# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 761289Orig1s000

# MULTI-DISCIPLINE REVIEW

**Summary Review**
**Office Director**
**Cross Discipline Team Leader 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 "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.**

[FDA will complete this section.]

| | |
|---|---|
| **Application Type** | BLA |
| **Application Number(s)** | 761289 |

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|---|---|
| **Priority or Standard** | Priority |
| **Submit Date(s)** | February 23, 2022 |
| **Received Date(s)** | February 23, 2022 |
| **PDUFA Goal Date** | October 23, 2022 |
| **Division/Office** | Division of Oncology 3 |
| **Review Completion Date** | October 21, 2022 |
| **Established Name** | tremelimumab |
| **(Proposed) Trade Name** | Imjudo |
| **Pharmacologic Class** | Anti-CTLA4 inhibitor |
| **Code name** | MEDI1123; formerly CP-675,206 (human IgG2 anti-CTLA-4 mAb) |
| **Applicant** | AstraZeneca AB (Sweden) |
| **Formulation(s)** | concentrate for solution for infusion 20mg/mL |
| **Dosing Regimen** | Tremelimumab 300 mg administered as a single dose intravenously followed by durvalumab 1500 mg intravenously on Day 1 of Cycle 1. Durvalumab 1500 mg is continued as a single agent every 4 weeks |
| **Applicant Proposed Indication(s)/Population(s)** | Tremelimumab in combination with durvalumab for the treatment of patients with unresectable hepatocellular carcinoma |
| **Recommendation on Regulatory Action** | Traditional Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | IMJUDO in combination with durvalumab is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC) |

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## Reviewers of Multi-Disciplinary Review and Evaluation

[FDA will complete this section.]

| | |
|---|---|
| **Regulatory Project Manager** | Christina Leach |
| **Pharmacology/Toxicology Reviewer(s)** | Brian Christmas, Melissa Pegues |
| **Pharmacology/Toxicology Team Leader(s)** | Matthew Thompson |
| **Office of Clinical Pharmacology Reviewer(s)** | Yue Xiang, Yuzhuo Pan |
| **Office of Clinical Pharmacology Team Leader(s)** | Hong Zhao, Jiang Liu |
| **Clinical Reviewer** | Timil Patel |
| **Clinical Team Leader** | Jamie Brewer |
| **Statistical Reviewer** | Jiaxin Fan |
| **Statistical Team Leader** | Joyce Cheng |
| **Associate Director for Labeling (ADL)** | William Pierce, Doris Auth |
| **Cross-Disciplinary Team Leader** | Jamie Brewer |
| **Division Director (DHOT)** | John Leighton |
| **Division Director (OCP)** | Nam Atiqur Rahman |
| **Deputy Division Director (OB)** | Yuan-Li Shen |
| **Division Director (OOD)** | 'Lola Fashoyin-Aje |
| **Office Director (or designated signatory authority)** | Paul Kluetz |

## Additional Reviewers of Application

| | |
|---|---|
| **OPQ** | Xu (Michael) Di, Ram Sihag |
| **Microbiology** | Maria Scott (DS)/Virginia Carroll TL<br>Zonglin Hu (DP)/Madushini Dharmasena TL |
| **OBP Labeling** | Vicky Borders-Hemphill |
| **OPDP** | Rebecca Falter, Emily Dvorsky |
| **OSI** | Michele Fedowitz, Karen Bleich |
| **OSE/DEPI** | Kate Gleperin, Fang Tian |
| **OSE/DMEPA** | Sarah Thomas, Janine Stewart, Ashleigh Lowery |
| **OSE/DRM** | Celeste Karpow, Naomi Boston |
| **Other** | |

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
DRM=Division of Risk Management



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# Glossary

| | |
|---|---|
| 1L | first-line |
| ΔQTcF | concentration-baseline adjusted QTcF |
| ADA | anti-drug antibody |
| ADME | absorption, distribution, metabolism, excretion |
| ADR | adverse drug reaction |
| AE | adverse event |
| AEPI | adverse event of possible interest |
| AEOSI | adverse event of special interest |
| AFP | alpha-fetoprotein |
| A/G | albumin-globulin ratio |
| ALK | anaplastic lymphoma kinase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| $AUC_{(0\text{-}24h)}$ | area under the concentration-time curve from 0 to 24 hours |
| $AUC_{0\text{-}inf}$ | area under the concentration-time curve from 0 to infinity |
| $AUC_{dose\ 1}$ | area under the concentration-time curve at dose 1 |
| $AUC_{ss}$ | area under the concentration-time curve at steady state |
| BCLC | Barcelona Clinic Liver Cancer |
| BICR | Blinded Independent Central Review |
| BID | twice daily |
| BLA | Biologics License Application |
| BLQ | below limit of quantification |
| BMI | body mass index |
| BOR | best overall response |
| BTD | breakthrough therapy designation |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CL | clearance |
| CLss | steady-state clearance |
| $C_{max}$ | maximum concentration |
| $C_{max,\ dose\ 1}$ | maximum concentration at dose 1 |
| $C_{max,\ ss}$ | maximum concentration at steady state |
| $C_{min}$ | minimum concentration |
| $C_{min,\ dose\ 1}$ | minimum concentration at dose 1 |
| $C_{min,\ ss}$ | minimum concentration at steady state |
| COA | clinical outcome assessment |
| Compl. | completed |
| COVID-19 | coronavirus disease 2019 |
| CPH | Cox proportional hazard |

| | |
|---|---|
| CR | complete response |
| CrCL | creatinine clearance |
| CRF | case report form |
| CSP | clinical study protocol |
| CSR | clinical study report |
| CV% | % coefficient of variation |
| CTCAE | Common Terminology Criteria for Adverse Event |
| CTLA-4 | cytotoxic T-lymphocyte antigen 4 |
| cyno | cynomolgus monkey |
| D | durvalumab monotherapy 1500 mg Q4W |
| DCO | data cutoff |
| DCR | disease control rate |
| Discont. | discontinued |
| DMF | Drug Master File |
| DoR | duration of response |
| EBE | Empirical Bayes Estimate |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eCTD | electronic common technical document |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| EGFR | epidermal growth factor receptor |
| EHS | extrahepatic spread |
| ELISA | enzyme-linked immunosorbent assay |
| EORTC QLQ | European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire |
| ER | exposure-response |
| ESMO | European Society for Medical Oncology |
| ES-SCLC | extensive-stage small cell lung cancer |
| F | female |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GCP | good clinical practice |
| GD | Gestation Day |
| GLP | good laboratory practice |
| GOF | goodness of fit |
| h | human |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HCC | hepatocellular carcinoma |
| HR | hazard ratio |
| HRP | horse radish peroxidase |
| HRQoL | health-related quality of life |
| IA | interim analysis |
| $ICI_{50}$ | half-maximal inhibitory concentration |
| ICH | International Conference on Harmonisation |

| | |
|---|---|
| IDMC | independent data monitoring committee |
| Ig | immunoglobulin |
| IIV | intraindividual variability |
| imAE | immune-mediated adverse event |
| IND | Investigational New Drug |
| IO | immuno-oncology |
| IP | investigational product |
| ITT | intent-to-treat |
| IV | intravenous |
| JSH | Japan Society of Hepatology |
| KD | equilibrium dissociation constant |
| KM | Kaplan-Meier |
| LDH | lactate dehydrogenase |
| LLOQ | lower limit of quantification |
| M | male |
| m | mouse |
| M1 | Please provide the definition of this term. |
| Max | maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Min | minimum |
| mOS | median overall survival |
| MTP | multiple testing procedure |
| MVI | macrovascular invasion |
| N | total number of patients |
| NA | not applicable |
| nAb | neutralizing antibody |
| NCI | National Cancer Institute |
| NCCN | National Comprehensive Cancer Network |
| ND | no data (animals deceased prior to observation point) |
| NDA | new drug application |
| NE | not evaluated |
| NI | noninferiority |
| NME | new molecular entity |
| NOAEL | no-observed-adverse-effect level |
| NSCLC | non-small cell lung cancer |
| OPQ | Office of Pharmaceutical Quality |
| ORR | objective response rate |
| OS | overall survival |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PD | progressive disease |
| PD-1 | programmed cell death protein 1 |
| PD-L1 | programmed cell death ligand-1 |
| PFS | progression-free survival |
| PK | pharmacokinetic(s) |

| | |
|---|---|
| PPK | population pharmacokinetic(s) |
| PR | partial response |
| PRO | patient-reported outcome |
| PT | preferred term |
| Q2W | every 2 weeks |
| Q3W | every 3 weeks |
| Q4W | every 4 weeks |
| QoL | quality of life |
| R | randomization |
| rcyno | recombinant cynomolgus monkey |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| REMS | risk evaluation and mitigation strategy |
| rh | recombinant human |
| S | sorafenib 400 mg twice daily |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS | Safety Analysis Set |
| sBLA | supplemental Biologics License Application |
| SC | subcutaneous |
| SCCHN | squamous cell carcinoma of head and neck |
| SCLC | small cell lung cancer |
| SD | standard deviation |
| SMQ | Standardized MedDRA query |
| SoC | standard of care |
| SPR | surface plasmon resonance |
| T750 | tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumor types) |
| T75+D | tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W |
| T300+D | tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W |
| T | tremelimumab |
| TBL | total bilirubin |
| TC | tumor cell |
| TIP | Tumor and Immune Cell Positivity |
| TK | toxicokinetic(s) |
| TKI | tyrosine kinase inhibitor |
| Tmax | time to maximum concentration |
| TTP | time to progression |
| TTR | time to onset of objective response |
| UC | urothelial carcinoma |
| uHCC | unresectable hepatocellular carcinoma |
| ULN | upper limit of normal |
| US | United States |
| v | version |
| VEGFR | vascular endothelial growth factor receptor |
| VPC | visual predictive check |

| | |
|---|---|
| vs | versus |
| Vss | steady-state volume of distribution |
| WBC | white blood cell |
| WHO | World Health Organization |

# 1. Executive Summary

## 1.1.Product Introduction

Imjudo (tremelimumab)

Tremelimumab is a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking antibody that binds to CTLA-4 and blocks the interaction with its ligands CD80 and CD86, releasing CTLA-4-mediated inhibition of T-cell activation.

