK to 120-minute infusion in randomized Study 04. Based on median  $C_{\text{trough}}$ , margetuximab is at steady-state by the end of Cycle 3 or in Cycle 4. Median  $C_{\text{trough}}$  remains consistently above the putative threshold target concentration (30  $\mu\text{g}/\text{mL}$ ) for margetuximab efficacy. Chemotherapy coadministration with margetuximab has no clinically meaningful effects on margetuximab PK ( $C_{\text{trough}}$  and  $C_{\text{max}}$ ). Exposure was comparable across study states (i.e., 120-minute infusions in Cycle 1, followed by either 60 minute [Stage A1] or 30-minute infusions in Cycle 2 onwards [Stages A2, B]).

Two of 80 evaluable subjects (2.5%) developed ADA on or after margetuximab therapy. None developed treatment-emergent neutralizing antibodies. Margetuximab ADA induction is modest.

Accelerated 30-minute margetuximab infusions demonstrated acceptable safety and tolerability. There were no Grade 3 or higher IRRs in this Infusion Substudy. Starting from Cycle 2, IRRs during 30-minute infusions had similar incidence and character when compared to 120-minute infusions, characteristically absent for both.

The Applicant's Position:

Although the Infusion Substudy population was more heavily pretreated than the randomized Study 04 population, AE incidence, type, and severity are generally consistent with Study 04. Reduction of infusion duration to 30 minutes for Cycle 2 and beyond does not adversely affect margetuximab safety or increase IRR risk or severity. Margetuximab can be safely administered, alone or with chemotherapy, as a 120-minute infusion for Cycle 1 then 30-minute infusion for Cycle 2 and beyond.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

## 8.2.9. Additional Safety Explorations

### Human Carcinogenicity or Tumor Development

The Applicant's Position:

See Pharmacology/Toxicology review ([Section 5](#)).

The FDA's Assessment:

FDA agrees with the Applicant's assessment

### Human Reproduction and Pregnancy

The Applicant's Position:

Labelled information for trastuzumab and other anti-HER products includes embryo-fetal toxicity warnings. Postmarketing reports describe use of trastuzumab during pregnancy, followed by cases of oligohydramnios manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death ([41](#)). NCCN Guidelines for Adolescent and Young Adult Oncology confirm that use of anti-HER2 antibodies is not recommended during pregnancy. An enhanced pre- and postnatal development nonclinical toxicology study ([Study 8329256](#)) confirmed that margetuximab causes oligohydramnios. Placental antibody transfer was detected. No studies were conducted on impairment of fertility in females or males of reproductive potential.

Pregnancy Registries are in place for approved trastuzumab, T-DM1, and pertuzumab. However, there is no such registry for recently approved trastuzumab biosimilars (e.g., HERZUMA<sup>®</sup>, TRAZIMERA<sup>™</sup>) or other anti-HER2 products, such as lapatinib and neratinib. Given current labeling of other anti-HER2 products, e.g., lapatinib and neratinib, the Sponsor believes that embryo-fetal risk can be managed through product labeling and routine pharmacovigilance surveillance. Proposed prescribing information discourages patients receiving margetuximab from becoming pregnant. Given FDA 06-May-2019 Pre-BLA meeting feedback, a pregnancy registry is not planned.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment. Please see section 5.5.4 of the nonclinical review for more information. In the USPI, FDA advises that all females of reproductive potential should have pregnancy status verified prior to initiating margetuximab. The USPI also includes the following information: that females of reproductive potential should use effective contraception during treatment and for at least 4 months following the last dose of margetuximab. Embryo-fetal toxicity is included as a black-box warning in the USPI.

**Pediatrics and Assessment of Effects on Growth**

The Applicant's Position:

Breast cancer is not reported to occur in the pediatric population. A full waiver from pediatric study requirements for margetuximab in the treatment of HER2-positive breast cancer is applicable because studies are impossible or highly impracticable to conduct (see **Agreed Initial Pediatric Study Plan** in the BLA submission).

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

**Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

The Applicant's Position:

There were no reports of overdose in margetuximab studies. Potential for drug abuse or dependence is not expected for an anti-HER2-targeted mAb. No reports of drug abuse with margetuximab have occurred. No withdrawal or rebound effects are expected with an anti-HER2-targeted mAb. No withdrawal or rebound effects have been observed in margetuximab clinical studies to date.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

### 8.2.10. Safety in the Postmarket Setting

#### Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable. Margetuximab is not marketed in any country.

The FDA's Assessment:

Not applicable

#### Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Toxicities have been adequately represented in Study 04. Potential safety concerns beyond risks conveyed in proposed labeling are not expected. Routine pharmacovigilance activities will monitor unexpected AEs.

The FDA's Assessment:

FDA generally agrees that the safety of margetuximab has been adequately characterized in Study 04 and the other studies reviewed as part of this application. The FDA will continue to monitor post-marketing reports and safety reports submitted after approval.

### 8.2.11. Integrated Assessment of Safety

The Applicant's Position:

Safety data from Studies 04, 01, and 02 were integrated in pooled safety analyses to assess consistency of safety data across studies. Nonetheless, Study 04 is the primary source of safety information for the proposed label as it is the only study with an active comparator group. All subjects in Study 04 received the proposed margetuximab regimen of 15 mg/kg Q3W. Overall, safety was well characterized in the intended target population.

Margetuximab has acceptable safety that is consistent across studies and similar to that of trastuzumab. In Study 04, the most common AEs on margetuximab were fatigue, nausea, neutropenia/neutrophil count decreased, and diarrhea. Backbone chemotherapy choice did not appear to influence the margetuximab safety profile.

More Study 04 subjects on margetuximab than trastuzumab (13.3% vs 3.4%) had IRRs, almost all on the first infusion only. Grade 3 (1.5%) and SAE (1.1%) IRRs were observed in the margetuximab group only, almost all on the first infusion only. This difference is not surprising because no subjects previously received margetuximab, whereas all received prior trastuzumab. Also, the observed IRR rate on margetuximab is consistent with that reported in the HERCEPTIN® (trastuzumab) USPI and published literature (16.2%) (37). IRR events on margetuximab were observed primarily on the first infusion only, with atypical recurrence in

later cycles. A majority of IRRs were CTCAE Grade 1 or 2. No IRR was Grade  $\geq 4$ . IRR symptoms were similar for margetuximab and trastuzumab, predominately chills and pyrexia with few events of hypertension and no hypotension.

The Study 04 Infusion Substudy investigated accelerated administration to 30 minutes duration from Cycle 2 onwards. IRRs were  $\leq$  Grade 2 and occurred predominantly during the first (120 minute) administration, as seen in randomized Study 04. From Cycle 2 onward, despite reduced infusion time, 1 subject only (1.1%) had a Grade 1 IRR. No  $\geq$  Grade 3 IRRs were observed. Reduction of infusion duration to 30 minutes for Cycle 2 and beyond does not adversely affect margetuximab safety or increase IRR risk or severity. These data support use of 30-minute margetuximab infusions from Cycle 2 forward. The proposed margetuximab label includes text in the Warnings and Precautions section to inform that infusions should be slowed or interrupted in case of IRR. Dosing should be permanently discontinued in case of life-threatening IRR. Patients should be observed closely for IRRs, especially during the first infusion of margetuximab.

Cardiotoxicity is an identified risk for trastuzumab. In Study 04, margetuximab and trastuzumab displayed similar potential for left ventricular dysfunction. All LVEF reductions detected by monitoring were asymptomatic. For all subjects with complete follow-up, LVEF reductions were reversible. The proposed margetuximab label includes text in the Warnings and Precautions section to inform that margetuximab may lead to reductions in LVEF. LVEF should be monitored during treatment and dosing withheld or discontinued, as appropriate. Dosing should be withheld for  $\geq 16\%$  decrease from baseline in LVEF or LVEF below institutional normal limits (or 50% if no limits are available) and  $\geq 10\%$  decrease from baseline. Dosing should be permanently discontinued if LVEF decline persists for  $> 8$  weeks or if dosing is interrupted for LVEF decline on more than 3 occasions. Patient counseling information will also present a description of this risk.

Embryofetal toxicity is an identified risk for anti-HER2 therapies, including trastuzumab. Nonclinical studies confirmed that margetuximab causes oligohydramnios in fetuses and undergoes placental transfer. The proposed margetuximab label will include text in the Warnings and Precautions section and Boxed Warning to inform that margetuximab may cause fetal harm when administered during pregnancy. Females of reproductive potential should use effective contraception during treatment and for 4 months after the last dose of margetuximab (consistent with FDA guidance “Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format”). Patient counseling information will also present a description of this risk.

In Study 04, neutropenia/neutrophil count decreased of all grades and Grade  $\geq 3$  were each about 5% more frequent on margetuximab than trastuzumab. However, clinical sequelae including febrile neutropenia and infections were higher on trastuzumab. Also, neutropenia is

not observed when margetuximab is administered as monotherapy. Thus, there is no evidence of a clinically meaningful difference between margetuximab and trastuzumab in generation of neutropenia. No specific monitoring for neutropenia is included in the proposed margetuximab label.

HERCEPTIN® (trastuzumab) USPI includes Boxed Warnings for pulmonary toxicity, including interstitial pneumonitis and acute respiratory distress syndrome. With the exception of a single Grade 1 unrelated AE of pneumonitis on margetuximab, no such events were reported on margetuximab in Study 04. Pulmonary toxicity SMQ analysis indicated mild to moderate events of dyspnea on margetuximab. Clinical significance of this difference is unknown. No specific monitoring for pulmonary toxicity is included in the proposed margetuximab label.

SMQ analysis did not reveal potential safety issues with regards to hepatic toxicity, agranulocytosis, thromboembolic events, or hypersensitivity reactions. No specific monitoring for these events is included in the proposed margetuximab label.

As with all therapeutic proteins, margetuximab has potential to be immunogenic in humans. New ADAs were observed at a low rate in Study 04 (1.5% of 263 subjects in the main study and 2.5% of 80 subjects in the Infusion Substudy). None persisted, and no treatment-emergent neutralizing antibodies were detected. No newly developed ADAs were observed in Study 01 or Study 02. Margetuximab ADAs had no clinical effect on margetuximab PK, safety, or efficacy. The proposed margetuximab label will include a summary of margetuximab immunogenicity.

Given reassuring PPK and AE by subgroup analyses, no dose adjustment or special monitoring is needed in special groups, including older patients and those with moderate renal or hepatic impairment. Currently, there is no data to inform if margetuximab dose should be adjusted in severe renal or hepatic impairment.

Overall, the margetuximab safety profile was acceptable and as expected for subjects undergoing treatment for advanced HER2+ MBC.

#### The FDA's Assessment:

FDA generally agrees that Study 04 adequately characterizes the safety profile of margetuximab plus chemotherapy. Study 04 provides evidence of the safety profile of margetuximab plus chemotherapy with supportive data from Studies 01 and 02. Furthermore, the safety data from Study 04 has adequately characterized the toxicities of margetuximab plus chemotherapy.

Study 04 is a multicenter, open-label, active-control, randomized study of margetuximab plus chemotherapy (N=264) vs trastuzumab plus chemotherapy (N=266) in patients with HER2+ advanced breast cancer that have received prior treatment with other HER2-directed therapies, one of which was for advanced disease. Study 04 also included an infusion substudy to evaluate

safety and tolerability of 30-minute infusions of margetuximab, starting from Cycle 2.

In Study 04, the proportion of patients who experienced an AE was similar between the margetuximab and trastuzumab treatment arms. Over 98% of patients treated on Study 04 experienced an AE. The most common TEAEs occurring in at least 10% of patients who received margetuximab plus chemotherapy included fatigue/asthenia, nausea, diarrhea, vomiting, constipation, headache, pyrexia, alopecia, abdominal pain, peripheral neuropathy, arthralgia/myalgia, cough, decreased appetite, dyspnea, infusion-related reactions, palmar-plantar erythrodysesthesia, and extremity pain.

Serious adverse events reported in Study 04 were also similar between the 2 treatment arms. Sixteen percent of patients who received margetuximab plus chemotherapy experienced a SAE. Serious adverse events occurring in > 1% of patients treated with margetuximab plus chemotherapy included febrile neutropenia, neutropenia/neutrophil count decrease (1.5% each) and infusion related reactions (1.1%). Fatal TEAEs occurred in 1.1% of patients who received margetuximab; these included viral pneumonia (0.8%) and aspiration pneumonia (0.4%). Permanent discontinuation due to an AE occurred in 3% of patients who received margetuximab. Treatment emergent adverse events leading to permanent discontinuation in >1% of patients who received margetuximab plus chemotherapy included LV dysfunction and IRR's. Dosage interruptions due to an TEAE occurred in 11% of patients who received margetuximab. IRR lead to dose interruption in > 5% of patients treated with margetuximab plus chemotherapy.

The infusion substudy of Study 04 showed that margetuximab maybe safely administered in a shorter duration. Consistent with the findings in the main study, IRRs in the substudy occurred predominantly during the first cycle administration. Despite reduced infusion time, IRRs observed in the substudy were ≤ Grade 2. Thus, reduction of infusion duration from 120 minutes to 30 minutes for Cycle 2 onward does not appear to increase the risk or severity of IRR, nor does it adversely affect the safety profile of margetuximab.

The section on Warnings and Precautions in the proposed margetuximab label includes text informing health care providers about IRRs and appropriate measures to take when these occur. In case of an IRR, infusion should be slowed or interrupted and be permanently discontinued in case of life-threatening IRR.

Margetuximab plus chemotherapy demonstrated an acceptable safety profile for the indicated population with a serious and life-threatening disease. FDA believes that the toxicities of margetuximab are manageable with labeling.

## SUMMARY AND CONCLUSIONS

### 8.3. Statistical Issues

#### The FDA's Assessment:

SOPHIA (Study-04) showed a statistically significant improvement in favor of the margetuximab arm with respect to the primary endpoint of PFS by BIRC. Co-primary endpoint of OS has not reached statistical significance at the second interim OS (70% of targeted OS events ) but does not appear to show any detriment in ITT population. Study-04 has three notable statistical issues:

1. The median PFS per BIRC advantage on margetuximab over trastuzumab is shorter than the imaging interval of 6 weeks. However, as trastuzumab is an active control and margetuximab replaces trastuzumab (does not add on to) in the treatment regimen there is a reasonable assurance that margetuximab confers, at the minimum, the same amount of benefit, if not more, as trastuzumab in this disease setting.
2. Although supportive, no claim of statistical significance can be made with respect to the key secondary endpoints of PFS per investigator assessment and ORR because an entire 0.05 alpha (two-sided) was allocated for testing primary endpoints PFS per BIRC and OS sequentially. Since OS was not found to be statistically significant at the second interim analysis, there is no alpha available for testing the key secondary endpoints. As a consequence, the p-values associated with these key secondary endpoints are considered nominal only.
3. A subgroup of patients with Fc-receptor CD16A-158 V/V homozygote have different outcomes in a direction unfavorable to margetuximab compared to overall study population and other subgroups. This is a mechanistically unexpected finding because margetuximab is specifically Fc-engineered to provide higher affinity, compared to trastuzumab, to both F-carriers and V/V alleles. Further post-hoc analysis accounting for moderate imbalance in prognostics factors did not yield a satisfactory explanation for this observed anomaly. Nonetheless, the subgroup analysis result should be interpreted with caution due to a small sample size (n=69), possible imbalances in patient characteristics between treatment arms, and no clear mechanistic basis to support the observed heterogeneity. More studies will be required to explain and better understand this apparent incongruity.

#### 8.4. Conclusions and Recommendations

The FDA's Assessment:

The clinical and statistical reviewers agree with regular approval for this BLA for the reasons stated in the FDA assessments above.

X

X

---

Anup Amatya, PhD  
Primary Statistical Reviewer

Mallorie Fiero, PhD  
Statistical Team Leader

X

X

---

Melanie Royce, MD, PhD  
Primary Clinical Reviewer

Christy Osgood, MD  
Clinical Team Leader

## 9 Advisory Committee Meeting and Other External Consultations

---

**The FDA's Assessment:**

No advisory committee consultations external to the FDA were deemed necessary for this BLA application.

## 10 Pediatrics

---

The Applicant's Position:

Not applicable. The proposed indication is not reported to occur in the pediatric population.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment given the extremely low incidence of breast cancer in the pediatric population.

## 11 Labeling Recommendations

**The Applicant’s Position:**

Labelling negotiations are pending.