Tremelimumab was not yet approved for any indication in the United States.

Imfinzi (durvalumab)

Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions release the inhibition of immune responses, without inducing antibody dependent cell-mediated cytotoxicity (ADCC).

Durvalumab initially received accelerated approval on May 1, 2017, for the for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. This indication was voluntarily withdrawn on February 22, 2021. Currently, durvalumab is approved for the following indications:

- for the treatment of adult patients with unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
- in combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).
- in combination with gemcitabine and cisplatin, as treatment of adult patients with locally advanced or metastatic biliary tract cancer (BTC).

The Applicant's proposed indication is as follows:

Tremelimumab in combination with durvalumab for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC).

The Applicant's proposed dosing regimen is tremelimumab 300 mg administered as a single

dose intravenously (IV) over 60 minutes followed by durvalumab 1500 mg administered IV over 60 minutes on Day 1 of Cycle 1. Durvalumab 1500 mg administered IV is continued every 4 weeks (Q4W). The Applicant proposed weight-based dosing for patients with a body weight less than 30 kg, as follows: tremelimumab 4 mg/kg administered IV over 60 minutes followed by durvalumab 20 mg/kg administered IV over 60 minutes on Day 1 of Cycle 1. Durvalumab 20 mg/kg administered IV is continued Q4W.

## 1.2.Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from an adequate and well controlled trial, HIMALAYA (NCT03298451), to support claims of safety and effectiveness for the proposed indication. HIMALAYA is a randomized, open-label, multicenter, global trial which evaluated tremelimumab in combination with durvalumab (T300+D), durvalumab monotherapy and sorafenib in 1171 patients with previously untreated, unresectable hepatocellular carcinoma (uHCC). Patients were randomized to receive treatment in one of 3 study arms: tremelimumab 300 mg as a one-time single IV infusion in combination with durvalumab 1500 mg IV on the same day, followed by durvalumab 1500 mg IV every 4 weeks (Q4W); durvalumab 1500 mg IV Q4W (an unapproved regimen for uHCC); or sorafenib 400 mg given orally twice daily until disease progression or unacceptable toxicity. The primary objective was to demonstrate the overall survival (OS) superiority of T300+D versus sorafenib. Key secondary endpoints were to demonstrate OS non-inferiority of durvalumab versus sorafenib, and OS superiority of durvalumab versus sorafenib. The Applicant requested approval of tremelimumab in combination with durvalumab. As such, FDA's assessment of the effectiveness of tremelimumab in combination with durvalumab focused on the results of the T300+D versus sorafenib, with the results of the durvalumab versus sorafenib comparison providing supportive evidence.

The Application contains substantial evidence that tremelimumab administered as a one-time 300 mg intravenous (IV) dose in combination with durvalumab 1500 mg IV during cycle 1, followed by durvalumab 1500 mg IV Q4W in adult patients with uHCC, is safe and effective. HIMALAYA demonstrated a statistically significant and clinically meaningful improvement in OS in patients randomized to the T300+D arm compared to those who were randomized to the sorafenib arm (stratified hazard ratio [HR] of 0.78 [95% CI: 0.66, 0.92], stratified log-rank 2-sided p-value = 0.0035).

Additional supportive data were from Study 22, a multi-part, open-label, multicenter study to evaluate the safety, tolerability, and clinical activity of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab, in adult patients with advanced HCC.

The magnitude of the improvement in OS in the HIMALAYA trial represents a clinical benefit in the indicated population that outweighs the risks associated with treatment. Although a nominally increased incidence of adverse events was observed on the T300+D arm compared to the sorafenib arm, the overall adverse event profile observed with the combination was consistent with that expected in patients receiving dual-checkpoint inhibitor therapy with an anti-PD-L1 and anti-CTLA-4 therapy. Despite

higher incidence of adverse events, the T300+D regimen resulted in a nominally lower incidence of permanent treatment discontinuations (14% vs 17%) and dose interruptions (35% vs 43%).

Therefore the review team recommends granting approval to tremelimumab in combination with durvalumab for the treatment of adult patients with unresectable HCC

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## 1.3.Benefit-Risk Assessment (BRA)

**Benefit-Risk Summary and Assessment**

An estimated 41,260 cases of liver and intrahepatic cancer will be diagnosed in the U.S. in 2022; this represents approximately 2.2% of all new cancer diagnoses with a 5-year relative survival of 20.8% (SEER). According to SEER data patients with regional disease have a 5-year relative survival of 12.8% while those with distant metastatic disease have a 5-year relative survival of 3.1%. FDA-approved therapies for the first-line treatment of uHCC include the tyrosine kinase inhibitors sorafenib and lenvatinib, and atezolizumab in combination with bevacizumab. All approved therapies have demonstrated improvement in survival.

The Applicant submitted data from the HIMALAYA trial to support approval of tremelimumab in combination with durvalumab for the treatment of adult patients with unresectable hepatocellular carcinoma. Substantial evidence of effectiveness has been established for the tremelimumab (300 mg IV x1 during Cycle 1) and durvalumab (1500 mg IV Q4W) regimen (T300+D) based on a demonstration of a statistically significant and clinically meaningful improvement in OS in patients who were randomized to the T300+D arm compared to those who were randomized to the sorafenib arm (stratified HR of 0.78 [95% CI: 0.66, 0.92], stratified log-rank 2-sided p-value = 0.0035).

The data submitted to support the safety review of T300+D is adequate to characterize toxicity in patients with uHCC. The safety event profile observed in patients who received T300+D is generally consistent with what has been observed in patients treated with anti-PD-(L)1 and anti-CTLA-4 immuno-oncology combination regimen and with what would be expected in a population with uHCC who may also have underlying liver disease. There was a slightly nominally higher incidence of Grade 5 AEs (30 (8%) vs 27 (7%)), SAEs (158 (41%) vs 111 (30%)) on the T300+D arm compared to the sorafenib arm. However, then lower incidence of permanent treatment discontinuations (53 patients (14%) vs 62 patients (17%)) and dose interruptions (136 patients (35%) vs 162 patients (43%)) on the T300+D arm suggests the regimen has acceptable tolerability when compared to sorafenib. A review of the safety dataset did not reveal any unexpected safety events associated with T300+D. Overall T300+D demonstrates a positive benefit-risk profile as a

treatment option for adult patients with uHCC.

Risk minimization strategies have been instituted through management guidelines included in the product labeling and Medication Guide. Adverse events thought to be clinically significant were identified in patients treated with T300+D. These clinically significant AEs include IMAEs that are listed in the Warnings and Precautions section of both the tremelimumab and durvalumab label.