**The FDA’s Assessment:**

The FDA’s labeling revisions to the Applicant’s proposed labeling are included in the table below.

| Summary of Significant Labeling Changes (High level changes and not direct quotations) |                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Section                                                                                | Applicant’s Proposed Labeling                                                                                                                                                                                                                                                                                                                                                | FDA’s Proposed Labeling                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Highlights                                                                             | <p>Boxed Warning for embryo-fetal toxicity.</p> <p>Indication and Usage did not specify adult patients</p> <p>Dosage and Administration specifies “Do not administer as an intravenous push or bolus. Do not mix (b) (4) with other drugs”</p> <p>Warnings and Precautions listed Left Ventricular dysfunction and had the following instructions (b) (4)</p> <p>(b) (4)</p> | <ul style="list-style-type: none"> <li>• Added Left ventricular dysfunction to the boxed warning</li> <li>• Revised pharmacologic class from (b) (4) to “HER2/neu receptor antagonist” to Indications and Usage</li> <li>• Added the word “adult” to Indications and Usage</li> <li>• Deleted sentences after “For intravenous use only.”</li> <li>• Moved Left Ventricular dysfunction from Warnings and Precautions to Boxed Warning</li> <li>• Revised wording of the instructions on management of Left Ventricular Dysfunction to “Evaluate cardiac function prior to and during treatment. Discontinue MARGENZA treatment for a confirmed clinically significant decrease in left ventricular function.”</li> </ul> |
| Boxed Warning                                                                          | Proposed Boxed Warning for embryo-fetal toxicity only                                                                                                                                                                                                                                                                                                                        | Moved Left Ventricular dysfunction, with the revised management instructions, from Warnings and Precautions to Boxed Warning                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 1 Indications and Usage                                                                |                                                                                                                                                                                                                                                                                                                                                                              | Added the word “adult”                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 2 Dosage and Administration                                                            | 3.1 Recommended Doses and Schedules                                                                                                                                                                                                                                                                                                                                          | • Added “Refer to the respective Prescribing Information for each                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

|  |                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <p>3.2 Dose Modification or Important Dosing Considerations – wording of first paragraph was revised</p> <p>2.3 Preparation for Administration</p> <p>First paragraph under Section 2.3 was revised.</p> <p>2<sup>nd</sup> bulleted instruction under preparation instruction was revised</p> <p>4<sup>th</sup> bulleted instruction under preparation instruction was revised</p> | <p>therapeutic agent administered in combination with MARGENZA for the recommended dosage information, as appropriate.”</p> <ul style="list-style-type: none"> <li>• Wording of first paragraph was revised to “If a patient misses a dose of MARGENZA, administer the scheduled dose as soon as possible. Adjust the administration schedule to maintain a 3-week interval between doses.</li> <li>• Moved the sentences after “Administer as an intravenous infusion.” from the first paragraph under Section 2.3 to the end of the preparation instruction of Section 2.3</li> <li>• 2<sup>nd</sup> bulleted instruction under preparation instructions was deleted</li> <li>• 4<sup>th</sup> bulleted instruction under preparation instructions was broken out into four bullets as follows:             <ul style="list-style-type: none"> <li>– Calculate the required volume of MARGENZA needed to obtain the appropriate dose according to patient’s body weight. The calculated total dose volume should be rounded to the nearest 0.1 mL.</li> <li>– Withdraw appropriate volume of MARGENZA solution from the vial(s) using a syringe.</li> <li>– Transfer MARGENZA into an intravenous bag containing 100 mL or 250 mL 0.9% Sodium Chloride Injection, USP. Polyvinyl chloride (PVC) intravenous bags or intravenous bags made with polyolefins (polyethylene and polypropylene) and polyamide or</li> </ul> </li> </ul> |
|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                              |                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                              |                                                                                                                                                                                                                                                                                                                                                                                 | <p>polyolefins only or copolymer of olefins may be used. Do not use 5% Dextrose Injection, USP solution.</p> <p>– The final concentration of the diluted solution should be between 0.5 mg/mL to 7.2 mg/mL.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 3 Dosage Forms and Strengths |                                                                                                                                                                                                                                                                                                                                                                                 | <p>Revised as “Injection: 250 mg/10 mL (25 mg/mL) clear to slightly opalescent, colorless to pale yellow or pale brown solution in a single-dose vial.”</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 5 Warnings and Precautions   | <p>Order of Warnings and Precautions proposed by the Sponsor was as follows:</p> <ul style="list-style-type: none"> <li>5.1 Embryo-Fetal Toxicity</li> <li>5.2 Left Ventricular Dysfunction</li> <li>5.3 Infusion-Related Reactions</li> </ul> <p>Proposed wording for various section included information that was either deleted or revised for clarity and conciseness.</p> | <ul style="list-style-type: none"> <li>• Reordered this section to:                             <ul style="list-style-type: none"> <li>5.1 Left Ventricular Dysfunction</li> <li>5.2 Embryo-Fetal Toxicity</li> <li>5.3 Infusion-Related Reactions</li> </ul> </li> <li>• Under 5.1, wording of first paragraph was revised to be more succinct and reads as “Left ventricular cardiac dysfunction can occur with MARGENZA. In SOPHIA, left ventricular dysfunction occurred in 1.9% of patients treated with MARGENZA. MARGENZA has not been studied in patients with a pretreatment LVEF value of &lt; 50%, a prior history of myocardial infarction or unstable angina within 6 months, or congestive heart failure NYHA class II-IV.”</li> <li>• Under 5.2, wording of the first paragraph was revised to read as “Based on findings in animals and mechanism of action, MARGENZA can cause fetal harm when administered to a pregnant woman. There are no available data on the use of MARGENZA in pregnant women to inform the drug-associated risk. In postmarketing reports, use of a HER2-directed</li> </ul> |

|  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  |  | <p>antibody during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities and neonatal death. In an animal reproduction study, intravenous administration of margetuximab-cmkb to pregnant cynomolgus monkeys once every 3 weeks starting at gestational day (GD) 20 until delivery resulted in oligohydramnios and delayed infant kidney development. Animal exposures were <math>\geq 3</math> times the human exposures at the recommended dose, based on C<sub>max</sub>.”</p> <ul style="list-style-type: none"><li>• Under 5.3, the following revisions were made:<ul style="list-style-type: none"><li>– IRR’s that were <math>\geq 5\%</math> were rounded to the nearest whole number throughout this section.</li><li>– First sentence in the first paragraph reads as “MARGENZA can cause infusion-related reactions (IRRs)”</li><li>– 2<sup>nd</sup> paragraph was revised to be more succinct and reads as “In SOPHIA, IRRs were reported by 13% of patients on MARGENZA plus chemotherapy. Most of the IRRs occur during Cycle 1. Grade 3 IRRs were reported in 1.5% of MARGENZA-treated patients. All IRRs resolved within 24 hours, irrespective of severity. In SOPHIA, IRRs leading to interruption of treatment occurred in 9% in patients treated with MARGENZA and chemotherapy. One patient</li></ul></li></ul> |
|--|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

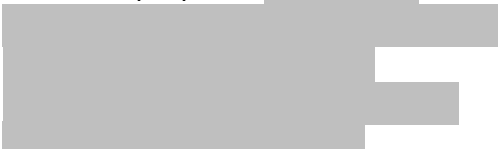
|                            |                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                            |                                                                                                                                                                                                                                                     | <p>(0.4%) on MARGENZA discontinued treatment due to IRR.”</p> <ul style="list-style-type: none"> <li>– 3<sup>rd</sup> paragraph was revised to be more succinct and reads as “An infusion substudy in 88 patients in SOPHIA evaluated MARGENZA administered over 120 minutes for the initial dose, then 30 minutes from Cycle 2 forward. IRRs were ≤ Grade 2 and most occurred during the first (120 minutes) administration of MARGENZA. From Cycle 2 onward, one patient (1.1%) had an IRR (Grade 1).”</li> <li>– 4<sup>th</sup> paragraph, first sentence was revised to “Monitor patients for IRRs during MARGENZA administration and as clinically indicated after completion of infusion.”</li> <li>– 5<sup>th</sup> paragraph, first sentence was revised to “In patients who experience mild or moderate IRRs, consider premedications, including antihistamines, corticosteroids, and antipyretics.”</li> <li>– Added “Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.” prior to the last sentence in section 5.3</li> </ul> |
| <p>6 Adverse Reactions</p> | <p>Section 6 was in part not consistent with OOD’s Best Labeling Practices. This section was reordered to be consistent with OOD’s Best Labeling Practices to present this information in a consistent manner and to make this information more</p> | <ul style="list-style-type: none"> <li>• Revised the order of the bullets to reflect information in the preceding Warnings and Precautions</li> <li>• Revisions to Section 6.1 Clinical Trials Experience:             <ul style="list-style-type: none"> <li>– Revised presentation of data and organization of, including rewording of the information to be more succinct.</li> </ul> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

|  |                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--|--------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <p>useful and accessible to healthcare providers (HCPs).</p> | <ul style="list-style-type: none"><li>- Revised the Table proposed in section 6.1 presenting AEs in Study 04. This was separated into 2 tables: Table 1 for AEs occurring in <math>\geq</math> (b) (4) of patients and Table 2 for select laboratory abnormalities (&gt;20%) that worsened from baseline.</li><li>- Added AEs in Table 1 that should be included regardless of attribution</li><li>- Deleted paragraph on (b) (4) since this was incorporated in the revision.</li><li>• Section 6.2 Immunogenicity:<ul style="list-style-type: none"><li>- Information presented was reorganized for clarity.</li><li>- The following information was added pertinent to Study 04: “Of these 4 patients, anti-margetuximab antibodies were detected prior to Cycle 7 of MARGENZA dosing in 1 patient, and more than 2 months after the last MARGENZA dose in 3 patients. In the infusion substudy, treatment-emergent anti-margetuximab antibodies were observed in 2 patients (3.8%). Of these 2 patients, anti-margetuximab antibodies were detected prior to Cycle 3 of MARGENZA dosing in 1 patient, and more than 6 months after the last MARGENZA dose in 1 patient. Due to the limited number of patients who developed antimargetuximab antibodies during treatment with MARGENZA, the impact of anti-margetuximab antibodies on the</li></ul></li></ul> |
|--|--------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                               |                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                               |                                                                                                                                          | PK, safety and efficacy of MARGENZA is unknown.”                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 7 Drug Interactions           | Proposed wording was not consistent with OOD’s Best Labeling Practices for Drug Interactions.                                            | <ul style="list-style-type: none"> <li>• Added “<u>Anthracyclines</u>” as a subheading</li> <li>• Revised wording to read as “Patients who receive anthracyclines less than 4 months after stopping MARGENZA [see Clinical Pharmacology (12.3)] may be at increased risk of cardiac dysfunction. While this interaction has not been studied with MARGENZA, clinical data from other HER2-directed antibodies warrants consideration. Avoid anthracycline-based therapy for up to 4 months after stopping MARGENZA. If concomitant use is unavoidable, closely monitor patient’s cardiac function.”</li> </ul>                                                                                                                                                            |
| 8 Use in Specific Populations | <p>Proposed wording did not contain sufficient details.</p> <p>Proposed 8.6 Renal Impairment and 8.7 Hepatic impairment were deleted</p> | <ul style="list-style-type: none"> <li>• Under 8.1 Pregnancy:                             <ul style="list-style-type: none"> <li>– First paragraph was revised to add clarity and details and reads as “Based on findings in animals and mechanism of action, MARGENZA can cause fetal harm when administered to a pregnant woman. There are no available data on use of MARGENZA in pregnant women to inform the drug-associated risk. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. In an animal reproduction study, intravenous administration of margetuximab-</li> </ul> </li> </ul> |

|  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|--|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  |  | <p>cmkb to pregnant cynomolgus monkeys once every 3 weeks, starting at gestational day (GD) 20 until delivery, resulted in oligohydramnios and delayed infant kidney development. Animal exposures were <math>\geq 3</math> times the human exposures at the recommended dose, based on Cmax (see Data). Advise patients of potential risks to a fetus. There are clinical considerations if MARGENZA is used during pregnancy or within 4 months prior to conception (see Clinical Considerations).”</p> <ul style="list-style-type: none"> <li>– Added subsection Human Data<br/>         “There are no human data available regarding the experience of MARGENZA and pregnancy.”</li> <li>– Revised Animal Data section for clarity.</li> <li>• Section 8.3 Females and Males of Reproductive Potential           <ul style="list-style-type: none"> <li>– Added “MARGENZA can cause fetal harm when administered to a pregnant woman.</li> <li>– Deleted the first sentence under Contraception Females</li> </ul> </li> <li>• Under 8.5 Geriatric Use: Revised to provide additional details and clarity and reads as “Of the 266 patients treated with MARGENZA 20% were 65 years of age or older and 4% were 75 years or older. No overall differences in efficacy were observed between patients <math>\geq 65</math> years of age compared to younger patients. There was a higher incidence of Grade <math>\geq 3</math> adverse reactions observed in patients age</li> </ul> |
|--|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                          |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|--------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                          |                                                                                 | 65 years or older (56%) compared to younger patients (47%), as well as adverse reactions associated with potential cardiotoxicity (35% vs 18%).”                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                          | (b) (4)                                                                         | Deleted because (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 11 Description           |                                                                                 | First paragraph was revised to read “Margetuximab-cmkb, a HER2/neu receptor antagonist, is a chimeric Fc-engineered IgG1 kappa monoclonal antibody.” (b) (4)<br>(b) (4) ere deleted.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 12 Clinical Pharmacology | Proposed organization and was not consistent with OOD’s Best Labeling Practices | <ul style="list-style-type: none"> <li>• Under 12.1 Mechanism of Action, wording was revised for clarity and succinctness to summarize the established mechanism(s) of action (MOA); and to remove (b) (4)</li> <li>• Under 12.2 Pharmacodynamics, proposed wording and (b) (4) was replaced with “The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of margetuximab-cmkb have not been fully characterized.”</li> <li>• Under 12.3 Pharmacokinetics</li> <li>• Information under first paragraph was parsed out into subheadings: Distribution, Elimination, Metabolism</li> <li>• Extraneous information was deleted, including proposed (b) (4) for clarity and succinctness.</li> </ul> |

|                           |                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                           |                                                     | <ul style="list-style-type: none"> <li>• Specific population: Information was condensed with additional details provided; proposed subheadings were deleted. This section now reads “No clinically significant differences in margetuximab-cmkb PK were observed based on age (29 to 83 years), sex, race (Caucasian, Black, Asian), mild to moderate (CLcr 30 to 89 mL/min estimated using the Cockcroft-Gault equation) renal impairment, mild hepatic impairment (total bilirubin ≤ ULN and AST &gt; ULN, or total bilirubin 1 to 1.5 ULN and any AST), HER2 expression level (0 to 3 by IHC), tumor burden (2 – 317 mm), ECOG score (0 to 2), albumin (24 to 50 g/L), FCGR3A (CD16A), FCGR2A (CD32A) and FCGR2B (CD32B) genotype, number of metastatic sites (≤ 2 or &gt; 2), number of prior therapy lines (≤ 2 or &gt; 2) or concurrent chemotherapies (capecitabine, gemcitabine, eribulin and vinorelbine).<br/>                 The effect of severe renal impairment (CLcr 15 to 29 mL/min), end-stage renal disease with or without hemodialysis, and moderate (total bilirubin &gt; 1.5 to ≤ 3 ULN and any AST) or severe hepatic impairment (total bilirubin &gt;3 ULN and any AST) on margetuximab-cmkb PK is unknown.”</li> </ul> |
| 13 Nonclinical Toxicology | Proposed section did not provide sufficient details | Removed proposed <span style="float: right;">(b) (4)</span><br>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

|                                      |                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------------|-----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                      |                                                                                                                 | (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 14 Clinical Studies                  | 14.1 Metastatic Breast Cancer proposed content and wording was revised to reflect OOD's Best Labeling Practices | <ul style="list-style-type: none"> <li>• Details on conduct, eligibility, and statistical analyses of Study 04 were revised for brevity.</li> <li>• Redundant information related to the (b) (4) were removed (b) (4)</li> <li>• Concise demographic information added per 21 CFR 201.57(c).</li> <li>• Efficacy results in Table 3 (and endpoint descriptions) was revised to include only PFS per BICR (b) (4) consistent with preferred statistical analysis plan for Study 04.</li> <li>• Figure 1 was revised to delete (b) (4) in the figure</li> <li>• (b) (4) was deleted</li> </ul> |
| 16 How Supplied/Storage And Handling |                                                                                                                 | <ul style="list-style-type: none"> <li>• Under 16.1 How Supplied, revised first paragraph as "MARGENZA (margetuximab-cmkb) injection is a clear to slightly opalescent, colorless to pale yellow or pale brown solution in a single-dose vial supplied as:"</li> </ul>                                                                                                                                                                                                                                                                                                                       |
| 17 Patient Counseling Information    |                                                                                                                 | <ul style="list-style-type: none"> <li>• Reversed the order to have LV Dysfunction first followed by Embryo-fetal Toxicity consistent with revisions to Section 5.</li> <li>• Added "... and for 4 months following the last dose" under last paragraph of Embryo-Fetal Toxicity.</li> </ul>                                                                                                                                                                                                                                                                                                 |

## 12 Risk Evaluation and Mitigation Strategies (REMS)

---

### The FDA's Assessment:

Based on the benefit-risk profile of margetuximab in combination with chemotherapy, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance. REMS are not required by the FDA for this new drug application.

## 13 Postmarketing Requirements and Commitment

---

### The FDA's Assessment:

The following Postmarketing requirements and commitments were agreed upon by FDA and the Applicant.

### Postmarketing Requirements (PMRs)

None

### Postmarketing Commitments (PMCs)

1. Submit the final overall survival analysis and datasets with the final report from clinical Study CP-MGAH22-04 titled "A Phase 3, Randomized Study of Margetuximab Plus Chemotherapy vs Trastuzumab Plus Chemotherapy in the Treatment of Patients With HER2+ Metastatic Breast Cancer Who Have Received Prior Anti-HER2 Therapies and Require Systemic Treatment", to further confirm the clinical benefit of margetuximab. The results from this study may inform product labeling.

Final Protocol Submission: 06/2020

Interim Report Submission: 03/2022

Study Completion: 12/2022

Final Report Submission: 06/2023

2. Provide the final report and dataset containing information pertinent to CD16A (FCGR3A) F158V genotype and patient outcome from clinical trials that correlate CD16A (FCGR3A) F158V genotype with trial efficacy endpoints to further characterize the clinical benefit of margetuximab that may inform product labeling.

Interim Report submission: 03/2022

Study Completion: 12/2022

Final Report Submission: 06/2023

3. Conduct a study to assess neutralizing antibody (nAb) responses against margetuximab in Study CP-MGAH22-04 and the infusion sub-study (CP-MGAH22-04) with an adequately validated nAb assay. NAb responses should be evaluated in all confirmed anti-drug antibody positive samples from Study CP-MGAH22-04 and the infusion substudy. Provide the final report and include information on the level of margetuximab in each patient's test sample at each sampling point, an assessment of the effect of nAb development on the anti-tumor activity of margetuximab in individual patients, and the nAb assessment data set.

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
{MARGENZA, margetuximab-cmkb}

Study Completion 12/2022  
Final Report Submission: 06/2023

4. Provide data from one media fill using the product-specific change parts, (b) (4) and equipment to support (b) (4) the 10 mL vial/20 mm stopper combination that is used for margetuximab DP.

Final Report Submission : 6/2021

5. Develop and validate a sensitive, accurate, and reliable assay for the detection of neutralizing antibodies to MARGENZA in the presence of drug levels that are expected to be present in the serum at the time of patient sampling. The neutralizing antibody assay procedure and method validation protocol and report should be submitted to the BLA as final study report.