A favorable benefit-risk assessment has been established and the review team recommends approval of tremelimumab in combination with durvalumab for the treatment of adult patients with uHCC.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • HCC and intrahepatic bile duct cancer accounts for 2.2% of all new cancers in the U.S. (SEER).<br>• The 5-year relative survival is 12.8% for locoregional disease and 3.1% for metastatic disease.<br>• The median survival for patients with unresectable (metastatic disease) is approximately 1 year (Llovet 2021).<br>• Incidence rates per 100,000 in the US for all stages of new cases of liver or intrahepatic bile duct cancers by race or ethnic group are as follows: Non-Hispanic White 7.7, Non-Hispanic Black 10.8, Non-Hispanic Asian/Pacific Islander 12.5, Non-Hispanic American Indian/Alaskan Native 21.2, and Hispanic 15.3 (SEER). | Unresectable HCC is a serious and life-threatening condition with a poor prognosis. |
| Current Treatment Options | • FDA-approved therapies for the first-line treatment of unresectable HCC include: atezolizumab with bevacizumab, sorafenib, and lenvatinib,<br>• In IMbrave150 atezolizumab in combination with bevacizumab demonstrated a statistically significant and clinically meaningful improvement in overall survival (mOS not reached vs 13.2 months; HR = 0.58; 95% CI: 0.42, 0.79; p=0.0006) and progression-free survival (mPFS 6.8 | Atezolizumab in combination with bevacizumab demonstrated a survival advantage over sorafenib and is approved for uHCC. However due to contraindications associated with bevacizumab not all patients will be able to |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | months vs 4.3 months; HR = 0.59; 95% CI: 0.47, 0.76; p=<0.0001) in patients who received atezolizumab/bevacizumab compared to those who received sorafenib.<br>• In the SHARP trial, sorafenib demonstrated a statistically significant advantage over placebo for overall survival in patients with uHCC (10.7 months vs 7.9 months; HR 0.69; 95% CI 0.6, 0.9; p=0.00058.<br>• The REFLECT trial demonstrated noninferiority of lenvatinib to sorafenib. The median overall survival in the lenvatinib arm was 13.6 months vs 12.3 months in the sorafenib arm, with a HR 0.92 (95% CI 0.79, 1.06). | receive this regimen. Patients who are ineligible for atezolizumab in combination with bevacizumab may receive sorafenib or lenvatinib which have demonstrated improved survival in patients with uHCC, however overall prognosis is still poor with median survival of approximately 1 year. There exists a need for novel therapies with a tolerable safety profile that can further improve long-term outcomes. |
| Benefit | • In the HIMALAYA trial, tremelimumab in combination with durvalumab (T300+D) demonstrated a statistically significant and clinically meaningful improvement in OS compared to sorafenib (stratified HR of 0.78 [95% CI: 0.66, 0.92], stratified log-rank 2-sided p-value = 0.0035).<br>• Key secondary endpoints for this study included an analysis of OS between the durvalumab monotherapy arm and sorafenib first for noninferiority and then for superiority.<br>• Durvalumab did not demonstrate OS superiority compared to sorafenib, which supported the necessity of tremelimumab to achieve the treatment effect. The treatment effect of the T300+D regimen observed on HIMALAYA was generally consistent with the treatment effect of the T300+D regimen in supportive Study 22. | The study met its primary objective with T300+D demonstrating superiority in OS over sorafenib. A statistically significant effect on OS that is also clinically meaningful can be used to support approval of drugs intended for the treatment of uHCC. |
| Risk and Risk Management | • The safety analysis population included 388 patients treated with T300+D and 374 patients treated with sorafenib on the HIMALAYA trial.<br>• Supportive safety data was presented from an HCC pool (n=462) that included all patients from the HIMALAYA trial and Study 22 who received at least one dose of study treatment. Additional safety data was presented from a Pan tumor pool of patients who had received either durvalumab monotherapy, tremelimumab monotherapy or another dosing regimen of | The observed safety profile of tremelimumab in combination with durvalumab (T300+D) is acceptable when assessed in the context of the treatment of a life-threatening disease. No additional significant safety signals were identified during the review. The majority of adverse |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | tremelimumab in combination with durvalumab.<br>• Immune-mediated adverse reactions are a risk of the T300+D combination regimen.<br>• The most common adverse reactions (≥ 20%) of patients with uHCC who were treated with T300+D are rash, diarrhea, fatigue, pruritus, musculoskeletal pain, and abdominal pain. The most common laboratory abnormalities (≥ 40%) of patients with uHCC who were treated with T300+D are AST increased, ALT increased, hemoglobin decreased, sodium decreased, bilirubin increased, alkaline phosphatase increased, and lymphocytes decreased.<br>• Serious adverse reactions occurred in 41% of patients who received tremelimumab with durvalumab. Fatal adverse reactions occurred in 8% of patients who received tremelimumab in combination with durvalumab. | reactions were manageable with dosage modifications. The risks of severe and serious adverse reactions, such as immune-mediated reactions, are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of the product labeling. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration of a Risk Evaluation Management Strategy (REMS). |

## 1.4.Patient Experience Data

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

| | | | | |
|---|---|---|---|---|
| ☐ | 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 | | |
| | | X | Patient-reported outcome (PRO) | Section 8.1 (Study Results: HIMALAYA and Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability) |
| | | ☐ | Observer reported outcome (ObsRO) | |
| | | ☐ | Clinician reported outcome (ClinRO) | |

| | | |
|---|---|---|
| | □ Performance outcome (PerfO) | |
| | □ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | |
| | □ Patient-focused drug development or other stakeholder meeting summary reports | [e.g., Section 2.1 Analysis of Condition] |
| | □ Observational survey studies designed to capture patient experience data | |
| | □ Natural history studies | |
| | □ Patient preference studies (e.g., submitted studies or scientific publications) | |
| | □ Other: (Please specify) | |
| □ | Patient experience data that was not submitted in the application, but was considered in this review. | |

X

Cross-Disciplinary Team Leader
Jamie Brewer, MD

# 2. Therapeutic Context

## 2.1.Analysis of Condition

The Applicant's Position:
Primary liver cancer is a major global health problem accounting for approximately 906,000 new cases and 830,000 deaths per year globally. In the US, there are approximately 42,000 new cases a year and around 30,000 deaths (American Cancer Society 2021). In Europe, there are approximately 87,000 new cases a year and around 78,000 deaths (WHO 2020). As of 2020, liver cancer was the seventh most common cancer worldwide and the third most common cause of cancer-related death (Sung et al 2021).

Hepatocellular carcinoma represents about 90% of primary liver cancers (European Association for the Study of the Liver 2018). The incidence of HCC increases progressively with advancing age in all populations, reaching a peak at 70 years (El-Serag 2012, White et al 2017). Rates of both incidence and mortality are 2 to 3 times higher among men than among women in most regions (Sung et al 2021).

The main risk factors for HCC are chronic infection with HBV or HCV, aflatoxin-contaminated foods, heavy alcohol intake, excess body weight, type 2 diabetes, and smoking. The major risk factors vary from region to region, which is reflected in the incidence of HCC across geographic regions (Sung et al 2021). The highest incidence rates are seen in East Asia and Sub-Saharan Africa, while lower rates are seen in Europe and North America (WHO 2019).

The HCC prognosis and treatment depend on factors such as tumor burden, degree of liver dysfunction, and clinical PS (Marrero et al 2018, Vogel et al 2019). HCC classically develops and grows in silent fashion, making its discovery challenging prior to the development of later stage disease (Bialecki and Di Bisceglie 2005). Patients are usually diagnosed late in its course, with a median survival following diagnosis of approximately 6 to 20 months (McGlynn et al 2015). HCC is a medically complex and difficult to treat disease as the majority of patients have underlying cirrhosis requiring management of both the malignancy and underlying liver disease.

Unresectable HCC remains a difficult to treat disease, and the majority of patients will ultimately die of either HCC or complications of liver disease.

The FDA's Assessment:
FDA generally agrees with the Applicant's description and characterization of HCC. According to SEER data (2012-2018) the 5-year relative survival for patients with liver and intrahepatic bile duct cancer is 12.8% for patients with regionally confined disease and 3.1% for patients with metastatic disease.

Incidence rates per 100,000 in the US for all stages of new cases of liver or intrahepatic bile duct cancers by race or ethnic group are as follows: Non-Hispanic White 7.7, Non-Hispanic Black 10.8, Non-Hispanic Asian/Pacific Islander 12.5, Non-Hispanic American Indian/Alaskan Native 21.2, and Hispanic 15.3 (SEER 2019). The highest incidence of liver and intrahepatic bile duct cancers occurs in the age group 55-64 years (33%) with a median age at diagnosis of 66 years (SEER 22 2015-2019).

## 2.2.Analysis of Current Treatment Options

The Applicant's Position:

Sorafenib, an oral TKI targeting multiple kinases, including VEGFR-1, -2, and -3 and BRAF, was the SoC for advanced HCC in the 1L setting since its approval in 2007 until 2020. Its approval was based on improvement vs placebo, establishing a median OS of 10.7 months (vs 7.9 months for placebo [Llovet et al 2008]). Subsequent studies have demonstrated a median OS ranging from 10.7 to 13.4 months (Finn et al 2021, Llovet et al 2008, Yamashita et al 2020).

In 2018, lenvatinib, another multiple kinase inhibitor against VEGFR-1, -2, and -3 and fibroblast growth factor receptor-1, -2, -3, and -4, was approved as 1L treatment for advanced HCC in patients without main portal vein invasion and ECOG PS 0 to 1. Lenvatinib demonstrated NI to sorafenib in a Phase III study, with a median OS of 13.6 months vs 12.3 months with sorafenib (Kudo et al 2018).

Atezolizumab (a PD-L1 inhibitor) in combination with bevacizumab (an angiogenesis inhibitor targeting vascular endothelial growth factor A) has been approved in the 1L setting, after the Phase III Imbrave150 study demonstrated statistically significant and clinically meaningful improvements in OS and PFS compared to sorafenib (Finn et al 2020b, Finn et al 2021). The NCCN, ESMO, and JSH guidelines were updated in 2020 to recommend atezolizumab in combination with bevacizumab as the preferred option to treat 1L HCC (NCCN Guidelines 2021, Kudo et al 2021 [ie, JSH 2021], Vogel and Martinelli 2021 [ie, ESMO Guidelines 2021]).