Study Completion: 10/2021  
Final Report Submission: 12/2021

6. Conduct a Drug Product (DP) shipping validation study of commercial DP shipped via commercial lanes to the selected third-party logistics warehouse. The study will include analytical characterization and cell-based potency determination of the DP both pre- and post-shipping. Submit results to the BLA as a final study report.

Study Completion: 12/2021  
Final Report Submission: 06/2022

7. Conduct a DP leachables study to evaluate the DP container closure system through the end of shelf-life when stored under the recommended conditions of 2-8oC. Analyses will include appropriate methods to detect organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS), semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS), including their chemical identification and quantitation. Testing will be performed at regular intervals throughout the shelf life with study results to be updated annually in the BLA Annual Report. The final report to be submitted to the BLA will include the complete data and risk evaluation for the potential impact of leachables on product safety and quality.

Study Results Submission: Annually  
Study Completion: 09/2024  
Final Report Submission: 03/2025

8. Reassess release and stability specifications for margetuximab drug substance

and/or drug product, as appropriate, by December 30, 2022 or following manufacture of 30 lots (if earlier) for the following assays: N-glycosylation (DS), residual host cell protein levels (DS), potency by CGI bioassay, HER2 binding ELISA, and FcγRIIIa binding ELISA (DS and DP), visible particles (DP), and protein content (DP). Submit the final report as a Changes Being Effected-30 Supplement (CBE-30).

Study Completion: 12/2022  
Final Report Submission: 03/2023

9. Conduct studies to optimize the three potency assays (CGI bioassay, HER2 binding ELISA, FcγRIIIa binding ELISA) for IC50 and EC50 reporting; tighten IC50 and EC50 acceptance criteria for reference standard stability assessment based on the study results. Submit the final report as a Prior Approval Supplement (PAS).

Study Completion: 06/2022  
Final Report Submission: 12/2022

10. Prospectively revalidate the (b) (4) operation as per Agency communications with (b) (4) following the 2020 pre-license inspection of the drug substance manufacturing facility. In addition, confirm (b) (4).  
Submit the results to the BLA as a Prior Approval Supplement (PAS).

Study Completion: 12/2021  
Final Report Completion: 03/2022

## 14 Division Director (DHOT) (NME ONLY)

---

X

---

John Leighton, PhD

## 15 Division Director (OCP)

---

X

---

Nam Atiqur Rahman, PhD

## 16 Division Director (OB)

---

X

---

Shenghui Tang, PhD

## 17 Division Director (Clinical)

---

X

---

Laleh Amiri-Kordestani, MD

## **18 Office Director (or designated signatory authority)**

---

*This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.*

X

---

Julia Beaver, MD

## 19 Appendices

---

### 19.1. References

#### The Applicant's References:

1. **Akram M, Iqbal M, Daniyal M, Khan AU.** Awareness and current knowledge of breast cancer. *Biol Res.* 2017;50(1):33.
2. **Arnould L, Gelly M, Penault-Llorca F, Benoit L, Bonnetain F, Migeon C, et al.** Trastuzumab-based treatment of HER2-positive breast cancer: an antibody-dependent cellular cytotoxicity mechanism? *Br. J Cancer.* 2006;94(2):259-67.
3. **Batra SK, Jain M, Wittel UA, Chauhan SC, Colcher D.** Pharmacokinetics and biodistribution of genetically engineered antibodies. *Curr Opin Biotechnol.* 2002;13(6):603-8.
4. **Bianchini G, Gianni L.** The immune system and response to HER2-targeted treatment in breast cancer. *Lancet Oncol.* 2014;15(2):e58-68.
5. **Cardoso F, Costa A, Senkus E, Aapro M, Andre F, Barrios CH, et al.** 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). *Ann Oncol.* 2017;28(12):3111.
6. **Christensen H, Hermann M.** Immunological response as a source to variability in drug metabolism and transport. *Front Pharmacol.* 2012;3:8.
7. **Clynes RA, Towers TL, Presta LG, Ravetch JV.** Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets. *Nat. Med.* 2000;6(4):443-6.
8. **Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH.** Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. *J Clin Oncol.* 2010;28(1):92-8.
9. **FDA Guidance.** Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. 2010.
10. **Forsythe A, Chandiwana D, Barth J, Thabane M, Baeck J, Tremblay G.** Progression-free survival/time to progression as a potential surrogate for overall survival in HR+, HER2-metastatic breast cancer. *Breast Cancer (Dove Med Press).* 2018;10:69-78.
11. **Gavin PG, Song N, Kim SR, Lipchik C, Johnson NL, Bandos H, et al.** Association of Polymorphisms in FCGR2A and FCGR3A With Degree of Trastuzumab Benefit in the Adjuvant Treatment of ERBB2/HER2-Positive Breast Cancer: Analysis of the NSABP B-31 Trial. *JAMA Oncol.* 2017;3(3):335-41.
12. **Gennari R, Menard S, Fagnoni F, Ponchio L, Scelsi M, Tagliabue E, et al.** Pilot study of the mechanism of action of preoperative trastuzumab in patients with primary operable breast tumors overexpressing HER2. *Clin Cancer Res.* 2004;10(17):5650-5.
13. **Hanley JA, Lippman-Hand A.** If nothing goes wrong, is everything all right? Interpreting zero numerators. *JAMA.* 1983;249(13):1743-5.

14. **Hudis CA.** Trastuzumab--mechanism of action and use in clinical practice. *N. Engl. J Med.* 2007;357(1):39-51.
15. **Hynes NE, Stern DF.** The biology of erbB-2/neu/HER-2 and its role in cancer. *Biochim Biophys Acta.* 1994;1198(2-3):165-84.
16. **Keizer RJ, Huitema AD, Schellens JH, Beijnen JH.** Clinical pharmacokinetics of therapeutic monoclonal antibodies. *Clin. Pharmacokinet.* 2010;49(8):493-507.
17. **Knutson KL, Clynes R, Shreeder B, Yeramian P, Kemp KP, Ballman K, et al.** Improved Survival of HER2+ Breast Cancer Patients Treated with Trastuzumab and Chemotherapy Is Associated with Host Antibody Immunity against the HER2 Intracellular Domain. *Cancer Res.* 2016;76(13):3702-10.
18. **Koene HR, Kleijer M, Algra J, Roos D, von dem Borne AE, de HM.** Fc gammaRIIIa-158V/F polymorphism influences the binding of IgG by natural killer cell Fc gammaRIIIa, independently of the Fc gammaRIIIa-48L/R/H phenotype. *Blood.* 1997;90(3):1109-14.
19. **Lehrnbecher T, Foster CB, Zhu S, Leitman SF, Goldin LR, Huppi K, et al.** Variant genotypes of the low-affinity Fc gamma receptors in two control populations and a review of low-affinity Fc gamma receptor polymorphisms in control and disease populations. *Blood.* 1999;94(12):4220-32.
20. **Li L, Pan Z.** Progression-Free Survival and Time to Progression as Real Surrogate End Points for Overall Survival in Advanced Breast Cancer: A Meta-Analysis of 37 Trials. *Clin Breast Cancer.* 2018;18(1):63-70.
21. **Magnes T, Melchardt T, Hufnagl C, Weiss L, Mittermair C, Neureiter D, et al.** The influence of FCGR2A and FCGR3A polymorphisms on the survival of patients with recurrent or metastatic squamous cell head and neck cancer treated with cetuximab. *Pharmacogenomics J.* 2018;18(3):474-9.
22. **Mahaweni NM, Olieslagers TI, Rivas IO, Molenbroeck SJJ, Groeneweg M, Bos GMJ, et al.** A comprehensive overview of FCGR3A gene variability by full-length gene sequencing including the identification of V158F polymorphism. *Sci Rep.* 2018;8(1):15983.
23. **Molina MA, Codony-Servat J, Albanell J, Rojo F, Arribas J, Baselga J.** Trastuzumab (herceptin), a humanized anti-Her2 receptor monoclonal antibody, inhibits basal and activated Her2 ectodomain cleavage in breast cancer cells. *Cancer Res.* 2001;61(12):4744-9.
24. **Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al.** Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. *N Engl J Med.* 2020;382(7):597-609.
25. **Musolino A, Naldi N, Bortesi B, Pezzuolo D, Capelletti M, Missale G, et al.** Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER-2/neu-positive metastatic breast cancer. *J Clin Oncol.* 2008;26(11):1789-96.
26. **Nimmerjahn F, Ravetch JV.** Fc gamma receptors as regulators of immune responses. *Nat. Rev. Immunol.* 2008;8(1):34-47.

27. **Nordstrom JL, Gorlatov S, Zhang W, Yang Y, Huang L, Burke S, et al.** Anti-tumor activity and toxicokinetics analysis of MGAH22, an anti-HER2 monoclonal antibody with enhanced Fc-gamma receptor binding properties. *Breast. Cancer Res.* 2011;13(6):R123.
28. **Norton N, Fox N, McCarl CA, Tenner KS, Ballman K, Erskine CL, et al.** Generation of HER2-specific antibody immunity during trastuzumab adjuvant therapy associates with reduced relapse in resected HER2 breast cancer. *Breast Cancer Res.* 2018;20(1):52.
29. **Persky DO, Dornan D, Goldman BH, Brazier RM, Fisher RI, Leblanc M, et al.** Fc gamma receptor 3a genotype predicts overall survival in follicular lymphoma patients treated on SWOG trials with combined monoclonal antibody plus chemotherapy but not chemotherapy alone. *Haematologica.* 2012;97(6):937-42.
30. **Shields RL, Namenuk AK, Hong K, Meng YG, Rae J, Briggs J, et al.** High resolution mapping of the binding site on human IgG1 for Fc gamma RI, Fc gamma RII, Fc gamma RIII, and FcRn and design of IgG1 variants with improved binding to the Fc gamma R. *J Biol. Chem.* 2001;276(9):6591-604.
31. **Shitara K, Ikeda J, Yokota T, Takahari D, Ura T, Muro K, et al.** Progression-free survival and time to progression as surrogate markers of overall survival in patients with advanced gastric cancer: analysis of 36 randomized trials. *Invest New Drugs.* 2012;30(3):1224-31.
32. **Siegel RL, Miller KD, Jemal A.** Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69(1):7-34.
33. **Stavenhagen JB, Gorlatov S, Tuailon N, Rankin CT, Li H, Burke S, et al.** Fc optimization of therapeutic antibodies enhances their ability to kill tumor cells in vitro and controls tumor expansion in vivo via low-affinity activating Fc gamma receptors. *Cancer Res.* 2007;67(18):8882-90.
34. **Tamura K, Shimizu C, Hojo T, Akashi-Tanaka S, Kinoshita T, Yonemori K, et al.** Fc gamma R2A and 3A polymorphisms predict clinical outcome of trastuzumab in both neoadjuvant and metastatic settings in patients with HER2-positive breast cancer. *Ann Oncol.* 2011;22(6):1302-7.
35. **Tanaka Y, Suzuki Y, Tsuge T, Kanamaru Y, Horikoshi S, Monteiro RC, et al.** Fc gamma RIIa-131R allele and Fc gamma RIIIa-176V/V genotype are risk factors for progression of IgA nephropathy. *Nephrol Dial. Transplant.* 2005;20(11):2439-45.
36. **Taylor C, Hershman D, Shah N, Suci-Foca N, Petrylak DP, Taub R, et al.** Augmented HER-2 specific immunity during treatment with trastuzumab and chemotherapy. *Clin Cancer Res.* 2007;13(17):5133-43.
37. **Thompson LM, Eckmann K, Boster BL, Hess KR, Michaud LB, Esteva FJ, et al.** Incidence, risk factors, and management of infusion-related reactions in breast cancer patients receiving trastuzumab. *Oncologist.* 2014;19(3):228-34.
38. **Varchetta S, Gibelli N, Oliviero B, Nardini E, Gennari R, Gatti G, et al.** Elements related to heterogeneity of antibody-dependent cell cytotoxicity in patients under trastuzumab therapy for primary operable breast cancer overexpressing Her2. *Cancer Res.* 2007;67(24):11991-9.

39. **von Minckwitz G, du Bois A, Schmidt M, Maass N, Cufer T, de Jongh FE, et al.**  
Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol. 2009;27(12):1999-2006.
40. **von Minckwitz G, Schwedler K, Schmidt M, Barinoff J, Mundhenke C, Cufer T, et al.**  
Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. Eur J Cancer. 2011;47(15):2273-81.
41. **Zagouri F, Sargentanis TN, Chrysikos D, Papadimitriou CA, Dimopoulos MA, Bartsch R.**  
Trastuzumab administration during pregnancy: a systematic review and meta-analysis. Breast Cancer Res. Treat. 2013;137(2):349-57.

The FDA's References:

No additional references for the FDA.

## 19.2. Financial Disclosure

The Applicant's Position:

In compliance with 21 CFR 54, the Applicant provided FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and a listing of clinical investigators for covered studies: CP-MGAH22-04 and CP-MGAH22-01. The Applicant has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Each listed clinical investigator was required to disclose if they had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b). None disclosed any such interests nor were any the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

**Covered Clinical Study (Name and/or Number):\* CP-MGAH22-04**

|                                                                                                                |                                         |                                                           |
|----------------------------------------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                 | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant) |
| Total number of investigators identified: <u>2270</u>                                                          |                                         |                                                           |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u> |                                         |                                                           |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>            |                                         |                                                           |
| If there are investigators with disclosable financial interests/arrangements, identify the                     |                                         |                                                           |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                         |                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in study: _____<br>Sponsor of covered study: _____ |                                         |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                               | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                  | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                               |                                         |                                                                  |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                                                                                                | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |

\*The table above should be filled by the Applicant, and confirmed/edited by the FDA.

**Covered Clinical Study (Name and/or Number):\* CP-MGAH22-01**

|                                                                                                                                                                                                                                                                                                                                                                                                     |                                         |                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                                                                                                                                                                                                                      | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant) |
| Total number of investigators identified: <u>73</u>                                                                                                                                                                                                                                                                                                                                                 |                                         |                                                           |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>                                                                                                                                                                                                                                                                                      |                                         |                                                           |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>                                                                                                                                                                                                                                                                                                 |                                         |                                                           |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____ |                                         |                                                           |

|                                                                                                                                                                               |                                         |                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in study: _____<br>Sponsor of covered study: _____ |                                         |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                   | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                      | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>                                                                                   |                                         |                                                                  |
| Is an attachment provided with the reason:                                                                                                                                    | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |

\*The table above should be filled by the Applicant, and confirmed/edited by the FDA.

### 19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

Not applicable. Refer to **Section 5**.

The FDA's Assessment:

N/A

### 19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

#### 19.4.1 Bioanalytical Method Performance Summary

The tables below provide the bioanalytical performance summary for Margetuximab:

**Table 28: Summary Method Performance of Bioanalytical Method RES-014 Ver 00, 01, 02 to Measure MGAH22 in Human Serum in CP-MGAH22-01**

|                                                                                |                                                                                                                                                                                                                                                                                                                                                           |
|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Bioanalytical method validation report name, amendments, and hyperlinks</b> | Validation of an ELISA Method for the Quantification of MGAH22 in Human Serum (R1-MTV-11-001)<br><br>Note: In response to an FDA IR, sponsor stated that the sequential Method RES-014 versions numbered 00, 01, and 02 resulted from internal review processes and administrative changes. There were no technical modifications or performance changes. |
|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

|                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                        |
|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| <b>Method description</b>                                       | Assay plates are coated with soluble HER2 protein overnight. After blocking non-specific sites with 0.5% BSA in 0.1% PBST, the plates are incubated with MGAH22 reference standard calibrators, quality control samples, matrix blank and test samples. MGAH22 present in the standard calibrators and test samples is captured by the immobilized soluble HER2. The captured MGAH22 is then detected by the sequential addition of biotinylated goat anti-MGAH22-Fv followed by streptavidin-HRP. The bound HRP activity is quantified by the color conversion of the TMB One component. The absorbance is measured at 450 nm after stopping the reaction with 1% of sulfuric acid. The standard curve is generated by fitting optical density (OD) signal from MGAH22 standards with a four-parameter logistic (4PL) model. The unknown concentrations of MGAH22 in test samples are determined from the interpolation of the samples' OD signal with the standard curve. |                        |
| <b>Materials used for calibration curve &amp; concentration</b> | MGAH22 Reference standard at 24.8 mg/mL<br><br>Calibration curve concentrations in buffer: 400, 200, 100, 50, 25, 12.5, 6.25, 3.1, 1.6, 0.8, 0.4 ng/mL (400, 0.8 and 0.4 ng/mL are anchor points) <sup>&amp;</sup><br><br>Equivalent to 10,000, 5000, 2500, 1250, 625, 312.5, 156.25, 77.5, 40, 20, 10 ng/mL in 'neat' solution prepared in buffer (10,000, 20 and 10 ng/mL are anchor points)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                        |
| <b>Validated assay range</b>                                    | 1 ng/mL <sup>s</sup> to 200 ng/mL<br><br>Equivalent to 25 <sup>s</sup> to 5000 ng/mL in neat solution                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                        |
| <b>Material used for QCs &amp; concentration</b>                | MGAH22 Reference standard at 24.8 mg/mL<br><br>QC concentrations: HQC: 2500 ng/mL; MQC: 625 ng/mL; LQC: 62.5 ng/mL in neat human serum                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                        |
| <b>Minimum required dilutions (MRDs)</b>                        | 1:5 in assay buffer used initially then updated to 1:25                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                        |
| <b>Source &amp; lot of reagents</b>                             | Per Applicant's response to bioanalytical summary IR:<br><br>MGAH22 reference standard, MacroGenics, Inc., Lot QC09037;<br><br>Goat anti-MGAH22-Fv-Biotin, MacroGenics, Inc., Lot P312.153<br><br>Her2-G2 (N297Q), MacroGenics, Inc., Lot P265.017                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                        |
| <b>Regression model &amp; weighting</b>                         | Four-parameter logistic nonlinear regression model, fixed weight for all points                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                        |
| <b>Validation parameters</b>                                    | <b>Method validation summary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>Source location</b> |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

|                                                                      |                                                                                                                    |               |                                   |
|----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|---------------|-----------------------------------|
| <b>Calibration curve performance during accuracy &amp; precision</b> | Number of standard calibrators from LLOQ to ULOQ                                                                   | X = 8         | Report R1-MTV-11-001, Section 2.2 |
|                                                                      | Cumulative accuracy (% bias) from LLOQ to ULOQ                                                                     | -2.8 – 7.5%   | Report R1-MTV-11-001, Table 1*    |
|                                                                      | Cumulative precision (%CV) from LLOQ to ULOQ                                                                       | ≤ 5.5%        | Report R1-MTV-11-001, Table 1     |
| <b>QCs performance during accuracy &amp; precision</b>               | <b>Cumulative accuracy (%bias) in 5 QCs</b><br>QCs: MGAH22 at 2500, 1000, 625, 100, 62.5 ng/mL in neat human serum | -5.4 to 15.2% | Report R1-MTV-11-001, Table 4     |
|                                                                      | <b>Inter-batch %CV</b><br>QCs: MGAH22 at 2500, 1000, 625, 100, 62.5 ng/mL in neat human serum                      | ≤ 8.2%        | Report R1-MTV-11-001, Table 4     |
|                                                                      | <b>Total error</b><br>QCs: MGAH22 at 2500, 1000, 625, 100, 62.5 ng/mL in neat human serum                          | ≤ 23.5%       | Report R1-MTV-11-001, Table 4     |
| <b>Selectivity &amp; matrix effect</b>                               | 10 lot were tested. 10 out of 10 acceptable at 25 ng/mL<br>Bias% range of 0.3 to 8.8%                              |               | Report R1-MTV-11-001, Table 6*    |
| <b>Interference &amp; specificity</b>                                | Not tested                                                                                                         |               | Not applicable (N/A)              |
| <b>Hemolysis effect</b>                                              | Not tested                                                                                                         |               | N/A                               |
| <b>Lipemic effect</b>                                                | Not tested                                                                                                         |               | N/A                               |
| <b>Dilution linearity &amp; hook effect</b>                          | Up to 512,000-fold dilution of 400,000 ng/mL sample                                                                |               | Report R1-MTV-11-001, Table 7     |
| <b>Bench-top/process stability</b>                                   | Up to 24 hours                                                                                                     |               | Report R1-MTV-11-001, Table 8     |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

|                                                                                                                                                                                                 |                                                                                                                                                      |                                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| <b>Freeze-Thaw stability</b>                                                                                                                                                                    | Up to 4 freeze (at -80°C) and thaw (at room temperature) cycles                                                                                      | Report R1-MTV-11-001, Table 10                            |
| <b>Long-term storage</b>                                                                                                                                                                        | Up to 2888 days when stored at -80°C. This stability duration was determined using the RES-014 ELISA method from 62.5 ng/mL to 2500 ng/mL.           | Memo # MEM-19-010 (located in RPT-19-036, Appendix 16.12) |
| <b>Parallelism</b>                                                                                                                                                                              | N/A                                                                                                                                                  | N/A                                                       |
| <b>Carry over</b>                                                                                                                                                                               | N/A                                                                                                                                                  | N/A                                                       |
| <b>Method performance in study number CP-MGAH22-01</b><br>Quantification of MGAH22 in Human Serum Samples Using a Validated ELISA Method (RES-014) for Clinical Study CP-MGAH22-01 (RPT-19-056) |                                                                                                                                                      |                                                           |
| <b>Assay passing rate</b>                                                                                                                                                                       | 63.7%                                                                                                                                                | Report RPT-19-056, Table 7-1*                             |
| <b>Standard curve performance</b>                                                                                                                                                               | <ul style="list-style-type: none"> <li>Cumulative bias range: -2.0 to 5.8%</li> <li>Cumulative precision: ≤ 9.3 % CV</li> </ul>                      | Report RPT-19-056, Table 6-2*                             |
| <b>QC performance</b>                                                                                                                                                                           | <ul style="list-style-type: none"> <li>Cumulative bias range: -12.5 to -2.7%</li> <li>Cumulative precision: ≤ 32% CV</li> <li>TE: ≤ 44.5%</li> </ul> | Report RPT-19-056, Table 6-4*                             |
| <b>Method reproducibility</b>                                                                                                                                                                   | Not conducted                                                                                                                                        | N/A                                                       |
| <b>Study sample analysis/stability</b>                                                                                                                                                          | 2888 days at -80°C from 62.5 ng/mL to 2500 ng/mL. This stability duration is adequate to cover the longest duration of sample analysis in Study 01.  |                                                           |

\*Calculated from the values in the corresponding table

&LLOQ was not included on the standard curve

\$LLOQ determination method not consistent with current FDA bioanalytical method development guidelines. This validation including LLOQ determination was subsequently updated in RES-014 Ver 03.

**Table 29: Summary Method Performance of Bioanalytical Method RES-014 Ver 03 to Measure MGAH22 in Human Serum in CP-MGAH22-02**

|                                        |                                                                                                                           |
|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| <b>Bioanalytical method validation</b> | Validation of the Assay for the Quantitation of MGAH22 in Human Serum Using an ELISA Method (RES-014 Ver 03) (RPT-19-036) |
|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------|

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

|                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                |                               |
|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|-------------------------------|
| <b>report name, amendments, and hyperlinks</b>                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                |                               |
| <b>Method description</b>                                            | The assay methodology is the same as Initial Method (Ver 00, 01, 02). In this method, assay plates are coated with soluble HER2 protein overnight. After blocking non-specific sites with 0.5% BSA in 0.1% PBST, the plates are incubated with MGAH22 reference standard calibrators, quality control samples, matrix blank and test samples. MGAH22 present in the standard calibrators and test samples is captured by the immobilized soluble HER2. The captured MGAH22 is then detected by the sequential addition of biotinylated goat anti-MGAH22-Fv followed by streptavidin-HRP. The bound HRP activity is quantified by the color conversion of the TMB One component. The absorbance is measured at 450 nm after stopping the reaction with 1% of sulfuric acid. The standard curve is generated by fitting optical density (OD) signal from MGAH22 standards with a four-parameter logistic (4PL) model. The unknown concentrations of MGAH22 in test samples are determined from the interpolation of the samples' OD signal with the standard curve. |                |                               |
| <b>Materials used for calibration curve &amp; concentration</b>      | MGAH22 Reference standard at 24.8 mg/mL<br><br>Calibration curve concentrations in 4% pooled normal human serum: 512, 256, 128, 64, 32, 16, 8, 4, 2, 1, 0.5 ng/mL (512 and 0.5 ng/mL are anchor points)<br><br>Equivalent to 12800, 6400, 3200, 1600, 800, 400, 200, 100, 50, 25, 12.5 in neat human serum                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                |                               |
| <b>Validated assay range</b>                                         | 25 ng/mL to 6400 ng/mL in neat serum                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                |                               |
| <b>Material used for QCs &amp; concentration</b>                     | MGAH22 Reference standard at 24.8 mg/mL<br><br>QC concentrations: HQC: 4800 ng/mL; MQC: 550 ng/mL; LQC: 62.5 ng/mL in neat human serum                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                |                               |
| <b>Minimum required dilutions (MRDs)</b>                             | 1:25 in assay buffer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                |                               |
| <b>Source &amp; lot of reagents</b>                                  | Per Applicant's response to bioanalytical summary IR:<br><br>MGAH22 reference standard, MacroGenics, Inc., Lot QC09037<br><br>Goat anti-MGAH22-Fv-Biotin, MacroGenics, Inc., Lot P312.153<br><br>Her2-G2 (N297Q), MacroGenics, Inc., Lot P265.017                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                |                               |
| <b>Regression model &amp; weighting</b>                              | 4-parameter logistic (4PL) fit, 1/response <sup>2</sup> weighted                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                |                               |
| <b>Validation parameters</b>                                         | <b>Method validation summary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                | <b>Source location</b>        |
| <b>Calibration curve performance during accuracy &amp; precision</b> | Number of standard calibrators from LLOQ to ULOQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 9              | Report RPT-19-036, Table 12-5 |
|                                                                      | Cumulative accuracy (% bias) from LLOQ to ULOQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -2.18 to 3.37% | Report RPT-19-036, Table 12-5 |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

|                                                                                                                                                                                                                                                                                              |                                                                                                                                                         |                 |                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|------------------------------------------------|
|                                                                                                                                                                                                                                                                                              | Cumulative precision (%CV) from LLOQ to ULOQ                                                                                                            | ≤ 4.49%         | Report RPT-19-036, Table 12-5                  |
| <b>QCs performance during accuracy &amp; precision</b>                                                                                                                                                                                                                                       | <b>Cumulative accuracy (%bias) in QCs</b><br>QCs: MGAH22 at 6400, 4800, 3200, 2400, 550, 62.5, 50, and 25 ng/mL in neat human serum                     | -8.54 to 18.15% | Report RPT-19-036, Table 12-9                  |
|                                                                                                                                                                                                                                                                                              | <b>Inter-batch %CV</b><br>QCs: MGAH22 at 6400, 4800, 3200, 2400, 550, 62.5, 50, and 25 ng/mL in neat human serum                                        | ≤ 10.47%        | Report RPT-19-036, Table 12-9                  |
|                                                                                                                                                                                                                                                                                              | <b>Total error</b><br>QCs: MGAH22 at 6400, 4800, 3200, 2400, 550, 62.5, 50, and 25 ng/mL in neat human serum                                            | ≤ 25.70%        | Report RPT-19-036, Table 12-9                  |
| <b>Selectivity &amp; matrix effect</b>                                                                                                                                                                                                                                                       | 20 lots were tested, 20 out of 20 acceptable at 62.5 ng/mL and no matrix effect was observed.<br>Bias range for selectivity sample was: -2.3 % to 14.3% |                 | Report RPT-19-036, Table 12-19 and Table 12-20 |
| <b>Interference &amp; specificity</b>                                                                                                                                                                                                                                                        | An irrelevant drug (MGA271; 500, 50, 12.8 and 4.8 µg/mL in neat serum) with similar structure as MGAH22 was evaluated and no cross activity was found   |                 | Report RPT-19-036, Table 12-18                 |
| <b>Hemolysis effect</b>                                                                                                                                                                                                                                                                      | Not tested                                                                                                                                              |                 | N/A                                            |
| <b>Lipemic effect</b>                                                                                                                                                                                                                                                                        | Not tested                                                                                                                                              |                 | N/A                                            |
| <b>Dilution linearity &amp; hook effect</b>                                                                                                                                                                                                                                                  | Up to 25,000-fold dilution of 500,000 ng/mL<br>No hook effect observed up to 500,000 ng/mL                                                              |                 | Report RPT-19-036, Table 12-12 and Table 12-13 |
| <b>Bench-top/process stability</b>                                                                                                                                                                                                                                                           | Up to 3 days                                                                                                                                            |                 | Report RPT-19-036, Table 12-15 and Table 12-16 |
| <b>Freeze-Thaw stability</b>                                                                                                                                                                                                                                                                 | Up to 5 freeze and thaw cycles                                                                                                                          |                 | Report RPT-19-036, Table 12-15 and Table 12-16 |
| <b>Long-term storage</b>                                                                                                                                                                                                                                                                     | Up to 2888 days when stored at -80°C from 62.5 ng/mL to 2500 ng/mL.                                                                                     |                 | Report RPT-19-036, Section 12.4                |
| <b>Parallelism</b>                                                                                                                                                                                                                                                                           | N/A                                                                                                                                                     |                 | N/A                                            |
| <b>Carry over</b>                                                                                                                                                                                                                                                                            | N/A                                                                                                                                                     |                 | N/A                                            |
| <b>Method performance in study number CP-MGAH22-02</b><br><b>(In addition to the report name, also provide hyperlink to the report)</b><br>Quantification of MGAH22 in Human Serum Samples Using a Validated ELISA Method for Clinical Study CP-MGAH22-02 (Report Number <b>RPT-19-079</b> ) |                                                                                                                                                         |                 |                                                |
| <b>Assay passing rate</b>                                                                                                                                                                                                                                                                    | Assay passing rate: 60.7% (include ISR plates)                                                                                                          |                 | Report RPT-19-079, Table 8-1 *                 |

|                                         |                                                                                                                                                                                                               |                                                                              |
|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <b>Standard curve performance</b>       | <ul style="list-style-type: none"> <li>Cumulative bias range: -2.0 to 2.9%</li> <li>Cumulative precision: <math>\leq 6.1\%</math> CV</li> </ul>                                                               | Report RPT-19-079, Table 6-2 *                                               |
| <b>QC performance</b>                   | <ul style="list-style-type: none"> <li>Cumulative bias range: -5.1 to 1.6 %</li> <li>Cumulative precision: <math>\leq 16.6\%</math> CV</li> <li>Percent total error (TE): <math>\leq 21.8\%</math></li> </ul> | Report RPT-19-079, Table 6-4 *                                               |
| <b>Method reproducibility</b>           | Incurred sample reanalysis was performed in 73.9% of study samples and 94.1 % of samples met the pre-specified criteria                                                                                       | Report RPT-19-079, Section 7 and Section 8<br>Report RPT-19-079, Table 7-1 * |
| <b>Study sample analysis/ stability</b> | 2888 days at -80°C from 62.5 ng/mL to 2500 ng/mL. This stability duration is adequate to cover the longest duration of sample analysis in Study 02.                                                           |                                                                              |

\*Calculated from the values in the corresponding table

**Table 30: Summary of Method RES-014 Ver 03 Modification(s) and Cross-validation Results**

|                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                    |                                                                                                                                     |
|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| <b>Bioanalytical method validation report name and hyperlink</b> | Cross Validation of <sup>(b) (4)</sup> Method ICD 638 versus MacroGenics Method RES-014 for the Quantitation of Margetuximab (MGAH22) in Human Serum ( <b>RPT-19-099</b> )<br><br>Note: Comparison of the initial method (Ver 00, Ver 01 and Ver 02) to current method (Ver 03) and <sup>(b) (4)</sup> method (ICD 638) was performed in this study. <b>The data presented below compare the initial ELISA method (Ver 00, 01, 02) to the current method (Ver 03).</b> |                                                                                                                                                    |                                                                                                                                     |
| <b>Changes in method</b>                                         | <b>Changed Parameter</b>                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>Initial Method (Ver 00, Ver 01 and Ver 02)</b>                                                                                                  | <b>Current Method (Ver 03)</b>                                                                                                      |
|                                                                  | 1) Standard Curve/Calibrator Concentrations                                                                                                                                                                                                                                                                                                                                                                                                                            | Concentrations of standard calibrators were 400, 200, 100, 50, 25, 12.5, 6.25, 3.1, 1.6, 0.8, 0.4 ng/mL (400, 0.8 and 0.4 ng/mL are anchor points) | Concentrations of standard calibrators were 512, 256, 128, 64, 32, 16, 8, 4, 2, 1, 0.5 ng/mL (512, and 0.5 ng/mL are anchor points) |
|                                                                  | 2) Standard Curve/Calibrator and Test Sample Matrix                                                                                                                                                                                                                                                                                                                                                                                                                    | Assay Buffer (0.5% BSA in PBST)                                                                                                                    | Assay Buffer (0.5% BSA in PBST) containing 4% Normal Human Serum (NHS)                                                              |
|                                                                  | 3) Mid and High-Quality Control Sample Concentrations                                                                                                                                                                                                                                                                                                                                                                                                                  | MQC: 625.0 ng/mL<br>HQC: 2500.0 ng/mL                                                                                                              | MQC: 550.0 ng/mL<br>HQC: 4800.0 ng/mL                                                                                               |
| <b>New validated assay range if any</b>                          | 25 – 6400 ng/mL in neat serum                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                    |                                                                                                                                     |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

| Validation parameters                                     | Cross-validation performance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                | Source location                                             |
|-----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|-------------------------------------------------------------|
| Calibration curve performance during accuracy & precision | Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | -2.2 to 10.5 % | Report RPT-19-099, Table 12-4                               |
|                                                           | Cumulative precision (%CV) from LLOQ to ULOQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | ≤ 6.8 %        | Report RPT-19-099, Table 12-4                               |
| QCs performance during accuracy & precision               | Cumulative accuracy (%bias) in QCs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | -5.6 to -1.2 % | Report RPT-19-099, Table 12-10*                             |
|                                                           | Inter-batch %CV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | ≤ 17.9%        | Report RPT-19-099, Table 12-10*                             |
|                                                           | Percent total error (TE)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | ≤ 23.5%        | Report RPT-19-099, Table 12-10*                             |
| Cross-validation                                          | <p>1.) Results from spiked samples</p> <p>3 pooled spikes prepared at 62.5, 550 and 4800 ng/mL were evaluated with both initial method (Ver 02) and current method (Ver 03) by 4 analysts over 3 days period.</p> <p>The bias% from Ver 02 was from -17.21 to -12.84%</p> <p>The bias% from Ver 03 was from -13.89 to -9.81%</p> <p>2.) Results from incurred samples</p> <p>40 individual samples from CP-MGAH22-04 were selected and assigned randomized number and were analyzed by both initial method (Ver 02) and current method (Ver03). All 40 (100%) samples were measured with concentration within ±30% between the two methods. No marked bias in ISR data was observed between the two ELISA methods; mean difference (ELISA V02-V03) = 0.9%.</p> |                | Report RPT-19-099 Table 12-15, Table 12-16, and Table 12-20 |

|                              |                                                                                                                             |  |  |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------------|--|--|
|                              | Both spiked samples and incurred sample met the acceptance criteria set for the cross-validation between the ELISA methods. |  |  |
| <b>List other parameters</b> | N/A                                                                                                                         |  |  |

\*Calculated from the values in the corresponding table

**Review comment:** *The detection antibody used in the ELISA assays is cross-reactive with trastuzumab due to shared margetuximab and trastuzumab complementarity-determining regions. Eight of 66 pre-dose samples (12.1%) in Study 01 and two of 21 pre-dose samples (11.5%) in Study 02 collected before the first margetuximab infusion had detectable levels (<1.5 µg/mL). These samples were excluded from and did not have a clinically meaningful impact on margetuximab population PK analysis.*