Atezolizumab in combination with bevacizumab has demonstrated a significant OS benefit compared with sorafenib in patients with advanced or uHCC and thus provides an important advance in treatment for patients with HCC. A higher incidence of bleeding, including fatal bleeding, infections, discontinuations, and dose interruptions due to Aes were, however, seen in the atezolizumab plus bevacizumab arm compared to sorafenib despite attempts to exclude patients at risk for gastrointestinal bleeding from the study (assessed via esophagogastroduodenoscopy). Although it is challenging to know how many patients were excluded from the Imbrave150 study due to potential bleeding risk, it is estimated that 43% of HCC patients with Child-Pugh Class A liver function have an increased bleeding risk (Boregowda et al 2019). Patients on atezolizumab in combination with bevacizumab should have adequate endoscopic evaluation and management for esophageal varices within approximately 6 months prior to treatment or according to institutional practice based on the assessment of bleeding risk (NCCN Guidelines 2021). In addition, the OS HR for patients who were atezolizumab ADA-positive by Week 6 (20%) was 0.93 vs sorafenib, whereas ADA-negative patients (80%) demonstrated an HR of 0.39. This exploratory subgroup analysis indicates that there is potential for ADAs to preclude benefit for a substantial number of patients treated with atezolizumab in combination with bevacizumab (TECENTRIQ Prescribing Information).

Lenvatinib and sorafenib provide alternate treatment options for patients with uHCC, but these therapies provide only a modest improvement in survival with safety profiles that require management. While sorafenib overall demonstrated a manageable tolerability profile in advanced HCC patients, certain Aes such as diarrhea, hand-foot skin reaction, and fatigue frequently occur in sorafenib-treated patients (Cheng et al 2009, Lencioni et al 2014, Llovet et al 2008); while not life-threatening, such Aes are often associated with superimposed complications such as infections and pain and can severely limit the activities and the QoL of the patients.

Due to the underlying liver cirrhosis, moderate liver dysfunction is expected in patients with HCC. This is an important consideration because the toxicity of systemic therapies, particularly VEGFR TKI, can

exacerbate the pre-existing hepatopathy and increase the risk of liver-related Aes (Cheng et al 2020).

Alternative therapeutic options are critical to provide long-term OS to more patients with advanced HCC. A significant unmet medical need exists for treatment strategies that are tolerable, can further delay tumor progression, and improve survival outcomes.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of the available therapies for patients with previously untreated unresectable hepatocellular HCC.

# 3. Regulatory Background

## 3.1. US Regulatory Actions and Marketing History

The Applicant's Position:
Durvalumab received accelerated approval on 01 May 2017 from the US FDA for the treatment of UC. Subsequently, durvalumab was approved for adult patients with Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy, and additionally, in combination with etoposide and either carboplatin or cisplatin as 1L treatment of adult patients with ES-SCLC. On 07 May 2021, the Applicant voluntarily withdrew the UC indication for durvalumab.

(b) (4)

Combination of tremelimumab and durvalumab is not approved in the US or any other region globally.

The FDA's Assessment:
FDA agrees with the Applicant's position.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
Table 1 provides key regulatory activity with the US FDA in reference to the proposed application (IND 125409). In addition, Orphan Drug Designation was granted on 15 January 2020 to durvalumab and tremelimumab for the treatment of HCC (19-7215 and 19-7214, respectively). A notification of intent to use a Rare Pediatric Disease Priority Review Voucher for the tremelimumab BLA 761289 was communicated in a submission made to IND 125409 on 24 November 2021 (eCTD Sequence 0624).

**Table 1: Summary of Key Regulatory Interactions with the US FDA**

| Date | Type of Interaction | Summary of Outcome |
|---|---|---|
| 01 March 2017 – 28 April 2017 | Type B/ End-of-Phase 2 Meeting | There was general agreement between the FDA and the Sponsor regarding study design, patient population, the selected active control, and stratification factors.<br>The Sponsor proposed to include a comparison of T300+D vs D as a prespecified secondary endpoint, and proposed that the determination of the incremental benefit of the addition of T to D during review of the efficacy supplement for D and BLA for T will consider the totality of the efficacy results for all endpoints and the safety information across treatment arms. There was no further discussion at that time. |
| 02 February 2020 – 15 April 2020 | Type C BLA Format and Content Meeting | There was general agreement with the proposed efficacy and safety content, including the pooled datasets, narratives, and the clinical pharmacology data package<br>The FDA acknowledged that there will be no formal statistical comparison of D in combination with T vs D and indicated that they would analyze the totality of the data for the comparison during the review.<br>The FDA cautioned the use of the IA results for NI for D as a single agent. The method used for the NI test in the case where the proportional hazard assumption was violated will be a review issue. |
| 20 October 2021 –16 December 2021 | Type B Pre BLA Meeting | FDA stated that clear and robust demonstration of the contribution of D and T to the treatment effect should be provided in the application dossier.<br>FDA raised no significant concerns regarding a durvalumab monotherapy application and requested data on post progression therapy to be provided in the dossier<br>FDA requested an evaluation of safety and efficacy data for patients that were rechallenged with T |
| 27 October 2021 – 10 November 2021 | Pre-BTD Request for FDA feedback | At a pre-Breakthrough Designation Request meeting with FDA on 10 November 2021, the Division of Oncology 3 discouraged the submission of a full BTD request. |

The FDA's Assessment:

FDA generally agrees with the Applicant's overview of the regulatory interactions during development. Additional details of some of these interactions include:

- Type B/EOP meeting on April 28, 2017:
  - At the time of this meeting, the primary objective of the HIMALAYA trial was to assess the OS of patients treated with durvalumab 1500 mg and tremelimumab 75 mg (T75_D) compared with patients treated with sorafenib. FDA stated that the Phase 3 study should be revised to include a comparison between the durvalumab monotherapy arm and the T75+D arm to demonstrate the contribution of tremelimumab to durvalumab.
- Information Amendment dated October 26, 2018,
  - The Applicant informed FDA of the decision to close enrollment into the T75+D arm in both Study 22 and HIMALAYA based on the results of a preplanned interim analysis of Study 22 as the efficacy of this arm did not meaningfully differentiate from durvalumab monotherapy.

- Preliminary Breakthrough Therapy Designation Request Meeting on November 10, 2021
    - FDA advised against formal submission of a BTDR as the data submitted to support BTD did not demonstrate a substantial improvement over available therapy.
    - FDA also stated that since HIMALAYA was not designed to evaluate the investigational regimen in patients unsuitable to receive some available therapies (i.e., atezolizumab in combination with bevacizumab) no conclusions could be made regarding whether T300+D provides substantial improvement over available therapy for patients who are not eligible to receive atezolizumab in combination with bevacizumab.
- Type B/Pre-BLA meeting on December 16, 2021
    - FDA stated that the evaluation of the contribution of tremelimumab to durvalumab would be a review issue.

# 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 3 consulted OSI to discuss an audit of overall trial conduct for the HIMALAYA study. Three clinical investigators were selected for audit, Drs. Chan (Site 3201), De Toni (Site 2604) and Kang (Site 6001). Inspections of Drs. De Toni (Site 2604) and Kang (Site 6001) were conducted on site. Due to travel restrictions related to the COVID-19 pandemic and country-specific restrictions, the inspection of Dr. Chan's site (Site 3201) was conducted as a remote regulatory assessment.

During the inspection of Site 6001 no discrepancies were identified between the source documents and the data line listings for patient enrollment. At the time of data cutoff, there were 81 patients screened, 57 patients enrolled and 39 were randomized and treated at the site. The source records for survival follow-up and subject disposition used to generate the primary endpoint of OS, and key secondary endpoints related to OS at different timepoints were reviewed and compared with the data listings. There were no discrepancies. The tumor assessment data for the secondary endpoints related to imaging (ORR, PFS, TTP, DCR, and DOR) were reviewed and compared to the data listings in the background material, and there were no discrepancies. All protocol required scans were taken at the study site in adherence to the protocol. The RECIST assessments were made by the CI or sub-investigator as specified in the protocol. No unreported protocol deviations were identified. No unreported adverse events were identified.

At the time of data cutoff, there were 37 patients screened, 30 patients enrolled and treated at Site 2604. The source documents were reviewed for all 37 patients for informed consent. During the inspection the complete source documents were reviewed for 16 of 30 patients (10 in the T300+D arm and 6 in the sorafenib arm). No discrepancies were identified between the source documents and the data line listings for patient enrollment. The survival documentation for the primary endpoint of OS was compared to the data listings and there were no discrepancies. The tumor assessment data for the secondary endpoints related to imaging were reviewed and compared to the data listings in the background material, and there were no discrepancies. All protocol required scans were taken at the study site in adherence to the protocol. No unreported protocol deviations were identified. No unreported adverse events were identified.

A remote regulatory assessment was conducted for Site 3201. At the time of data cutoff there were 48 patients screened and 33 patients enrolled at the site with 6 patients having

completed the trial. There were no significant discrepancies between the source documents and the data line listing for patient enrollment and disposition. The remote regulatory assessment reviewed redacted records for all 12 patients in the T300+D arm, all eleven patients in the sorafenib arm and 3 of 10 patients in the durvalumab arm.

The survival documentation for the primary endpoint of OS was compared to the data listings and there were no discrepancies. The imaging source were compared to the data listings and no discrepancies were identified for patients enrolled in the T300+D arm or the sorafenib arm. There was a single patient with a protocol discrepancy in the durvalumab arm: Subject (b) (6) was evaluated with a CT dated (b) (6) and found to have progressive disease due to a new lesion. As per the protocol, the patient was continued on treatment and had a follow up CT on (b) (6) which confirmed PD. The date of progression was entered as (b) (6) instead of the correct date (b) (6) which is the time of progression. No significant unreported adverse events were identified; no unreported SAEs were identified.