**Table 31: Summary Method Performance of Bioanalytical Method ICD 638 to Measure Margetuximab in Human Serum in CP-MGAH22-04**

|                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Bioanalytical method validation report name, amendments, and hyperlinks</b> | Validation of an Electrochemiluminescent Method for the Quantitation of Margetuximab (MGAH22) in Human Serum ( <b>RERD2</b> )<br><br>Cross-Validation of an Electrochemiluminescent Method for the Quantitation of Margetuximab (MGAH22) in Human Serum – <sup>(b) (4)</sup> Method ICD 638 versus MacroGenics Initial and Current ELISA Assays ( <b>RERD5</b> )                                                                                                                                                                                                           |
| <b>Method description</b>                                                      | Margetuximab (MGAH22) is quantitatively measured in human serum using an electrochemiluminescent immunoassay. In this assay, goat anti-MGAH22-Biotin is coated onto a GOLD 96-well Streptavidin SECTOR Plate. Margetuximab then binds to the biotinylated goat anti-MGAH22. Sulfo-TAG HER2 (HER2-ST) is added for detection. The plate is washed and Meso Scale Discovery (MSD) read buffer is added. When voltage is applied to the plate, formed complexes produce an electrochemiluminescence (ECL) signal that is measured in ECL units using a MSD S600 Plate Reader. |
| <b>Materials used for calibration curve &amp; concentration</b>                | MGAH22 Reference standard at 25.9 mg/mL<br>Calibration curve concentrations: 4.88, 9.77, 19.5, 39.1, 78.1, 156, 313, 625, 1250, and 2500 ng/mL in neat serum                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Validated assay range</b>                                                   | 4.88 to 2500 ng/mL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Material used for QCs &amp; concentration</b>                               | MGAH22 reference standard at 25.9 mg/mL<br>QC concentrations: 15.0 (low QC), 150 (mid QC), and 2000 (high QC) ng/mL in neat serum                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Minimum required dilutions (MRDs)</b>                                       | 1:25 in assay buffer (0.5% BSA in 1X PBS-T)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

|                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                  |                                                                                                      |
|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------------------------------------------------------------------------------------------|
| <b>Source &amp; lot of reagents</b>                                  | MGAH22 reference standard, MacroGenics, Inc, Lot QC15019<br><br>Goat anti-MGAH22 Biotin (Trastuzumab Absorbed): MacroGenics, Inc., Lot P753.203 or P851.113<br><br>Human HER2-G2 (N297Q) used to prepare HER2-ST: MacroGenics, Inc., Lot P883.036                                                                                                                                                                                                                                                                                                                                                                                |                  |                                                                                                      |
| <b>Regression model &amp; weighting</b>                              | Four-parameter logistic, 1/response <sup>2</sup> weighted                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                  |                                                                                                      |
| <b>Validation parameters</b>                                         | <b>Method validation summary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                  | <b>Source location</b>                                                                               |
| <b>Calibration curve performance during accuracy &amp; precision</b> | Number of standard calibrators from LLOQ to ULOQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 10               | Report RERD2, Table 2A                                                                               |
|                                                                      | Cumulative accuracy (% bias) from LLOQ to ULOQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | -2.96 to 2.11%   | Report RERD2, Table 2A                                                                               |
|                                                                      | Cumulative precision (%CV) from LLOQ to ULOQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | ≤ 2.96%          | Report RERD2, Table 2A                                                                               |
| <b>QCs performance during accuracy &amp; precision</b>               | <b><u>Cumulative accuracy (%bias) in 5 QCs</u></b><br>QCs: MGAH22 at 4.88, 9.77, 15.0, 150, 2000, and 2500 ng/mL in neat human serum.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -2.66 to 3.14% * | Report RERD2, Table 3D                                                                               |
|                                                                      | <b><u>Inter-batch %CV</u></b><br>QCs: MGAH22 at 4.88, 9.77, 15.0, 150, 2000, and 2500 ng/mL in neat human serum                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | ≤ 5.20%*         | Report RERD2, Table 3D                                                                               |
|                                                                      | <b><u>Total error</u></b><br>QCs: MGAH22 at 4.88, 9.77, 15.0, 150, 2000, and 2500 ng/mL in neat human serum                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | ≤ 7.70%          | Report RERD2, Table 3D                                                                               |
| <b>Selectivity &amp; matrix effect</b>                               | Acceptable with nine out of 10 healthy human serum selectivity lots fortified at the LLOQ level (4.88 ng/mL) meeting the acceptance criteria.**<br>Acceptable with nine out of 10 healthy human serum selectivity lots fortified at the high QC level (2000 ng/mL) meeting the acceptance criteria.<br>Acceptable with 10 out of 10 breast cancer human serum (BCS) selectivity lots fortified at the LLOQ level (4.88 ng/mL) meeting the acceptance criteria.**<br>Acceptable with nine out of 10 breast cancer human serum (BCS) selectivity lots fortified at the high QC level (2000 ng/mL) meeting the acceptance criteria. |                  | Report RERD2, Table 11I, Table 11A, Table 13G, Table 13A, Table 10A, Table 10B, Table 12A, Table 12B |
| <b>Interference &amp; specificity</b>                                | No effect of trastuzumab (Herceptin) at 300 µg/mL on the quantitation of margetuximab (MGAH22).<br>Acceptable with 20 out of 20 unfortified healthy human serum individual specificity lots meeting the acceptance criteria.<br>Acceptable with 20 out of 20 unfortified breast cancer human serum (BCS) individual specificity lots meeting the acceptance criteria.                                                                                                                                                                                                                                                            |                  | Report RERD2, Table 16, Table 10A, Table 10B, Table 12A, Table 12B                                   |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

|                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                      |                                                                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| <b>Hemolysis effect</b>                                                                                                                                                                                                                                                                                                                                                                                                                  | No effect from hemolysis up to 5% fully lysed whole blood on the quantitation of margetuximab (MGAH22) (from one lot/donor).                                                                                                                                                                                                                         | Report RERD2, Table 14                                             |
| <b>Lipemic effect</b>                                                                                                                                                                                                                                                                                                                                                                                                                    | No effect from lipemia (>300 mg/dL of triglycerides) on the quantitation of margetuximab (MGAH22) (from pooled matrix).                                                                                                                                                                                                                              | Report RERD2, Table 15B                                            |
| <b>Dilution linearity &amp; hook effect</b>                                                                                                                                                                                                                                                                                                                                                                                              | Dilutional linearity: 250000 ng/mL diluted up to 1:1250<br>No hook effect observed at concentrations up to 250000 ng/mL                                                                                                                                                                                                                              | Report RERD2, Table 5, Table 6A, Table 6B                          |
| <b>Bench-top/process stability</b>                                                                                                                                                                                                                                                                                                                                                                                                       | 24.5 hours at room temperature                                                                                                                                                                                                                                                                                                                       | Report RERD2, Table 8                                              |
| <b>Freeze-Thaw stability</b>                                                                                                                                                                                                                                                                                                                                                                                                             | Five cycles at room temperature                                                                                                                                                                                                                                                                                                                      | Report RERD2, Table 7                                              |
| <b>Long-term storage</b>                                                                                                                                                                                                                                                                                                                                                                                                                 | 36 days at approximately -80 °C and -25 °C at 15 ng/ml and 2000 ng/mL using ICD 638 ECL assay; per the report further evaluations of analyte stability in frozen human serum at appropriate time points are ongoing. 2888 days at approximately -80 °C using RES-014 ELISA assay (MacroGenics Memo MEM-19-010; appendix 16.12 of report RPT-19-036). | Report RERD2, Table 9B and 9A                                      |
| <b>Parallelism</b>                                                                                                                                                                                                                                                                                                                                                                                                                       | N/A                                                                                                                                                                                                                                                                                                                                                  | N/A                                                                |
| <b>Carry over</b>                                                                                                                                                                                                                                                                                                                                                                                                                        | N/A                                                                                                                                                                                                                                                                                                                                                  | N/A                                                                |
| <b>Method performance in study number CP-MGAH22-04</b>                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                      |                                                                    |
| Study/protocol CP-MGAH22-04, (b) (4) project RERG is ongoing. Two interim reports have been finalized as of 03 Feb 2020, both titled “Electrochemiluminescent Analysis for the Quantitation of Margetuximab (MGAH22) in Human Serum”. Interim Report 1 was submitted in the original BLA submission; Interim Report 2 was under preparation during BLA finalization and was submitted in response to an FDA IR during the review period. |                                                                                                                                                                                                                                                                                                                                                      |                                                                    |
| <b>Assay passing rate</b>                                                                                                                                                                                                                                                                                                                                                                                                                | 85.3% (including ISR)                                                                                                                                                                                                                                                                                                                                | Interim Report 1 RERG, Table 6, and Interim Report 2 RERG, Table 4 |
| <b>Standard curve performance</b>                                                                                                                                                                                                                                                                                                                                                                                                        | <ul style="list-style-type: none"> <li>Cumulative bias range: -2.27 to 2.21% (interim report 1) and -3.23 to 2.07% (interim report 2)</li> <li>Cumulative precision: ≤ 5.66% CV (interim report 1) and ≤ 3.72% CV (interim report 2)</li> </ul>                                                                                                      | Interim Report 1 RERG, Table 8; Interim Report 2 RERG, Table 6     |
| <b>QC performance</b>                                                                                                                                                                                                                                                                                                                                                                                                                    | <ul style="list-style-type: none"> <li>Cumulative bias range: -5.30 to 5.78% (interim report 1)<sup>s</sup> and -0.575 to 3.01% (interim report 2)</li> <li>Cumulative precision: ≤ 15.1% CV (interim report 1)<sup>s</sup> and ≤ 8.05% CV (interim report 2)</li> <li>1. TE: ≤ 20.9% (interim report 1) and ≤ 10.8% (interim report 2)</li> </ul>   | Interim Report 1 RERG, Table 10 and Interim Report 2 RERG, Table 7 |
| <b>Method reproducibility</b>                                                                                                                                                                                                                                                                                                                                                                                                            | Incurred sample reanalysis was performed in 11.1% of study samples and 89.8% of samples met the pre-specified criteria                                                                                                                                                                                                                               | Interim Report 1 RERG, Appendix F and Interim                      |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                              |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Report 2<br>RERG, Table<br>8 |
| <b>Study sample analysis/stability</b> | 2888 days at approximately -80 °C stability coverage for samples (MacroGenics Memo MEM-19-010; appendix 16.12 of report RPT-19-036). This stability duration was determined using the RES-014 ELISA method from 62.5 ng/mL to 2500 ng/mL. This stability duration is adequate to cover the longest duration of sample analysis in Study 04. Limited number of samples (mostly pre-dose on C1D1 or during follow up) are <62.5 ng/mL therefore acceptable. Additional long term stability testing of margetuximab in frozen human serum using the ICD 638 ECL assay is ongoing and should additionally cover the maximum length of storage of the present study samples. |                              |

\* Excluding 1 outlier at the LLOQ, acceptable as value appears anomalous  
 \*\* Passes after multiple failed selectivity experiments; Applicant attributes selectivity issues to dilution challenges going from high concentrations of stock material to concentrations near the low QC level and not to true selectivity problems with the assay. Data from spiked preparation controls in pooled blank human serum used to assess the accuracy of pipetting (table on page 16 of ICD 638 Validation Report) supports Applicant’s rationale.  
 † Excluding 1 outlier at LQC, acceptable as value appears anomalous

**Table 32: Summary of Method ICD 638 Modification(s) and Cross-validation Results**

|                                                                      |                                                                                                                                                                                                                                                                                                                                                                                     |                 |                        |
|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|------------------------|
| <b>Bioanalytical method validation report name and hyperlink</b>     | Cross-Validation of <sup>(b) (4)</sup> Method ICD 638 versus MacroGenics Method RES-014 for the Quantitation of Margetuximab (MGAH22) in Human Serum ( <b>RPT-19-099</b> ; located in <b>RPT-19-099</b> , Section 17.6)                                                                                                                                                             |                 |                        |
|                                                                      | Note: Comparison of the initial method (Ver 00, Ver 01 and Ver 02) to current method (Ver 03) and <sup>(b) (4)</sup> method (ICD 638) was performed in this study. The data presented below compare the initial and current ELISA methods to the ECL method.                                                                                                                        |                 |                        |
| <b>Changes in method</b>                                             | <ol style="list-style-type: none"> <li>1.) Assay platform changed from ELISA OD absorbance at 450 to MSD ECL method.</li> <li>2.) Capture reagent changed from Her2-G2 (N297Q) to Goat anti-MGAH22-Fv-Biotin (this change eliminated the cross-reactivity with trastuzumab)</li> <li>3.) The detection reagent changed from Goat anti-MGAH22-Fv-Biotin to Her2-Sulfo-tag</li> </ol> |                 |                        |
| <b>New validated assay range if any</b>                              | From 4.88 ng/mL to 2500 ng/mL                                                                                                                                                                                                                                                                                                                                                       |                 |                        |
| <b>Validation parameters</b>                                         | <b>Cross-validation performance</b>                                                                                                                                                                                                                                                                                                                                                 |                 | <b>Source location</b> |
| <b>Calibration curve performance during accuracy &amp; precision</b> | Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ                                                                                                                                                                                                                                                                                                               | -3.92 to 5.8%   | Report RERD5, Table 3  |
|                                                                      | Cumulative precision (%CV) from LLOQ to ULOQ                                                                                                                                                                                                                                                                                                                                        | ≤ 1.78%         | Report RERD5, Table 3  |
| <b>QCs performance during accuracy &amp; precision</b>               | Cumulative accuracy (%bias) in QCs                                                                                                                                                                                                                                                                                                                                                  | -7.87 to -0.68% | Report RERD5, Table 4  |

|                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |          |                                                                    |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|--------------------------------------------------------------------|
|                              | Inter-batch %CV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | ≤ 10.3%  | Report RERD5, Table 4                                              |
|                              | Percent total error (TE)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | ≤ 11.65% | Report RERD5, Table 4 *                                            |
| <b>Cross-validation</b>      | <p>1.) Result from spiked samples:</p> <p>3 pooled spikes prepared at 62.5, 550 and 4800 ng/mL were evaluated using method ICD 638 by 2 analysts over 3 days period. The bias% range was from -0.044 to 5.72%. The result of the spiked samples met the acceptance criteria. However, a systematic negative bias was observed, whereby ELISA method results were consistently lower than ECL method results (about 10% for spiked samples, ranging from -9.8% to -17.2%; see Table 3).</p> <p>2.) Results from incurred samples</p> <p>40 individual samples previously analyzed by method ICD 638 from CP-MGAH22-04 were randomly selected by (b) (4) and provided to MacroGenics with blinded sample information. The 40 blinded samples were analyzed using method RES-014 (Ver03) at MG site; 57.5% of ISR samples were measured within ±30% of original test result. Using RES-014 (Ver02) at MG site, 65% of ISR samples were measured within ±30% of original test result, which is less than the 2/3 of the total ISR samples. The result of incurred samples therefore did not meet the acceptance criteria (2/3 of the total incurred samples within +/- 30% difference) for both ELISA methods.</p> <p>Mean difference (V03- ICD 638) = -23.5%<br/>                     Mean difference (V02- ICD 638) = -22.5%</p> |          | <p>Report RERD5, Table 5</p> <p>Report RPT-19-099, Table 12-20</p> |
| <b>List other parameters</b> | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |          |                                                                    |

\*Calculated from the values in the corresponding table

## 19.4.2 Pharmacometrics Review

### Population PK analyses

**Objectives:** There are four main objectives addressed in the population PK analyses: 1) To establish and evaluate a population PK model for margetuximab in adults with HER2+ breast cancer; 2) To identify demographic and other factors that influence margetuximab disposition; 3) To evaluate relationships

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

between ADA and margetuximab PK; and 4) To estimate margetuximab exposure for each Study 04 subject for use in the E-R analyses.

**Data:** The PK data from Study 01, Study 02, and Study 04 were included in the population PK analyses. Key design/data details of each study were summarized in Table 1. The study population is characterized by age (29 to 83 years), race (Caucasian, Black, Asian), sex, mild (CLcr 60 to 89 mL/min estimated using the Cockcroft-Gault equation) or moderate (CLcr 30 to 59 mL/min) renal impairment, mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate amino transferase [AST] > ULN or total bilirubin 1 - 1.5 times ULN and any AST), HER2 expression level (0 to IHC3+), tumor burden (2 – 317 mm), ECOG score (0-2), albumin (24 to 50 g/L), FcγR (CD16A, CD32A, and CD32B) genotype, number of metastatic sites, , number of prior therapy lines, concurrent chemotherapies (capecitabine, gemcitabine, eribulin and vinorelbine) (See Table 2).

Table 33 General Design/Data Characteristics of Clinical Studies Pooled in Population PK Analysis

| Design/Data Characteristic                                 | Study 01                                                                                                                                                           | Study 02                                                                                          | Study 04                                                                  |
|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Study Phase                                                | 1                                                                                                                                                                  | 2                                                                                                 | 3                                                                         |
| Margetuximab Dose and Regimens                             | 0.1, 0.3, 1, 3, or 6 mg/kg QW;<br>10, 15, or 18 mg/kg Q3W                                                                                                          | 6 mg/kg QW;<br>15 mg/kg Q3W                                                                       | 15 mg/kg Q3W                                                              |
| Number of Cycles                                           | Generally received 1 to 3                                                                                                                                          | 7 planned                                                                                         | Median 6<br>(range 1 to 34)                                               |
| Margetuximab Assay Method                                  | ELISA                                                                                                                                                              | ELISA                                                                                             | ECL                                                                       |
| Nominal PK Sampling Scheme                                 | <b>Serial:</b><br>Cycle 1: pre-dose, 1, 2, 4,<br>6, 24, 27, and 96 h after end of<br>infusion;<br><br>Additional cycles:<br>pre-dose; 1 h after end of<br>infusion | <b>Sparse (3/cycle):</b><br>pre-dose; 1 h after end of<br>infusion; 24 h after end of<br>infusion | <b>Sparse (2/cycle):</b><br>pre-dose; 0 to 5 min after end<br>of infusion |
| Number of PK observations and subjects in the PPK analysis | 1166 PK observations<br>from 66 subjects                                                                                                                           | 117 PK observations<br>from 22 subjects                                                           | 2913 PK observations<br>from 261 subjects                                 |
| Number of PK observations included in PPK analysis         | 1131                                                                                                                                                               | 117                                                                                               | 2704                                                                      |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

|                                                        |    |   |     |
|--------------------------------------------------------|----|---|-----|
| Number of PK observations excluded from PPK analysis a | 35 | 0 | 209 |
|--------------------------------------------------------|----|---|-----|

Abbreviations: ECL: electrochemiluminescent; ELISA: enzyme-linked immunosorbent assay; h: hours; min: minutes; PK: pharmacokinetic(s); PPK: population PK; Q3W: every 3 weeks; QW: once weekly.