The results of these inspections did not identify any issues to indicate the study was not conducted adequately. The data generated by the inspected entities appear to be acceptable in support of this BLA.

## 4.2.Product Quality

The Office of Biotechnology Products (OPQ) CDER, recommends approval of BLA 761289 for tremelimumab (Imjudo) manufactured (b) (4) (drug substance) and (b) (4) (drug product), for AstraZeneca Pharmaceutical. The data submitted in this application are adequate to support the conclusion that the manufacture of tremelimumab 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.
During the review cycle, the Applicant agreed to two postmarketing commitments to perform a shipping validation study to evaluate the impact on the drug product of shipping from the AstraZeneca labeling and packaging site in Sweden to the US Distribution Center and to implement (b) (4) monitoring (b) (4) validated by the microbial retention study. See Section 13 for additional information regarding the postmarketing commitments. Refer to the OPQ full review for additional details of the product quality submission.

No new product information was submitted for durvalumab.

## 4.3.Clinical Microbiology

Refer to the OPQ Executive Summary and full review. No new information was submitted for durvalumab.

## 4.4. Devices and Companion Diagnostic Issues

This submission did not require a device or companion diagnostic.

# 5. Nonclinical Pharmacology/Toxicology

## 5.1.Executive Summary

Tremelimumab (CP-675,206, MEDI1123) is an IgG2 monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4). CTLA-4 and CD28 are receptors expressed on T cells and share the ligands CD80 (B7.1) and CD86 (B7.2) on antigen presenting cells. The interaction of CD28 with CD80/86 results in T cell activation and proliferation; however, CTLA-4 is an inhibitory receptor and binds CD80/86 with higher affinity than CD28, thus limiting T cell activity by preventing CD28-mediated T cell co-stimulation (Alegre et al., 2001). Tremelimumab binds to CTLA-4 and blocks binding to its ligands CD80 and CD86 on antigen presenting cells, thereby blocking an inhibitory signal, and enhancing T cell-mediated immune responses. The established pharmacologic class for tremelimumab is a CTLA-4 blocking antibody.

The Applicant proposes to use tremelimumab at 300 mg once as a single priming dose in combination with durvalumab. Durvalumab (IMFINZI®) is a human IgG1 monoclonal antibody targeting human programmed death ligand 1 (PD-L1). Programmed cell death ligand-1 (PD-L1) is expressed on tumor cells and immune cells in the tumor microenvironment. PD-L1 inhibits T cell activation through its interaction with programmed death protein 1 (PD-1) on activated T cells. Durvalumab binds PD-L1 and blocks its binding to PD-1, releasing inhibition of immune responses, including anti-tumor immune responses, without inducing ADCC. Because durvalumab is approved for multiple oncology indications, the focus of this review is the pharmacology and toxicology of tremelimumab.

As assessed by surface plasmon resonance, tremelimumab binds human and cynomolgus CTLA-4 with KDs of 0.29 nM and 0.98 nM, respectively. Tremelimumab also binds CTLA-4 expressed on human and cynomolgus T cells stimulated to express CTLA-4, but did not bind stimulated mouse, rat, hamster, or rabbit T cells; tremelimumab demonstrated minimal binding to unstimulated CD3 T cells from humans or monkeys. Tremelimumab demonstrated >500-fold higher selectivity for CTLA-4 than CD28, CD86 or IgG1. Tremelimumab blocked CTLA-4 binding to CD80 and CD86 in an enzyme-linked immunosorbent assay (ELISA) with $IC_{50}$s of 0.78 nM and 0.46 nM, respectively and enhanced IL-2 and IFNγ release from primary human T cells co-cultured with Raji human lymphoma cells endogenously expressing CD80 and CD86. At a concentration of 30 µg/mL, tremelimumab enhanced activation of T cells in peripheral blood mononuclear cells (PBMC) and whole blood samples stimulated with an anti-CD3 antibody and staphylococcal enterotoxin A (SEA); tremelimumab similarly enhanced IL-2 release (up to 460% higher than an isotype control antibody) in PBMC and whole blood samples from healthy donors and patients with different types of cancer, including solid tumors and lymphomas. Additionally, tremelimumab enhanced IL-2 release from monkey T cells stimulated with SEA. In an in vitro co-culture assay, tremelimumab did not reverse the ability of human peripheral regulatory T cells (Tregs) to suppress activity and proliferation of stimulated human effector T cells. Aggregated or surface bound tremelimumab did not inhibit T cell activation in SEA-stimulated human PBMC or whole blood cultures at concentrations ≤100 µg/mL. Tremelimumab did not bind FcγRs in a competitive in vitro binding assay or mediate antibody-dependent cellular cytotoxicity (ADCC) against activated human T cells.

Tremelimumab did not mediate release of TNF-α, IL-6, or IL-1β from unstimulated human PBMCs or reduce platelets in an in vitro cytokine release assay.

A surrogate tremelimumab anti-CTLA-4 antibody prolonged survival in multiple subcutaneous mouse tumor models when administered alone and demonstrated increased response rates when administered in combination with an anti-mouse PD-L1 antibody. Additionally, administration of a surrogate anti-mouse CTLA-4 antibody alone or in combination with an anti-mouse PD-L1 antibody reduced Tregs in tumors in mice implanted with CT26 mouse colon cancer tumors and increased proliferating intratumoral T cells in multiple syngeneic mouse tumor models at doses ≥20 mg/kg.

The Applicant evaluated the safety of tremelimumab administered intravenously, the intended route of administration, using cynomolgus monkeys in GLP-compliant 1- and 6-month repeat-dose toxicology studies. Mortalities occurred in the 6-month toxicology study in monkeys administered 50 mg/kg/week due to persistent diarrhea that correlated with minimal to moderate inflammation in the small and large intestines. Gastrointestinal (GI) toxicity occurred in both 1- and 6-month studies at doses ≥5 mg/kg with signs of loose stools and decreased food consumption; weight loss occurred at 50 mg/kg in the 6-month study. Liver findings occurred at doses ≥15 mg/kg in the 1-month study and at doses ≥5 mg in the 6-month study and included increased AST in some animals and increased liver weight that correlated with minimal to mild periportal mononuclear cell infiltrates. Decreased red blood cells, hemoglobin, and hematocrit occurred at doses ≥5 mg/kg in the 1-month study and at doses ≥15 mg/kg in the 6-month study.

Tremelimumab-related effects on the immune system included histological findings of hyperplasia in multiple lymphoid organs (spleen, lymph nodes, bone marrow, GALT) at doses ≥15 mg/kg in the 1-month study and ≥5 mg/kg in the 6-month study. Increases in circulating leukocytes, lymphocytes, and T cells were observed at doses ≥50 mg/kg in both studies. Clinical signs of swollen lymph nodes and histological findings of mononuclear cell infiltration with inflammation in multiple organs occurred at doses ≥5 mg/kg in the 6-month study. These findings improved after a drug-free period of 2 or 3 months in the 1- and 6-month studies, respectively.

Additional target organs in the 6-month study were the skin with clinical signs of abrasion, open sores, and/or rash in animals administered 50 mg/kg and the thyroid with findings of decreased T3/T4, increased TSH, and marked atrophy at doses ≥15 mg/kg. Tremors were observed in individual animals at doses ≥15 mg/kg. Consistent with nonclinical findings, diarrhea, decreased appetite, rash, hypothyroidism, and anemia have been seen clinically and the IMJUDO (tremelimumab) label includes warnings for immune-mediated adverse events and infusion reactions.

There were no adverse or notable effects on the male or female reproductive organs in the 1- and 6-month repeat-dose toxicology studies conducted in sexually mature cynomolgus monkeys.

Carcinogenicity or genetic toxicology studies were not warranted for this product based on the advanced cancer patient population and the nature of the biologic, respectively.

Based on mechanism of action of tremelimumab and data from a literature-based risk assessment, there is a warning for embryo-fetal toxicity in the label for IMJUDO. In animal models, the CTLA-4 signaling pathway is important for the maintenance of pregnancy through induction of maternal-fetal immune tolerance and immune regulation in newborns. Once weekly IV administration of tremelimumab to pregnant monkeys during the period of organogenesis did not result in maternal toxicity or embryo-fetal development toxicity at doses ≤30 mg/kg (approximately 31 times the human AUC at the recommended dose); however, CTLA-4 blockade resulted in increased resorptions and fewer live fetuses in a mouse model. Additionally, literature studies using genetically engineered mice demonstrated that CTLA-4 deficient mice died from lymphoproliferative disorders 3 to 4 weeks after birth. Human immunoglobulin G2 (IgG2) is known to cross the placenta; therefore, tremelimumab has the potential to be transmitted from the mother to the developing fetus. Consistent with the recommendation for non-genotoxic drugs that are teratogenic or embryo-fetal lethal as described in the FDA Guidance for Industry Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations, and considering the half-life of 18.2 days for tremelimumab, FDA recommends advising females of reproductive potential to use effective contraception during treatment with IMJUDO and for 3 months after the last dose. The Applicant did not evaluate the presence of tremelimumab in milk; however, because of the potential adverse effects of IMJUDO on a breastfed child, the review team recommends advising patients not to breastfeed during treatment with IMJUDO and for 3 months after the last dose.

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of IMJUDO.

## 5.2.Referenced NDAs, BLAs, DMFs

The Applicant's Position:
No new information concerning nonclinical pharmacology/toxicology for durvalumab is provided in the sBLA 761069. Nonclinical pharmacology/toxicology for tremelimumab is summarized in this document.

## 5.3.Pharmacology

Primary pharmacology

**Table 2: Primary Pharmacology Studies Supporting Mechanism of Action of Tremelimumab**

| Study Number/ eCTD Location | Study Objective(s) | Test System | Test Methods | Noteworthy Findings |
|---|---|---|---|---|
| 06-CP-675,206/ Module 4.2.1.1 | Selectivity of binding of tremelimumab to rhCTLA-4-Ig relative to rhCD28-Ig, rhCD86 (B7.2)-Ig, and hIgG1 | rhCTLA-4-Ig, rhCD28-Ig, rhCD86-Ig, and hIGg1 coated onto plates (at a concentration of 1 µg/mL); Tremelimumab and HRP-conjugated anti-human IgG2 | ELISA | Tremelimumab demonstrated > 500-fold higher selectivity for rhCTLA-4-Ig over rhCD28-Ig, rhCD86-Ig, and hIgG1 |

| Study Number/ eCTD Location | Study Objective(s) | Test System | Test Methods | Noteworthy Findings |
|---|---|---|---|---|
| 14-CP-675,206/ Module 4.2.1.1 | Binding affinity of tremelimumab for rhCTLA-4 and rcynoCTLA-4 | rhCTLA-4 or rcynoCTLA-4 (at a concentration of 50 µg/mL); Tremelimumab (666 nM to 0.01 nM) | SPR | Tremelimumab binds to:<br>• rhCTLA-4 with KD of 0.28 nM<br>• rcynoCTLA-4 with KD of 0.98 nM |
| 03-CP-675,206/ Module 4.2.1.1 | Ability of tremelimumab to inhibit the binding of rhCTLA-4-Ig to rhCD80 (B7.1)-Ig and rhCD86 (B7.2)-Ig | rhCD80-Ig (4 nM) and rhCD86-Ig (3 nM); rhCTLA-4-Ig (0.3 nM); Tremelimumab (15.5 to 0.02 nM); HRP-conjugated anti-human IgG4 | ELISA | Tremelimumab inhibits the binding of rhCTLA-4-Ig to:<br>• rhCD80 in a concentration-dependent manner with an $IC_{50}$ of 0.78 nM<br>• rhCD86 in a concentration-dependent manner with an $IC_{50}$ of 0.46 nM |

**Table 3: Complete Responses in Antitumor Efficacy Studies Conducted with EMT6, CT26, or MCA205 Syngeneic Tumor Lines Administered anti-mouse CTLA-4 Monoclonal Antibody as Monotherapy or in Combination with an Anti-mouse PD-L1**

| Study Number/ eCTD location: ONC1123-0001/4.2.1.1 | | Anti-mouse PD-L1 clone 80 | | Anti-mouse CTLA-4 clone 9D9 mIgG1 | | Anti-PD-L1 clone 80 + Anti-mouse CTLA-4 clone 9D9 mIgG1 | |
|---|---|---|---|---|---|---|---|
| **Tumor model** | **Mouse strain** | **Experiment 1** | **Experiment 2** | **Experiment 1** | **Experiment 2** | **Experiment 1** | **Experiment 2** |
| EMT6 breast cancer | Balb/c | 7 of 12 (58%) | 10 of 12 (83%) | 7 of 12 (58%) | 7 of 12 (58%) | 10 of 12 (83%) | 11 of 12 (92%) |
| CT26 colon cancer | Balb/c | 2 of 12 (17%) | 2 of 12 (17%) | 1 of 12 (8.3%) | 2 of 12 (17%) | 9 of 12 (75%) | 6 of 12 (50%) |
| MCA205 sarcoma | C57BL/6 | 0 of 11 (0%) | 4 of 11 (36%) | 0 of 12 (0%) | 0 of 11 (0%) | 2 of 12 (17%) | 4 of 11 (36%) |

The anti-mouse CTLA-4 monoclonal antibody clone 9D9 mIgG1 (tremelimumab surrogate) was administered to mice engrafted with syngeneic tumors either as monotherapy or in combination with an anti-mouse PD-L1 murine surrogate antibody.

The FDA's Assessment:

The FDA generally agrees with the Applicant's summary. In addition to these findings, the FDA notes the following results which support the monkey as the only pharmacologically relevant species:

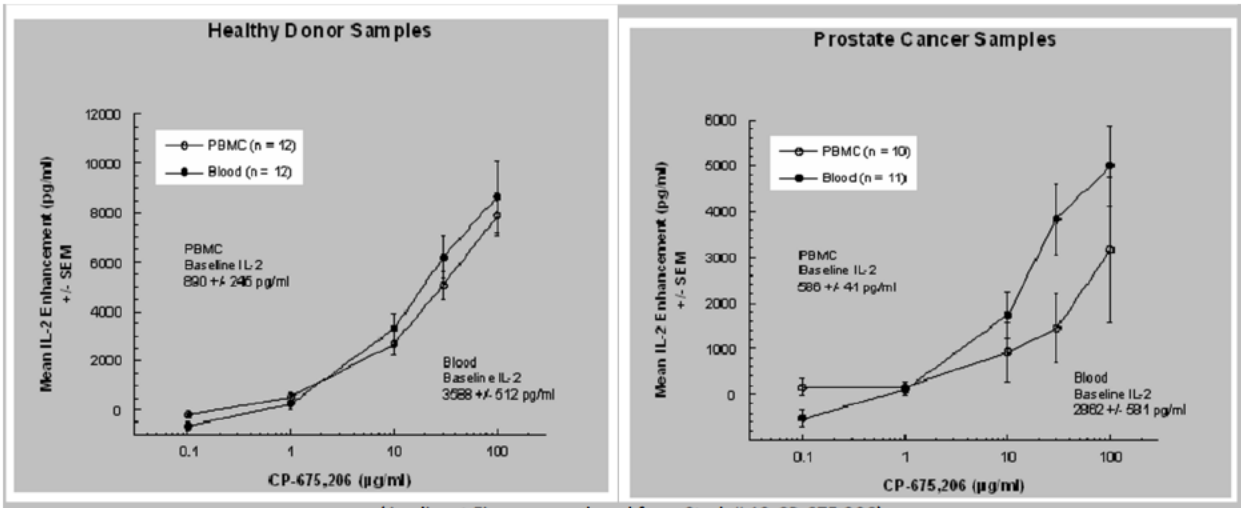
- At a concentration of 10 µg/mL, tremelimumab bound human and cynomolgus T cells treated with phytohemagglutinin (PHA) to stimulate expression of CTLA-4, but did not bind mouse, rat, hamster, or rabbit PHA-stimulated T cells (Study# 15-CP-675,206).

- Tremelimumab demonstrated minimal surface or intracellular binding to unstimulated T cells from monkeys or humans.

The Applicant assessed the ability of tremelimumab to enhance T cell responses by co-culturing, PHA-stimulated human T cells with Raji human B lymphoblast cells endogenously expressing CD80 and CD86 in the presence of 30 µg/ml tremelimumab or an isotype control. After 72 hours, treatment with 30 µg/mL tremelimumab resulted in higher IL-2 (510%) and IFNγ (54%) release than co-cultures treated with an isotype control (Study# 02-CP-675,206).

To evaluate the ability of tremelimumab to enhance T cell activation in vitro, the Applicant designed an assay in which T cell activity is dependent upon CD80 and CD86 signaling through CD28, an activating receptor expressed on T cells. In this assay, PBMCs or whole blood were cultured in the presence of staphylococcal enterotoxin A (SEA) and an immobilized anti-CD3 antibody, then IL-2 release into the supernatant was measured by ELISA to assess T cell activation. The addition of CTLA-4-Ig, an anti-human CD80 antibody, or an anti-human CD86 antibody inhibited IL-2 release, suggesting that activating signals mediated by CD80/CD86 interaction with CD28 is needed for T cell activation. In contrast, the addition of tremelimumab increased IL-2 release compared to an isotype control antibody, suggesting that blocking competitive CTLA-4 binding to CD28 allows for increased activating signals mediated through CD80/86 interactions with CD28 (Study# 08-CP-675,206). Using this assay the Applicant evaluated the ability of tremelimumab to enhance activation human T cells from healthy donors and donors with multiple types of cancer. Compared to an isotype control, treatment with 30 µg/mL tremelimumab resulted in 120% and 400% higher IL-2 release in whole blood and PBMCs from healthy donors, respectively (Study# 01-CP-675,206).Using PBMCs and whole blood from patients with different types of cancers, including solid tumors and lymphomas, tremelimumab resulted in 180% to 460% higher IL-2 release than controls for all types of cancer evaluated, indicating that tremelimumab can similarly enhance activation of T cells from healthy donors and patients with cancer (Figure 1, Study# 13-CP-675,206). Additionally, in a similar assay using whole monkey blood, tremelimumab resulted in 91% higher IL-2 release compared to samples treated with an isotype control (Study# 04-CP-675,206).