Source: Table 2.7.2-5 in Summary of Clinical Pharmacology Studies.

Table 34. Summary of Covariates.

|           |                                 |                              | Total                 | Study CP-MGAH22-      |                       |                       |
|-----------|---------------------------------|------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|           |                                 |                              |                       | 01                    | 02                    | 04                    |
| Subjects  |                                 |                              | 349                   | 66                    | 22                    | 261                   |
| Covariate | Description                     | Units                        | Median (Range)        |                       |                       |                       |
| BWT       | Body Weight                     | kg                           | 65<br>[34 - 151]      | 63<br>[43 - 107]      | 64.4<br>[44.2 - 122]  | 65.3<br>[34 - 151]    |
| HT        | Height                          | cm                           | 162<br>[143 - 188]    | 160<br>[143 - 188]    | 159<br>[150 - 174]    | 163<br>[148 - 180]    |
| BMI       | Body Mass Index                 | kg/m <sup>2</sup>            | 24.8<br>[14.2 - 55.5] | 24.3<br>[15.9 - 41.8] | 24.8<br>[17.6 - 47.9] | 25.1<br>[14.2 - 55.5] |
| BSA       | Body Surface Area               | m <sup>2</sup>               | 1.7<br>[1.2 - 2.46]   | 1.67<br>[1.3 - 2.31]  | 1.65<br>[1.37 - 2.14] | 1.71<br>[1.25 - 2.46] |
| AGE       | Age                             | years                        | 56 [29 - 83]          | 59 [36 - 83]          | 59 [43 - 80]          | 55 [29 - 83]          |
| ALB       | Albumin                         | g/L                          | 41 [24 - 50]          | 40 [24 - 48]          | 38 [29 - 43]          | 41 [26 - 50]          |
| ALT       | Alanine amino-transferase       | U/L                          | 22 [5 - 174]          | 22 [6 - 153]          | 24 [9 - 174]          | 22 [5 - 131]          |
| AST       | Aspartate amino-transferase     | U/L                          | 31 [8 - 186]          | 25.5 [8 - 119]        | 31.5 [14 - 186]       | 33 [11 - 178]         |
| ALP       | Alkaline Phosphatase            | U/L                          | 97<br>[32 - 1050]     | 89<br>[32 - 275]      | 92.5<br>[56 - 535]    | 99<br>[36 - 1050]     |
| BILI      | Bilirubin                       | umol/L                       | 6.84<br>[2.5 - 30.1]  | 10.3<br>[3.42 - 29.1] | 7.7<br>[3.42 - 22.2]  | 6<br>[2.5 - 30.1]     |
| LDH       | Lactate Dehydrogenase           | µkat/L                       | 3.77<br>[1.7 - 97.8]  | 4.28<br>[2.42 - 61]   | Not Collected         | 3.63<br>[1.7 - 97.8]  |
| CREAT     | Creatinine                      | umol/L                       | 54.8 [27 - 136]       | 69.4<br>[44.2 - 136]  | 59.2<br>[31.8 - 118]  | 53<br>[27 - 133]      |
| CRCL      | Creatinine Clearance            | mL/min                       | 101<br>[25.6 - 150]   | 80.4<br>[25.6 - 150]  | 91.9<br>[30.8 - 150]  | 109<br>[33.5 - 150]   |
| CRCLN     | Normalized Creatinine Clearance | mL/min/(1.73m <sup>2</sup> ) | 104<br>[30.8 - 150]   | 86.6<br>[30.8 - 150]  | 96.5<br>[35.1 - 150]  | 111<br>[42.3 - 150]   |
| GFR       | Glomerular Filtration Rate      | mL/min                       | 100<br>[32.3 - 150]   | 92.6<br>[32.3 - 121]  | 97<br>[38.1 - 123]    | 103<br>[37.7 - 150]   |
| TMBD      | Tumor Burden                    | mm                           | 85<br>[2 - 317]       | 68<br>[15 - 317]      | 62<br>[14 - 230]      | 91<br>[2 - 155]       |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

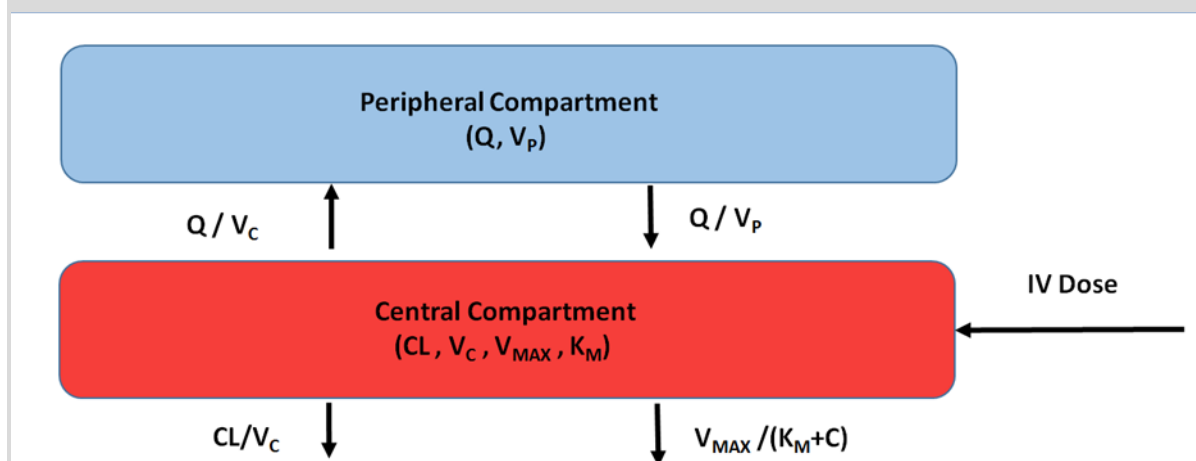
| Covariate | Description                                                                                                        | Level                                                             | N (Percent) Subjects |                  |               |                |
|-----------|--------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|----------------------|------------------|---------------|----------------|
|           |                                                                                                                    |                                                                   | Total<br>(N=349)     | Study CP-MGAH22- |               |                |
|           |                                                                                                                    |                                                                   |                      | 01<br>(N=66)     | 02 (N=22)     | 04<br>(N=261)  |
| REG       | Nominal<br>Dose and<br>Frequency                                                                                   | 0.1 mg/kg QW                                                      | 3 (0.9%)             | 3 (4.5%)         | ---           | ---            |
|           |                                                                                                                    | 0.3 mg/kg QW                                                      | 3 (0.9%)             | 3 (4.5%)         | ---           | ---            |
|           |                                                                                                                    | 1.0 mg/kg QW                                                      | 3 (0.9%)             | 3 (4.5%)         | ---           | ---            |
|           |                                                                                                                    | 3.0 mg/kg QW                                                      | 6 (1.7%)             | 6 (9.1%)         | ---           | ---            |
|           |                                                                                                                    | 6.0 mg/kg QW                                                      | 33<br>(9.5%)         | 19<br>(28.8%)    | 14<br>(63.6%) | ---            |
|           |                                                                                                                    | 10.0 mg/kg<br>Q3W                                                 | 6 (1.7%)             | 6 (9.1%)         | ---           | ---            |
|           |                                                                                                                    | 15.0 mg/kg<br>Q3W                                                 | 289<br>(82.8%)       | 20<br>(30.3%)    | 8<br>(36.4%)  | 261<br>(100%)  |
|           |                                                                                                                    | 18.0 mg/kg<br>Q3W                                                 | 6 (1.7%)             | 6 (9.1%)         | ---           | ---            |
| SEXF      | Gender                                                                                                             | Male                                                              | 29<br>(8.3%)         | 29<br>(43.9%)    | ---           | ---            |
|           |                                                                                                                    | Female                                                            | 320<br>(91.7%)       | 37<br>(56.1%)    | 22 (100%)     | 261<br>(100%)  |
| RACEN     | Race                                                                                                               | White                                                             | 234<br>(67%)         | 17<br>(25.8%)    | 17<br>(77.3%) | 200<br>(76.6%) |
|           |                                                                                                                    | Black or African<br>American                                      | 21 (6%)              | 3 (4.5%)         | 2 (9.1%)      | 16 (6.1%)      |
|           |                                                                                                                    | Asian                                                             | 68<br>(19.5%)        | 46<br>(69.7%)    | 2 (9.1%)      | 20 (7.7%)      |
|           |                                                                                                                    | Other                                                             | 26 (7.4%)            | ---              | 1 (4.5%)      | 25 (9.6%)      |
| ADA       | Treatment-<br>emergent<br>Anti-drug<br>Antibodies                                                                  | Negative                                                          | 345<br>(98.9%)       | 66<br>(100%)     | 22 (100%)     | 257<br>(98.5%) |
|           |                                                                                                                    | Positive                                                          | 4 (1.1%)             | ---              | ---           | 4 (1.5%)       |
| IHC       | Immuno -<br>histo-<br>chemistry                                                                                    | Missing                                                           | 4 (1.1%)             | ---              | ---           | 4 (1.5%)       |
|           |                                                                                                                    | 0 (HER2-<br>negative)                                             | 10 (2.9%)            | 10<br>(15.2%)    | ---           | ---            |
|           |                                                                                                                    | 1 (HER2-<br>negative)                                             | 3 (0.9%)             | ---              | 3 (13.6%)     | ---            |
|           |                                                                                                                    | 2 (ISH<br>amplified)                                              | 149<br>(42.7%)       | 17<br>(25.8%)    | 19<br>(86.4%) | 113<br>(43.3%) |
|           |                                                                                                                    | 3 (IHC 3+)                                                        | 183<br>(52.4%)       | 39<br>(59.1%)    | ---           | 144<br>(55.2%) |
| RENALGFR  | Renal<br>Function<br>/Impairment<br>at baseline<br>as estimated<br>by GFR<br>computed<br>using CKD-<br>EPI formula | Normal<br>(GFR ≥ 90<br>mL/min<br>/1.73m <sup>2</sup> )            | 267<br>(76.5%)       | 41<br>(62.1%)    | 16<br>(72.7%) | 210<br>(80.5%) |
|           |                                                                                                                    | Mild (GFR ≥ 60<br>and < 90<br>mL/min<br>/1.73m <sup>2</sup> )     | 64<br>(18.3%)        | 19<br>(28.8%)    | 3 (13.6%)     | 42<br>(16.1%)  |
|           |                                                                                                                    | Moderate (GFR<br>≥ 30 and < 60<br>mL/min<br>/1.73m <sup>2</sup> ) | 18 (5.2%)            | 6 (9.1%)         | 3 (13.6%)     | 9 (3.4%)       |
| HEPATIC   | Hepatic<br>Function<br>/Impairment<br>at baseline                                                                  | Normal                                                            | 218<br>(62.5%)       | 55<br>(83.3%)    | 14<br>(63.6%) | 149<br>(57.1%) |
|           |                                                                                                                    | Mild                                                              | 129 (37%)            | 11<br>(16.7%)    | 8 (36.4%)     | 110<br>(42.1%) |
|           |                                                                                                                    | Moderate                                                          | 2 (0.6%)             | ---              | ---           | 2 (0.8%)       |

Source: Adapted from Tables 11 and 13 in Margetuximab Population PK Report.

### Population PK model development

**Model Building Procedure:** The model building procedure starts with a base model with the structure as shown in Figure 1. Covariate effects of weight and sex on all parameters and mechanistically plausible dependencies of clearance on albumin (ALB) and tumor burden (TMBD) were assessed in the full covariate model. covariates of interest (race, hepatic and renal impairment, age, ECOG score, tumor type, LDH, CD16A status, ADA, and HER2 expression level) on clearance were also investigated. The selected final model based on objective function value is a two-compartment model contained parallel linear and Michaelis-Menten elimination including sex effect on CL, Q an Vc, body weight effect on CL, Q, Vc and Vp, and effects of ALB and TMBD on CL. The estimated model and derived PK parameters are summarized in Table 3. All structural model parameters were estimated precisely (RSE < 8% except for KM with RSE of 18.0%). Effects of covariates on CL, Q, Vc, and Vp were also estimated precisely (RSE <15%), except for TMBD on CL (RSE of 22%). RSE values of random effect variance parameters were less than 20%, with the exception of the random effect on Q (RSE= 28.8%). Shrinkage of random effects was low (< 24%) for all parameters except VMAX (shrinkage of 46.7%) and Q (shrinkage of 51.5%). Shrinkage of residual error was low (4.6%).

Figure 5 Margetuximab PPK Model Scheme and Model Equations



Note: PPK Model Equations  $C = A1/Vc$

$$dA1/dt = -Q/Vc \cdot A1 + Q/Vp \cdot A2 - CL/Vc \cdot A1 - Vmax \cdot A1/(Km+C) \quad dA2/dt = Q/Vc \cdot A1 - Q/Vp \cdot A2$$

Abbreviations: A1: drug amount in the central compartment; A2: drug amount in the peripheral compartment; C: drug concentration in the central compartment; CL: non-specific linear clearance; IV: intravenous; Km: Michaelis-Menten constant; PPK: population pharmacokinetic; Q: inter-compartment clearance; Vc: volume of the central compartment; Vmax: maximum Michaelis-Menten (target-mediated) elimination rate; Vp: volume of the peripheral compartment.

Source: Margetuximab Population PK Report - Figure 1.

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

Table 35 Margetuximab Population Pharmacokinetic Parameter Estimates (Final Model 103, Study 01, 02, and 04)

| Fixed Effect Parameter                 |                  | Estimate                                                                                                    | RSE (%) | 95% CI          |           |       |
|----------------------------------------|------------------|-------------------------------------------------------------------------------------------------------------|---------|-----------------|-----------|-------|
| CL (L/day)                             | $\vartheta_1$    | 0.241                                                                                                       | 1.79    | 0.233 - 0.250   |           |       |
| Vc (L)                                 | $\vartheta_2$    | 2.86                                                                                                        | 1.18    | 2.79 - 2.93     |           |       |
| Q (L/day)                              | $\vartheta_3$    | 0.556                                                                                                       | 6.68    | 0.483 - 0.629   |           |       |
| Vp (L)                                 | $\vartheta_4$    | 2.66                                                                                                        | 3.81    | 2.46 - 2.85     |           |       |
| Km ( $\mu\text{g/mL}$ )                | $\vartheta_5$    | 0.700                                                                                                       | 18.0    | 0.453 - 0.947   |           |       |
| Vmax ( $[\mu\text{g/mL}]/\text{day}$ ) | $\vartheta_6$    | 1.34                                                                                                        | 7.13    | 1.15 - 1.52     |           |       |
| CL, Q ~ WT                             | $\vartheta_7$    | 0.578                                                                                                       | 10.2    | 0.463 - 0.694   |           |       |
| Vc, Vp ~ WT                            | $\vartheta_8$    | 0.369                                                                                                       | 11.0    | 0.289 - 0.449   |           |       |
| CL, Q ~ SEX                            | $\vartheta_9$    | 1.35                                                                                                        | 5.82    | 1.20 - 1.51     |           |       |
| CL ~ ALB                               | $\vartheta_{10}$ | 0.682                                                                                                       | 14.4    | 0.489 - 0.876   |           |       |
| Vc ~ SEX                               | $\vartheta_{11}$ | 1.29                                                                                                        | 3.90    | 1.19 - 1.39     |           |       |
| CL ~ TMBD                              | $\vartheta_{12}$ | 0.133                                                                                                       | 21.5    | 0.0766 - 0.189  |           |       |
| Variance Parameter                     | Estimate         | RSE (%)                                                                                                     | 95%CI   | Variability     | Shrinkage |       |
| $\omega^2\text{CL}$                    | $\Omega(1,1)$    | 0.0425                                                                                                      | 9.22    | 0.0348 - 0.0502 | CV=20.6%  | 11.8% |
| $\omega^2\text{Vc}$                    | $\Omega(2,2)$    | 0.0276                                                                                                      | 9.63    | 0.0224 - 0.0328 | CV=16.6%  | 5.9%  |
| $\omega^2\text{Q}$                     | $\Omega(3,3)$    | 0.197                                                                                                       | 28.8    | 0.0858 - 0.307  | CV=44.3%  | 51.5% |
| $\omega^2\text{Vp}$                    | $\Omega(4,4)$    | 0.197                                                                                                       | 13.6    | 0.145 - 0.25    | CV=44.4%  | 23.2% |
| $\omega^2\text{Vmax}$                  | $\Omega(5,5)$    | 0.241                                                                                                       | 19.2    | 0.15 - 0.332    | CV=49.1%  | 46.7% |
| $\omega^2\sigma$                       | $\Omega(6,6)$    | 0.113                                                                                                       | 8.23    | 0.0949 - 0.131  | CV=33.6%  | 0.2%  |
| $\sigma^2$                             | $\Sigma(1,1)$    | 0.014                                                                                                       | 4.75    | 0.0127 - 0.0153 | CV=11.8%  | 4.6%  |
| Derived Parameters                     |                  |                                                                                                             |         |                 |           |       |
| Distribution half-life (day)           | 1.58             | Distribution and terminal half-lives were computed using parameters CL, Q, VC, and VP of a typical subject. |         |                 |           |       |
| Terminal half-life (day)               | 17.3             |                                                                                                             |         |                 |           |       |

Abbreviations: ALB: serum albumin (g/dL) at baseline; CI: confidence interval; CL: non-specific linear clearance; Km: Michaelis-Menten constant; PE: parameter estimate; Q: inter-compartment clearance; RSE: relative standard error (%) [100·SE/PE]; SE:

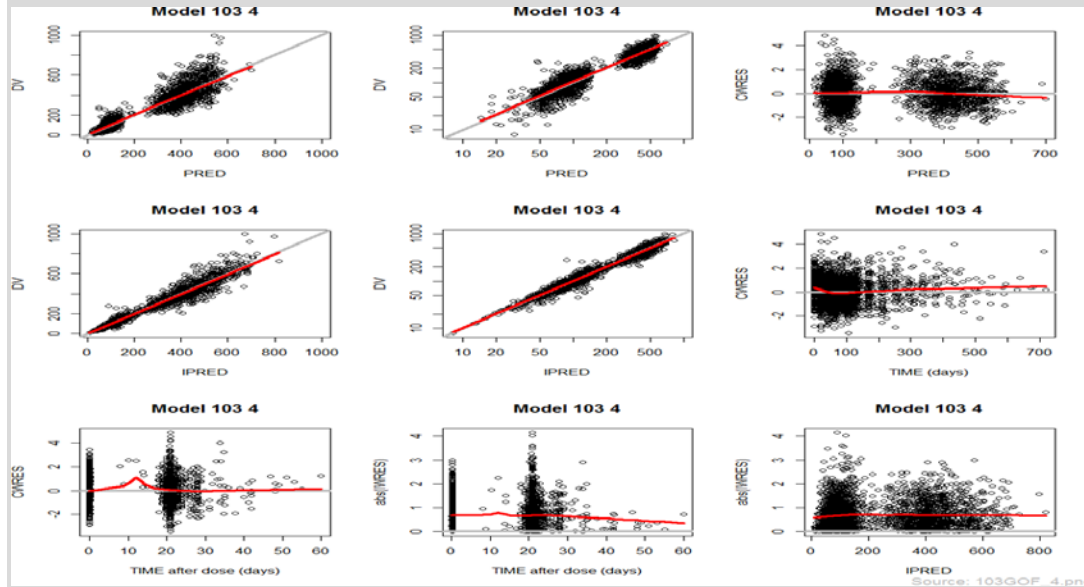
NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
{MARGENZA, margetuximab-cmkb}

standard error; TMBD: tumor burden (sum of tumor diameters, mm); Vc: volume of distribution of the central compartment; Vmax: maximum target-mediated elimination rate; Vp: volume of distribution of the peripheral compartment; WT: body weight.