**Figure 1: Effect of Tremelimumab on IL-2 Release from PBMC and Whole Blood from Healthy Donors and Patients with Cancer**




(Applicant Figure reproduced from Study# 13-CP-675,206)

To evaluate the effect of tremelimumab on regulatory T cell (Treg)-mediated suppression of conventional T cells, $CD4^+CD25^-$ conventional T cells were co-cultured with $CD4^+CD25^+$ Tregs in the presence of 30 or 100 µg/ml tremelimumab or an isotype control antibody. Co-culture of conventional T cells with Tregs reduced IFNγ release and proliferation compared to culture of conventional T cells alone; however, the addition of tremelimumab to co-cultures did not result in increased IFNγ release or proliferation. This finding suggests that tremelimumab does not reverse the ability of human peripheral T regs to suppress activity and proliferation of stimulated peripheral human conventional T cells (Study# 11-CP-675,206).

The Applicant investigated the potential of aggregated (plate-bound) tremelimumab to inhibit T cell activation through high-level aggregation of CTLA-4 on T cells using SEA-stimulated human PBMC and whole blood cultures treated with immobilized tremelimumab. After 72 hours, treatment with plate-bound tremelimumab did not result in increased IL-2 production compared to isotype control, suggesting that aggregated or surface bound tremelimumab does not inhibit T cell activation in SEA - stimulated human PBMC or whole blood cultures at concentrations ≤100 µg/mL (Study# 07-CP-675,206).

In an in vitro cytokine release assay, treatment of unstimulated human PBMCs or whole blood cultures with soluble tremelimumab for up to 48 hours did not result in release of TNF-α, IL-6, or IL-1β compared to untreated controls (Study# 05-CP-675,206). Treatment with tremelimumab for up to 24 hours did not reduce platelet counts in whole blood from healthy human donors in an in vitro assay (Study# 10-CP-675,206).

The ability of tremelimumab to bind FcγRs was assessed in a competitive binding assay using human PBMCs from healthy donors or patients with prostate cancer treated with unlabeled and/or radio-labeled tremelimumab or an isotype control antibody. Treatment with unlabeled and radio-labeled tremelimumab did not result in reduced binding of radio-labeled tremelimumab as assessed by counts per minute (CPM) compared to treatment with radio-labeled tremelimumab alone. In comparison, treatment with a radio-labeled isotype control antibody and unlabeled isotype control antibody resulted in ≤ -53.3% binding of the radio-labeled isotype compared to treatment with the radio-labeled isotype

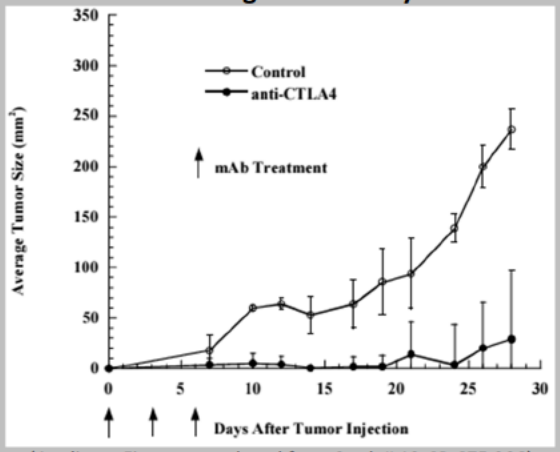
control antibody alone. This result indicated that tremelimumab does not bind to human FcγRs (Study# 16-CP-675,206).

The Applicant investigated the ability of tremelimumab to mediate antibody-dependent cellular cytotoxicity (ADCC) using activated human NK cells as effector cells and naïve T cells or CD3/CD28-stimulated T cells from the same donor as target cells. Tremelimumab did not result in increased cytotoxicity of either target cell compared to untreated and isotype treated controls, suggesting that tremelimumab does not mediate ADCC (Study# 09-CP-675,206).

In addition to the mouse tumor studies described by the Applicant, administration of a surrogate anti-mouse CTLA-4 antibody inhibited growth of SA1N murine fibrosarcoma tumors when administered as a 200 µg injection on Days 0, 3, and 6 after tumor inoculation. (Figure 4, Study# 12-CP-675,206).

In mice bearing CT26 tumors, treatment with an anti-mouse CLTA-4 antibody alone or in combination with an anti-mouse PD-L1 antibody reduced the percentage of Foxp3$^+$ Tregs in the tumors, but not draining lymph nodes or spleens. Additionally, higher percentages of Ki-67$^+$ proliferating T cells were identified in EMT6, CT26, and MCA205 tumors from mice administered a surrogate anti-CTLA-4 antibody alone or in combination with an anti-mouse PD-L1 antibody (Study# ONC1123-0001).

**Figure 2: Effect of An Anti-Mouse CTLA-4 Surrogate Antibody on SA1N Mouse Fibrosarcoma Tumors**




(Applicant Figure reproduced from Study# 12-CP-675,206)

Secondary Pharmacology

Secondary pharmacodynamic studies of tremelimumab were not conducted.

The FDA's Assessment:

The FDA agrees.

Safety Pharmacology

Stand-alone studies evaluating safety pharmacology of tremelimumab have not been conducted. However imp, safety pharmacology parameters including neurological, cardiovascular, and respiration rate were evaluated following IV administration of tremelimumab in the acute single-dose (Study 99-1985-01), the 1-month (Study 00-1985-04), and the 6-month (Study 2004-0150) repeat-dose toxicity

studies in cynomolgus monkeys.

The FDA's Assessment:
No tremelimumab-related effects on cardiovascular or respiration parameters were observed in male and female cynomolgus monkeys at tremelimumab doses up to 50 mg/kg administered once weekly for up to 6 months. In the 6-month toxicology study, tremors occurred in one female at 15 mg/kg and one female at 50 mg/kg.

## 5.4.ADME/PK

The Applicant's Position:
The nonclinical PK and TK program with tremelimumab in cynomolgus monkeys consisted of the 3 single-dose non-GLP PK studies following IV (Studies DM2003-675206-011, DM2003-675206-012) or SC (Report DM2003-675206-009) administration and 5 toxicity studies including a non-GLP and GLP single-dose (Studies 00-1985-06 and 99-1985-01), 1-month repeat-dose (Report 00-1985-04), and 6-month repeat-dose toxicity study (Report 2004-0150), and an embryofetal development study (Report 2501-001) following IV administration.

The PK of tremelimumab was characterized in cynomolgus monkeys following a single IV administration at a dose level of 0.75 mg/kg of both clonally and nonclonally derived tremelimumab in phosphate buffered solution (pH 7.4) and sodium acetate buffer (pH 5.5), respectively. The PK of clonally and nonclonally derived tremelimumab was characterized by low plasma clearance (4.4 to 4.9 mL/day/kg) and small steady state volume of distribution (54 to 71 mL/kg), resulting in a long mean elimination half-life of 9.1 to 11 days. Differences in the PK of clonally and non clonally derived tremelimumab were not statistically significant. In addition, the observed ADA responses were similar between clonally and non clonally derived tremelimumab. The mean SC bioavailability of tremelimumab was moderate (54.2%).

The TK of tremelimumab was evaluated in cynomolgus monkeys following IV administrations of tremelimumab in a single-dose (10, 30, and 100 mg/kg), 1-month (5, 15, and 50 mg/kg/week;) and 6-month (5, 15, and 50 mg/kg/week) toxicologic studies, and an embryofetal development (5, 15, and 30 mg/kg/week) toxicologic study. In the toxicologic studies with tremelimumab in cynomolgus monkeys, systemic exposures to tremelimumab, as assessed by mean $C_{max}$ and mean AUC, increased dose proportionally within the dose ranges examined following single or multiple IV administrations. In the 6-month repeat-dose study, the steady state $C_{max}$ and cumulative AUC were 2030 µg/mL and 776,000 µg.h/mL, respectively, following weekly (6 or 7 weeks) IV administrations of 50 mg/kg tremelimumab. No evidence of non linearity and gender-related differences in exposures were observed in any of the studies. Mean accumulation of tremelimumab was less than expected in these studies. This is probably due to the development of ADA in 7 animals resulting in accelerated clearance and decreased systemic exposures. All of ADAs were nAbs.