Source: *Margetuximab Population PK Report - Table 16.*

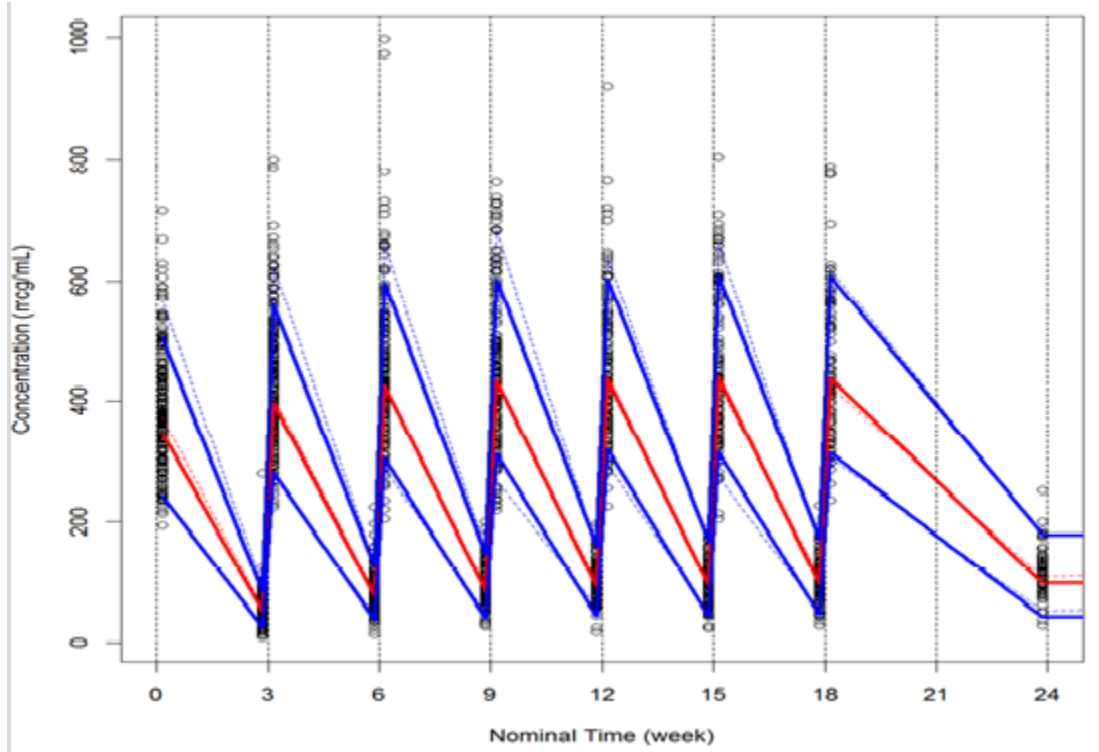
**Model Evaluation:** The final model was evaluated graphically by goodness-of-fit plots and visual predictive checks (VPCs). Goodness of fit for study CP-MGAH22-04 is shown in Figure 2 and Visual predictive check for study CP-MGAH22-04 is shown in Figure 3.

Figure 6 Goodness of Fit for Study CP-MGAH22-04



Source: *Margetuximab Population PK Report -Figure 105.*

Figure 7 Visual Predictive Check for Study CP-MGAH22-04, Final Model 103

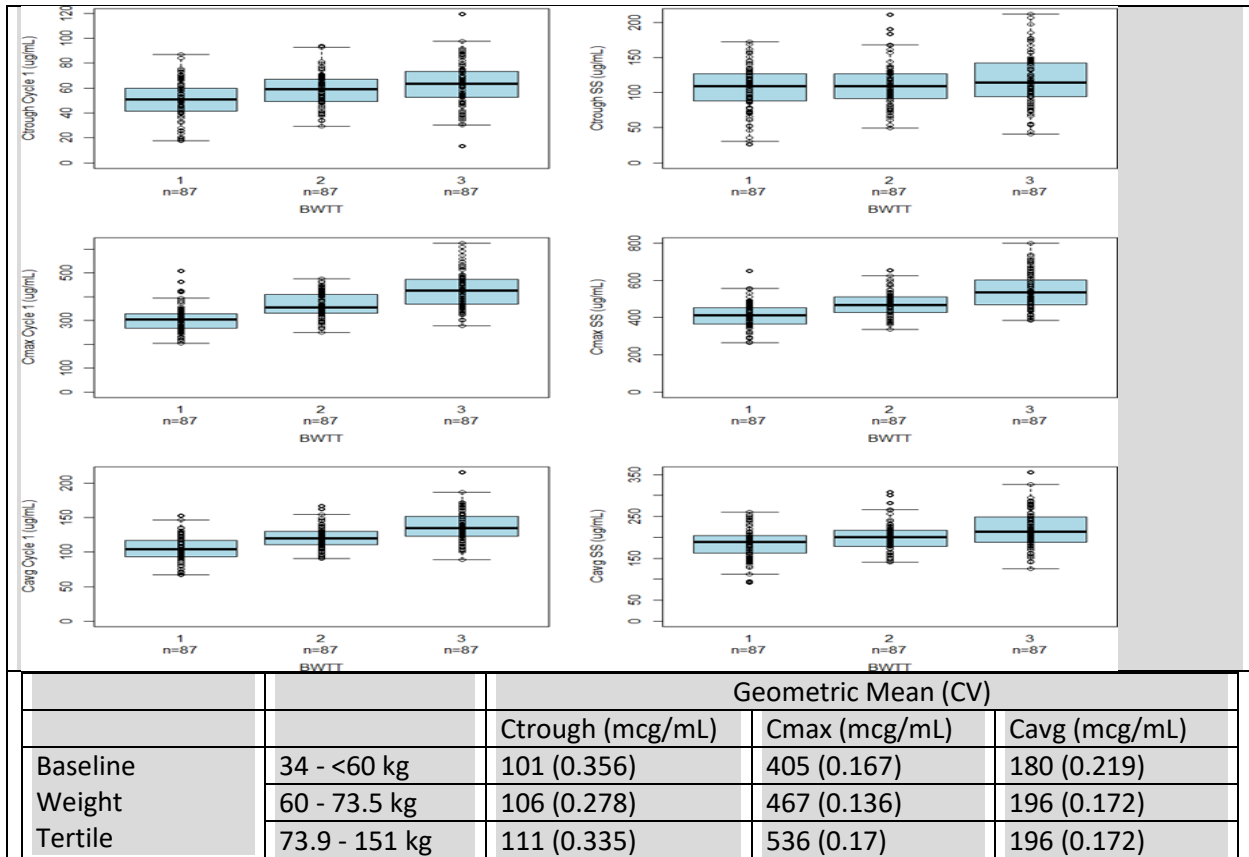


The colored dashed lines show median (red), and the 5th and 95th percentiles (blue) of the observed concentrations (shown as open circles). The solid lines show these quantities obtained by simulations. The simulated values were computed from 1000 trials with dosing, sampling, and the covariate values of the analysis data set. The vertical dashed lines show times of doses.

Source: *Margetuximab Population PK Report -Figure 191.*

**Impact of Covariates on Margetuximab Exposure:** A sensitivity analysis was performed to examine the influence of covariates on the exposure of margetuximab following 15 mg/kg IV infusion Q3W. The influence of covariates on average concentration over 1 treatment cycle of 3 weeks and at the steady state ( $C_{avg}$ ), maximum concentration during cycle 1 and at the steady state ( $C_{max}$ ), and concentration at the end of cycle 1 and at the steady state ( $C_{trough}$ ) is shown in Figure 4 and Figure 5.

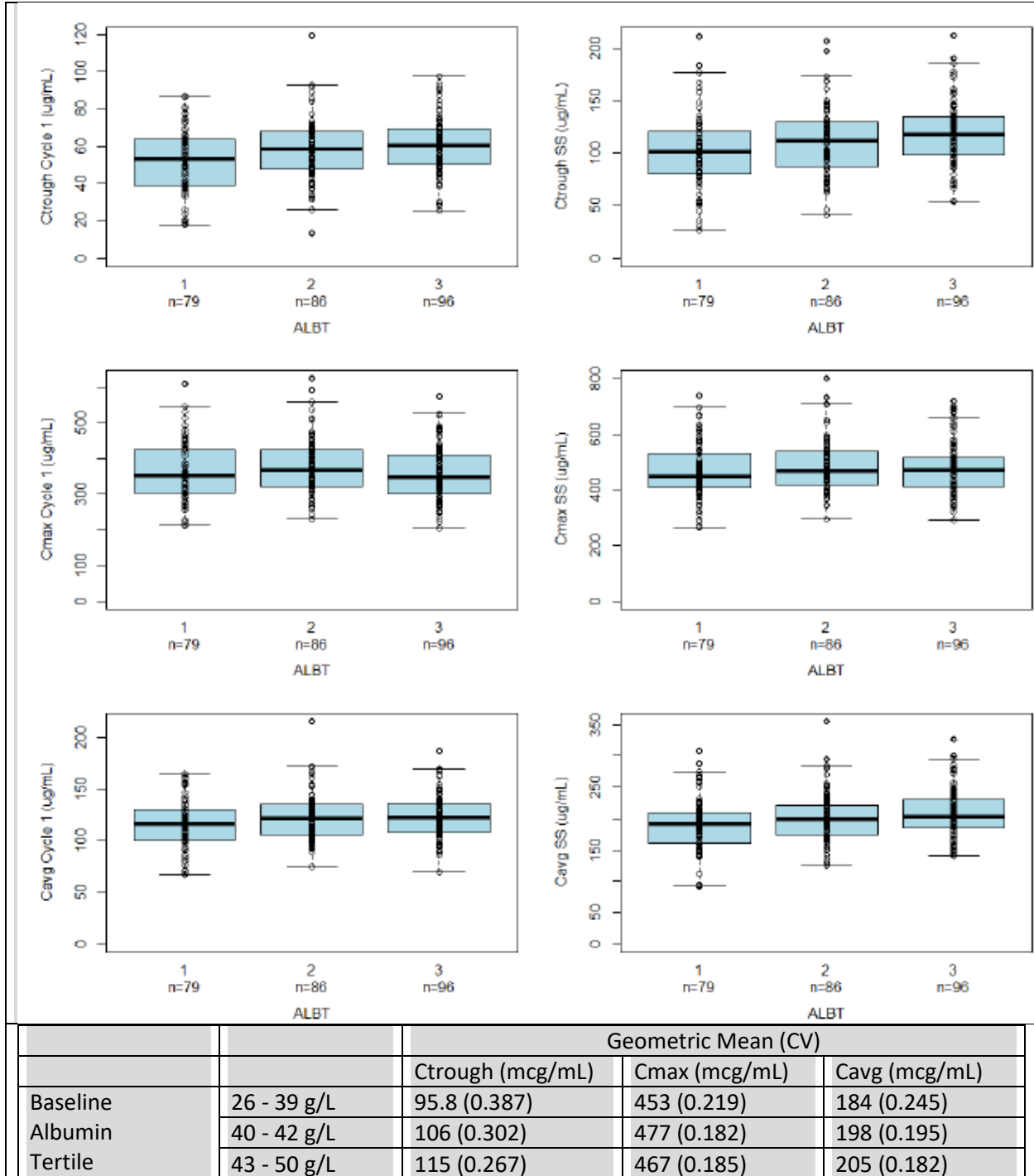
Figure 8 Relationship Between Margetuximab Exposure and Tertiles of Body Weight (Final Model 103, Study 04)



Source: *Margetuximab Population PK Report -Figure 201 and Table 24.*

Figure 9. Relationship Between Margetuximab Exposure and Tertiles of ALB (Final Model 103, Study 04)

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}



Source: Margetuximab Population PK Report -Figure 202 and Table 24.

**Special Populations:** There is not an obvious trend observed across the groups of renal impairment in subjects with breast cancer: normal 0 (n=184), mild 1 (n=63), and moderate 2 (n=14). There is not an obvious trend observed across the groups of hepatic impairment in subjects with breast cancer: normal 0 (n=149), mild 1 (n=110), and moderate 2 (n=2). This supports the proposed labeling statement that no clinically significant differences in margetuximab-cmkb PK were observed based on mild (CLcr 60 to 89 mL/min estimated using the Cockcroft-Gault equation) or moderate (CLcr 30 to 59 mL/min) renal impairment, mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 ULN and any AST).

**Simulations:** The final model was used to simulate individual PK profiles after multiple dosing with 15 mg/kg Q3W dosing regimen for subjects from the analysis data set, as well as to evaluate and compare PK parameters and exposure metrics based on these simulations.

#### PK Parameters

For subjects from Study CP-MGAH22-04, the geometric mean (%CV) steady-state volume of distribution is 5.47 L (22%); and the geometric mean (%CV) terminal half-life is 19.2 days (28%) and clearance is 0.221 L/day (24%). In addition, the median of the terminal half-life is 18.5 days per simulation and is comparable with the terminal half-life 17.3 days using parameters CL, Q, Vc, and Vp of a typical subject in the population PK data set.

#### Exposure Metrics

Exposure metrics including: C<sub>max</sub>, AUC, and Trough concentration (C<sub>trough</sub>) geometric mean (% coefficient of variation) in a dosing interval of 21 days at Cycle 1 and at steady-state for 261 female subjects with breast cancer are shown in Table 4.

Table 36. Summary of Exposures for Subjects from Study CP-MGAH22-04

| Period       | C <sub>max</sub><br>(µg/mL) | AUC<br>(µg•day/mL) | C <sub>trough</sub><br>(µg/mL) |
|--------------|-----------------------------|--------------------|--------------------------------|
| First Dose   | 356 (21%)                   | 2490 (19%)         | 54.6 (32%)                     |
| Steady-state | 466 (20%)                   | 4120 (21%)         | 106 (33%)                      |

Source: Adapted from Margetuximab Population PK Report -Table 19

#### Infusion

The influence of a shorter 30-minute duration of infusion compared to a 120-minute infusion on margetuximab PK was assessed via simulations. Differences in exposure were minimal (<1%) as shown in Table 5.

Table 37 PPK Predicted Margetuximab Pharmacokinetic Parameters by Infusion Duration (15 mg/kg Every 3 weeks)

| Parameter                                    | Unit         | Median (Range)       |                      |
|----------------------------------------------|--------------|----------------------|----------------------|
|                                              |              | 120-min Infusion     | 30-min Infusion      |
| <i>First Dose Parameters (Cycle 1)</i>       |              |                      |                      |
| <i>C<sub>max</sub></i>                       | <i>µg/mL</i> | <i>351 (203-623)</i> | <i>354 (204-631)</i> |
| <i>Parameters at Steady-State (Cycle 16)</i> |              |                      |                      |
| <i>C<sub>max</sub></i>                       | <i>µg/mL</i> | <i>460 (265-798)</i> | <i>464 (266-806)</i> |

Source: *Margetuximab Population PK Report - Table 23.*

### **Washout**

Time to washout, which is defined as time needed for concentrations to decline to 3.5 µg/mL, was estimated via simulations. Results indicated that washout time was below 71 days (10 weeks) in 50% of subjects and below 110 days (16 weeks) for 95% of subjects following discontinuation of 15 mg/kg Q3W dosing regimen.

### **Exposure-Response Analysis**

The exposure-response analysis includes exposure-efficacy and exposure-safety analyses. Study CP-MGAH22-04 data from randomized subjects was used in the analysis. Covariate data were extracted from the data used for the population PK analysis and included body size measures, age, gender, race/ethnicity, alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin [BILI], alkaline phosphatase [ALP], serum creatinine [CREAT], calculated creatinine clearance (CRCL), renal function/impairment, hepatic function/impairment, serum albumin [ALB], and lactate dehydrogenase [LDH]; tumor type [TMTP], tumor burden [TMBD], number of metastatic sites, number of prior therapies, baseline Eastern Cooperative Oncology Group [ECOG] score, immunohistochemistry (IHC) for HER2 testing, polymorphisms of CD16A, CD32A, and CD32B, assigned chemotherapy [CHEMTR] and presence of treatment-emergent anti-drug antibodies.

**Exposure-Efficacy Analysis:** The objectives of the exposure-efficacy analysis include the evaluation of the relationships between margetuximab exposure and progression-free survival assessed by an independent review committee (PFS-IRC), progression-free survival assessed by investigators (PFS-INV), overall survival (OS), objective response rate assessed by investigators (ORR-INV), objective response rate assessed by an independent review committee (ORR-IRC), clinical benefit rate assessed by investigators (CBR-INV), and clinical benefit rate assessed by an independent review committee (CBR-IRC). Average steady-state margetuximab concentration by nominal dosing history (CavgSS) was used for exposure-response analyses.

Time-to-event (TTE) survival analyses were performed for three TTE efficacy endpoints: PFS-INV, PFS-IRC, and OS. The exposure -TTE relationship was described by a semi-parametric CPH model to evaluate effect of exposure on survival, including effects of prognostic factors on the relationship between exposure and TTE. The final CPH model for PFS-INV is summarized Table 6. The full model confirmed a

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

statistically significant reduction in hazard of progression with increasing exposure ( $p < 0.001$ ). Among covariates, increased BSA and log(LDH) increased hazard of progression, whereas increased age and HER2 3+ expression decreased hazard of progression ( $p < 0.01$ ). The hazard of progression was higher in subjects with CD16A V/V allele ( $p = 0.051$ ). Under the assumption of proportional hazard, hazard ratio was calculated with respect to 2, 3, and 4 changes in CavgSS and was summarized in Table 7. This reviewer further did case-control analysis via matching each exposure quantile to the placebo group via the covariates BSA, age, LDH, IHC, and CD16A. The results were summarized in Table 8.

The same analysis was repeated for PFS-IRC and gave results similar to PFS-INV. For OS, as of 10-Oct-2018, the full model confirmed a decreased hazard of death with increased exposure, but this relationship was not statistically significant at the  $\alpha=0.05$  level ( $p = 0.091$ ). OS duration appeared shorter in subjects with lowest margetuximab exposure (1st Quartile) than in the trastuzumab control group. The interpretation of this result should be cautious, since OS data as of 10-Oct-2018 is immature for this analysis. In addition, exposure-matched analysis would be more informative. However, that is not possible because trastuzumab exposure data are not available. When OS data is mature, further evaluation of magnitude and causation of variation in the OS response would be helpful to characterize the drug performance.

Table 38 CPH Models for PFS-INV: Final Model

| Model       | Coefficient | SE       | RSE (%) | HR     | HR 95%CI       | p-value  |
|-------------|-------------|----------|---------|--------|----------------|----------|
| log(CavgSS) | -1.517      | 0.4272   | 28.16   | 0.2194 | 0.09496-0.5068 | 0.00038  |
| BSA         | 1.601       | 0.4844   | 30.25   | 4.959  | 1.919-12.82    | 0.00095  |
| AGE         | -0.02264    | 0.007958 | 35.15   | 0.9776 | 0.9625-0.993   | 0.0044   |
| log(LDH)    | 0.8282      | 0.1726   | 20.85   | 2.289  | 1.632-3.211    | 0.000002 |
| IHC 3+      | -0.4532     | 0.1652   | 36.45   | 0.6356 | 0.4598-0.8786  | 0.0061   |
| CD16A VV    | 0.4727      | 0.2418   | 51.15   | 1.604  | 0.9988-2.577   | 0.051    |

Source: Margetuximab Population Exposure Response Report - Table 8.

Table 39 Summary of Hazard Ratios for PFS with respect to quantiles of CavgSS, Study 04

| Quantile (%) | Cavgss | Fold Change | Hazard Ratio | 95% upper | 95% lower |
|--------------|--------|-------------|--------------|-----------|-----------|
| 25           | 173.9  | 1           | 1            | 1         | 1         |
| 50           | 197.5  | 1.1357      | 0.9196       | 0.8378    | 0.9634    |
| 75           | 220.8  | 1.2697      | 0.8544       | 0.7174    | 0.9325    |

Source: Reviewer.

Table 40 Summary of Hazard Ratios for PFS by each quantile vs. placebo\*

| Cavgss Exposure Quantile (%) | Hazard Ratio | 95% upper | 95% lower |
|------------------------------|--------------|-----------|-----------|
|                              |              |           |           |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

|                                                                                                                                                                                           |      |      |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------|------|
| (0, 25]                                                                                                                                                                                   | 0.90 | 0.62 | 1.29 |
| (25, 50]                                                                                                                                                                                  | 0.87 | 0.61 | 1.25 |
| (50-75]                                                                                                                                                                                   | 0.71 | 0.50 | 1.00 |
| (75-100]                                                                                                                                                                                  | 0.55 | 0.38 | 0.80 |
| *note that one subject MGAH22-04- (b) (6) has extremely high baseline LDH 97.8 $\mu$ kat/L was removed from the Cox regression analysis with covariates BSA, AGE, LogLDH, IHC, and CD16A. |      |      |      |

Source: Reviewer.

Four binary measures of efficacy were investigated: ORR-IRC, ORR-INV, CBR-IRC, and CBR-INV. Logistic regression models were implemented to assess correlation of probability of response with exposure. Probability of response increased with increasing exposure although in general these relationships were not statistically significant.

**Exposure-Safety Analysis:** The objectives of the exposure-safety analysis include evaluation of relationships between margetuximab exposure and occurrence of the following classes of treatment-emergent adverse events (AE): Serious adverse events (SAE) of any grade and of grade > 3, Infusion-related reactions (IRR) of any grade and of grade > 3, AEs of left ventricular dysfunction (LVD) of any grade and of grade > 3, AEs of neutropenia of any grade and of grade > 3, AEs of febrile neutropenia of any grade and of grade > 3, AEs of vascular disorders of any grade and of grade > 3, and AEs of any grade and of grade > 3. For each type of adverse event, correlations of probability of AE with exposure were investigated using logistic regression analyses. There was no noticeable increase in probability of adverse events of any type with exposure.

**Review Summary**

In general, the Applicant’s population PK analysis is considered acceptable for the purpose of supporting analyses objectives. The Applicant’s analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in Table 9.

Table 41. Specific Comments on Applicant’s Final Population PK model

| Utility of the final model                                                             |                  |                                                                                                                                                                                                                                                                                                                                                                      | Reviewer’s Comments          |
|----------------------------------------------------------------------------------------|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| Support Applicant’s proposed labeling statements about intrinsic and extrinsic factors | Intrinsic factor | “No clinically significant differences in margetuximab-cmkb PK were observed based on age (29 to 83 years), race (Caucasian, Black, Asian), sex, mild (CLcr 60 to 89 mL/min estimated using the Cockcroft-Gault equation) or moderate (CLcr 30 to 59 mL/min) renal impairment, mild hepatic impairment (total bilirubin $\leq$ ULN and AST > ULN, or total bilirubin | The statement is acceptable. |

|                                                        |                  |                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                    |
|--------------------------------------------------------|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                        |                  | 1 to 1.5 ULN and any AST), HER2 expression level (0 to 3 by IHC), tumor burden (2 – 317 mm), ECOG score (0 to 2), albumin (24 to 50 g/L), FCGR3A (CD16A), FCGR2A (CD32A) and FCGR2B (CD32B) genotype, number of metastatic sites.” |                                                                                                                                                                                                                                                                                                                    |
|                                                        | Extrinsic factor | “No clinically significant differences in margetuximab-cmkb PK were observed based on number of prior therapy lines, concurrent chemotherapies (capecitabine, gemcitabine, eribulin and vinorelbine).”                             | The statement is acceptable.                                                                                                                                                                                                                                                                                       |
| Derive exposure metrics for Exposure-response analyses | CavgSS           |                                                                                                                                                                                                                                    | The Applicant’s final model is generally acceptable for generating exposure metrics for exposure-response analyses (Table 6). However, the shrinkages for VMAX (shrinkage of 46.7%) and Q (shrinkage of 51.5%) are high and therefore the corresponding post-hoc individual estimates should be used with caution. |
| Predict exposures at alternative dosing regimen        | NA               |                                                                                                                                                                                                                                    | NA                                                                                                                                                                                                                                                                                                                 |

### 19.5. Additional Safety Analyses Conducted by FDA

The FDA’s Assessment:

Refer to the safety Section 8.2 for any other additional analyses conducted by the FDA.

## Signatures

| DISCIPLINE                         | REVIEWER                                                                                                                                                                                                                                                                                                             | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED                                                                                                 |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------------------|--------------------------------------------------------------------------------------------------------------------|
| Nonclinical Reviewer               | C. J George Chang                                                                                                                                                                                                                                                                                                    | OOD/DHOT        | Sections: 5                 | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                    | <b>Signature: Ching Jey G. Chang -S</b><br><small>Digitally signed by Ching Jey G. Chang -S<br/>                     DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000350983, cn=Ching Jey G. Chang -S<br/>                     Date: 2020.12.15 13:08:15 -05'00'</small>       |                 |                             |                                                                                                                    |
| Nonclinical Team Leader            | Tiffany Ricks                                                                                                                                                                                                                                                                                                        | OOD/DHOT        | Sections: 5                 | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                    | <b>Signature: Tiffany K. Ricks -S</b><br><small>Digitally signed by Tiffany K. Ricks -S<br/>                     DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000497170, cn=Tiffany K. Ricks -S<br/>                     Date: 2020.12.15 11:39:53 -05'00'</small>             |                 |                             |                                                                                                                    |
| Nonclinical Team Division Director | John Leighton                                                                                                                                                                                                                                                                                                        | OOD/DHOT        | Sections: 5                 | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                    | <b>Signature: John K. Leighton -S</b><br><small>Digitally signed by John K. Leighton -S<br/>                     DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300085260, cn=John K. Leighton -S<br/>                     Date: 2020.12.15 11:45:20 -05'00'</small>             |                 |                             |                                                                                                                    |
| Clinical Pharmacology Reviewer     | Kirthika Shetty                                                                                                                                                                                                                                                                                                      | OTS/OCP/DCP-1   | Sections: 6, 19.4           | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                    | <b>Signature: Krithika-arun Shetty -S</b><br><small>Digitally signed by Krithika arun Shetty -S<br/>                     DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002698440, cn=Krithika arun Shetty -S<br/>                     Date: 2020.12.15 11:07:10 -05'00'</small> |                 |                             |                                                                                                                    |
| Clinical Pharmacology Team Leader  | Pengfei Song                                                                                                                                                                                                                                                                                                         | OTS/OCP/DCP-II  | Sections: 6, 19.4           | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                    | <b>Signature: Pengfei Song -S</b><br><small>Digitally signed by Pengfei Song -S<br/>                     DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Pengfei Song -S, 0.9.2342.19200300.100.1.1=2000464900<br/>                     Date: 2020.12.15 11:21:02 -05'00'</small>                         |                 |                             |                                                                                                                    |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

| DISCIPLINE                                 | REVIEWER                                                                                                                                                                                                                                                                                                           | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED                                                                                     | AUTHORED/ APPROVED                                                                                                 |
|--------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| Clinical Pharmacology<br>Division Director | Nam Atiqur Rahman                                                                                                                                                                                                                                                                                                  | OTS/OCP/DCP-II  | Sections: 6, 19.4                                                                                               | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                            | <b>Signature: Nam A. Rahman -S</b><br><small>Digitally signed by Nam A. Rahman -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S,<br/>           0.9.2342.19200300.100.1.1=1300072597<br/>           Date: 2020.12.15 10:56:55 -05'00'</small>                         |                 |                                                                                                                 |                                                                                                                    |
| Pharmacometrics<br>Reviewer                | Junshan Qiu                                                                                                                                                                                                                                                                                                        | OTS/OCP/DPM     | Sections: 6, 19.4                                                                                               | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                            | <b>Signature: Junshan Qiu -S</b><br><small>Digitally signed by Junshan Qiu -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,<br/>           ou=People, cn=Junshan Qiu -S,<br/>           0.9.2342.19200300.100.1.1=2000348577<br/>           Date: 2020.12.15 13:48:57 -05'00'</small>                |                 |                                                                                                                 |                                                                                                                    |
| Pharmacometrics<br>Team Leader             | Jingyu Jerry Yu                                                                                                                                                                                                                                                                                                    | OTS/OCP/DPM     | Sections: 6, 19.4                                                                                               | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                            | <b>Signature: Jingyu Yu -S</b><br><small>Digitally signed by Jingyu Yu -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,<br/>           cn=Jingyu Yu -S, 0.9.2342.19200300.100.1.1=2000794699<br/>           Date: 2020.12.15 10:58:23 -05'00'</small>                                     |                 |                                                                                                                 |                                                                                                                    |
| Genomics Reviewer                          | Jeffrey Kraft                                                                                                                                                                                                                                                                                                      | OCP/DTPM        | Sections: 6                                                                                                     | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                            | <b>Signature: Jeffrey B. Kraft Jr -S</b><br><small>Digitally signed by Jeffrey B. Kraft Jr -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,<br/>           0.9.2342.19200300.100.1.1=2000828011, cn=Jeffrey B. Kraft Jr -S<br/>           Date: 2020.12.15 10:53:02 -05'00'</small>       |                 |                                                                                                                 |                                                                                                                    |
| Genomics Leader                            | Rosane Charlab Orbach                                                                                                                                                                                                                                                                                              | OCP/DTPM        | Sections: 6                                                                                                     | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                            | <b>Signature: Rosane Charlaborbach -S</b><br><small>Digitally signed by Rosane Charlaborbach -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,<br/>           0.9.2342.19200300.100.1.1=1300436672, cn=Rosane Charlaborbach -S<br/>           Date: 2020.12.15 11:23:12 -05'00'</small>    |                 |                                                                                                                 |                                                                                                                    |
| Clinical Reviewer                          | Melanie Royce                                                                                                                                                                                                                                                                                                      | OOD/DO1         | Sections: 2, 3, 4, 7, 8.1.2,<br>8.2.1 to 8.2.5, 8.2.7 to<br>8.2.11, 8.4, 9, 10, 11, 12, 13,<br>19.1, 19.2, 19.5 | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                            | <b>Signature: Melanie E. Royce -S</b><br><small>Digitally signed by Melanie E. Royce -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,<br/>           ou=People, 0.9.2342.19200300.100.1.1=2002842365,<br/>           cn=Melanie E. Royce -S<br/>           Date: 2020.12.15 11:02:48 -05'00'</small> |                 |                                                                                                                 |                                                                                                                    |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
 {MARGENZA, margetuximab-cmkb}

| DISCIPLINE                            | REVIEWER                                                                                                                                                                                                                                                                                               | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED                             | AUTHORED/ APPROVED                                                                                                 |
|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|---------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| Biostatistics Reviewer                | Anup Amatya                                                                                                                                                                                                                                                                                            | OTS/OB/DBV      | Sections: 1,8                                           | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                       | <b>Signature: Anup K. Amatya -S</b><br><small>Digitally signed by Anup K. Amatya -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Anup K. Amatya -S 0 9 2342.19200300.100.1.1 2002706863<br/>           Date: 2020.12.15 10:48:04 -05'00'</small>                          |                 |                                                         |                                                                                                                    |
| Biostatistics Team Leader             | Mallorie Fiero                                                                                                                                                                                                                                                                                         | OTS/OB/DBV      | Sections: 1, 8                                          | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                       | <b>Signature: Mallorie H. Fiero -S</b><br><small>Digitally signed by Mallorie H. Fiero -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002084959, cn=Mallorie H. Fiero -S<br/>           Date: 2020.12.15 11:58:03 -05'00'</small>                |                 |                                                         |                                                                                                                    |
| Division Director (OB)                | Shenghui Tang                                                                                                                                                                                                                                                                                          | OTS/OB/DBV      | Sections: 1,8                                           | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                       | <b>Signature: Shenghui Tang -S</b><br><small>Digitally signed by Shenghui Tang -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shenghui Tang -S, 0 9 2342.19200300.100.1.1=1300224175<br/>           Date: 2020.12.15 14:16:33 -05'00'</small>                            |                 |                                                         |                                                                                                                    |
| Associate Director of Labeling (ADL)  | William Pierce                                                                                                                                                                                                                                                                                         | OCE/OOD         | Sections: 11, Prescribing Information, Patient Labeling | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                       | <b>Signature: William F. Pierce -S5</b><br><small>Digitally signed by William F. Pierce -S5<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S5<br/>           Date: 2020.12.15 10:44:53 -05'00'</small>             |                 |                                                         |                                                                                                                    |
| Cross-Disciplinary Team Leader (CDTL) | Christy Osgood                                                                                                                                                                                                                                                                                         | OOD/DO1         | Sections: Authored 1/Approved All                       | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                       | <b>Signature: Christy Osgood -S</b><br><small>Digitally signed by Christy Osgood -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Christy Osgood -S, 0.9.2342.19200300.100.1.1=2001693552<br/>           Date: 2020.12.15 11:16:58 -05'00'</small>                         |                 |                                                         |                                                                                                                    |
| Division Director (Clinical)          | Laleh Amiri-Kordestani                                                                                                                                                                                                                                                                                 | OOD/DO1         | Sections: All                                           | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                       | <b>Signature: Laleh Amiri-kordestani -S</b><br><small>Digitally signed by Laleh Amiri-kordestani -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0014338688, cn=Laleh Amiri-kordestani -S<br/>           Date: 2020.12.15 10:03:52 -05'00'</small> |                 |                                                         |                                                                                                                    |

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761150}  
{MARGENZA, margetuximab-cmkb}

| DISCIPLINE                    | REVIEWER                                                          | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED                                                                                      |
|-------------------------------|-------------------------------------------------------------------|-----------------|-----------------------------|---------------------------------------------------------------------------------------------------------|
| Office Director<br>(Clinical) | Julia Beaver                                                      | OOD             | Sections: All               | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                               | <b>Signature:</b> <i>{See appended electronic signature page}</i> |                 |                             |                                                                                                         |

---

**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

---

/s/  
-----

CLARA J LEE  
12/16/2020 11:18:48 AM

JULIA A BEAVER  
12/16/2020 02:42:05 PM