The FDA's Assessment:
The FDA generally agrees with the Applicant's summaries of the nonclinical ADME/PK data. Additional results and comments are below.

| Type of Study | Major Findings |
|---|---|
| **Absorption** | |

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Pharmacokinetics of CP-675,206 in Cynomolgus Monkeys Following Subcutaneous Administration/ DM2001-675206-009</td><td>
• Monkeys (2/sex) were administered a single subcutaneous dose of 5 mg/kg tremelimumab<br>
• No sex differences, thus data was combined<br>
PK Parameters in Monkeys:
<table>
<tr><td>$C_{max}$ (µg/mL)</td><td>33.39</td></tr>
<tr><td>$AUC_{last}$ (µg·hr/mL)</td><td>15200</td></tr>
<tr><td>$T_{max}$ (hr)</td><td>84.0</td></tr>
</table>
Hr = hours
</td></tr>
<tr><td>Plasma Concentrations of CP-675,206 in Cynomolgus Monkeys Following a Single IV Dose in the Acute Toxicity Assessment/ DM2000-675206-001</td><td>
• Monkeys (3/sex) were administered a single IV dose of 10, 30, or 100 mg/kg tremelimumab<br>
• No sex differences<br>
PK Parameters in Monkeys:
<table>
<tr><th rowspan="2">Dose (mg/kg)</th><th colspan="2">$C_{max}$ (µg/mL)</th><th colspan="2">$AUC_{last}$ (µg·hr/mL)</th><th colspan="2">$T_{max}$ (hr)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>10</td><td>190.84</td><td>311.48</td><td>27600</td><td>30500</td><td>2.0</td><td>0.8</td></tr>
<tr><td>30</td><td>755.74</td><td>620.99</td><td>75100</td><td>58600</td><td>0.08</td><td>8.05</td></tr>
<tr><td>100</td><td>2265.41</td><td>3669.19</td><td>213000</td><td>206000</td><td>0.08</td><td>0.08</td></tr>
</table>
Hr = hours
</td></tr>
<tr><td>Distribution</td><td>Not conducted</td></tr>
<tr><td>Metabolism</td><td>Not conducted</td></tr>
<tr><td>Excretion</td><td>Not conducted</td></tr>
<tr><td>TK data from general toxicology studies<br>1 Month Intravenous Toxicity Study with 2 Month Post-Dose Observation in Cynomolgus Monkeys (Study# 00-1985-04)</td><td>
Monkey<br>
$T_{1/2}$: Not calculated; $T_{max}$: 0.5-5.0 hours<br>
Dose proportionality: $C_{max}$ and AUC increased increased approximately dose-proportionally on Days 1 and 29.<br>
Accumulation: None<br>
Sex differences: None<br>
Anti-drug antibodies (ADA): ADAs were detected at all dose levels
<table>
<tr><th rowspan="2">Day</th><th rowspan="2">Dose (mg/kg)</th><th colspan="2">$C_{max}$ (µg/mL)</th><th colspan="2">$AUC_{0-24}$ (µg·hr/mL)</th><th colspan="2">$T_{max}$ (hr)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td rowspan="3">1</td><td>5</td><td>111</td><td>103</td><td>1930</td><td>1690</td><td>0.5</td><td>0.5</td></tr>
<tr><td>15</td><td>330</td><td>384</td><td>6070</td><td>6940</td><td>0.5</td><td>2.0</td></tr>
<tr><td>50</td><td>1140</td><td>1050</td><td>19980</td><td>19700</td><td>0.5</td><td>0.5</td></tr>
<tr><td rowspan="3">29</td><td>5</td><td>148</td><td>180</td><td>2850</td><td>3660</td><td>0.5</td><td>5.0</td></tr>
<tr><td>15</td><td>483</td><td>383</td><td>8640</td><td>6240</td><td>0.5</td><td>0.5</td></tr>
<tr><td>50</td><td>1530</td><td>1430</td><td>29800</td><td>26700</td><td>0.5</td><td>0.5</td></tr>
</table>
Hr = hours
</td></tr>
<tr><td>6-Month Intravenous Toxicity Study of CP-657,206 in Monkeys (Study# 2004-0150)</td><td>
Monkey<br>
$T_{1/2}$: Not calculated; $T_{max}$: 0.5-3.0 hours<br>
Dose proportionality: $C_{max}$ increased less than dose proportionally and $AUC_{0-24}$ decreased from 5 mg/kg to 15 mg/kg for males on Day 176.<br>
Accumulation: None<br>
Sex differences: At 15 mg/kg, $AUC_{0-24}$ was 3.0-fold higher in females compared to males on Day 176.
</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>Anti-drug antibodies (ADA): ADAs were detected at 5 mg/kg (1F), 15 mg/kg (3M, 1F), and 50 mg/kg (1M, 1F) as early as Day 22 and remained elevated throughout the remainder of the study.
<table>
<tr><th rowspan="2">Day</th><th rowspan="2">Dose (mg/kg)</th><th colspan="2">$C_{max}$ (µg/mL)</th><th colspan="2">$AUC_{0-24}$ (µg·hr/mL)</th><th colspan="2">$T_{max}$ (hr)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td rowspan="3">1</td><td>5</td><td>141</td><td>149</td><td>2590</td><td>2950</td><td>0.5</td><td>2.4</td></tr>
<tr><td>15</td><td>421</td><td>415</td><td>7510</td><td>7830</td><td>0.5</td><td>0.5</td></tr>
<tr><td>50</td><td>1390</td><td>1410</td><td>27700</td><td>25700</td><td>3.0</td><td>1.8</td></tr>
<tr><td rowspan="3">29</td><td>5</td><td>221</td><td>247</td><td>4350</td><td>4900</td><td>0.5</td><td>0.5</td></tr>
<tr><td>15</td><td>431</td><td>579</td><td>5840</td><td>10500</td><td>0.5</td><td>0.5</td></tr>
<tr><td>50</td><td>1920</td><td>2140</td><td>36900</td><td>41800</td><td>0.5</td><td>1.8</td></tr>
<tr><td rowspan="2">176</td><td>5</td><td>247</td><td>137</td><td>5040</td><td>2700</td><td>0.5</td><td>0.5</td></tr>
<tr><td>15</td><td>309</td><td>579</td><td>3860</td><td>11800</td><td>0.5</td><td>0.5</td></tr>
</table>
Hr = hours</td></tr>
<tr><td>TK data from reproductive toxicology studies<br>CP-675,206 Intravenous Embryo-Fetal Development Study in the Cynomolgus Monkey (Study# 05-1985-08)</td><td>$T_{1/2}$: Not calculated; $T_{max}$: 1.1-3.1 hours<br>Dose proportionality: $C_{max}$ and $AUC_{0-t}$ increased approximately dose-proportionally<br>Accumulation: None
<table>
<tr><th>Day</th><th>Dose (mg/kg)</th><th>$C_{max}$ (µg/mL)</th><th>$AUC_{0-24}$ (µg·h/mL)</th><th>$T_{max}$ (h)</th></tr>
<tr><td rowspan="3">GD 28</td><td>5</td><td>154</td><td>2830</td><td>2.4</td></tr>
<tr><td>15</td><td>498</td><td>9050</td><td>2.1</td></tr>
<tr><td>30</td><td>954</td><td>18600</td><td>2.1</td></tr>
<tr><td rowspan="3">GD 48</td><td>5</td><td>187</td><td>3680</td><td>3.1</td></tr>
<tr><td>15</td><td>707</td><td>12900</td><td>2.5</td></tr>
<tr><td>30</td><td>1230</td><td>23800</td><td>1.1</td></tr>
</table>
Hr = hours</td></tr>
</table>

## 5.5.Toxicology

### 5.5.1. General Toxicology

<u>The Applicant's Position:</u>

Overall, the Nonclinical Toxicology program adequately assessed the nonclinical safety and tolerability profile of tremelimumab.

The toxicology profile of tremelimumab was assessed following IV administration in cynomolgus monkeys in 2 single-dose studies (Study Nos. 00-1985-06 and 99-1985-01) and repeat-dose studies of 1-month (Study No. 00-1985-04) and 6-months (Study No. 2004-0150) duration.

Local tolerance of IV administered tremelimumab was assessed following single-dose administration at doses up to 100 mg/kg and following repeat administration at doses up to 50 mg/kg. No adverse tremelimumab-related changes were observed at the site of injection.

Following repeat administration at doses up to 50 mg/kg for either 1 month (5 doses) or 6 months (26 doses), signs comprised intermittent diarrhea, which in some animals at 50 mg/kg in the 6-month repeat-dose study became persistent and was associated with weight loss and inappetence, resulting in the cessation of dosing and/or euthanasia of these animals and termination of the group following 6 or 7 weekly doses. Target tissues for tremelimumab-induced toxicity included secondary lymphoid tissues of the gastrointestinal tract, the skin, spleen, lymph nodes, and thyroid tissues and the hematologic system. Most toxicities observed were either reversible or showed a trend toward reversibility following a 10-week treatment-free period following the 1-month or 6-month dosing period. A dose of 5 mg/kg was considered to be the NOAEL following 1 month of dosing, and following 6 months of dosing a NOAEL was not established but 15 mg/kg was considered to be the maximum tolerated dose.

**Table 4: 6-Month Intravenous Toxicity Study of CP-675,206 in Monkeys**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Species / Strain:** Cynomolgus monkey | | **Duration of dosing:** Once weekly for up to 6 months | | | | | **Study number:** 2004-0150 | | |
| **Age at start of dosing:** 2.5 – 5 years | | **Duration of post-dose:** 99 days | | | | | **GLP compliance:** Yes | | |
| **Date of first dose:** 20 July 2004 | | **Method of administration:** Bolus intravenous injection | | | | | **eCTD Location:** Module 4.2.3.2 | | |
| **Special features:** Assessments of lymphocyte immunophenotyping and of the development of primate anti-CP-675,206 human antibodies (PAHA) were also conducted. | | **Vehicle / Formulation:** Solution in (b) (4) 0.2 mg/mL polysorbate 80, pH 5.5 | | | | | | | |
| **No observed adverse-effect level:** Not determined | | | | | | | | | |
| **Daily Dose (mg/kg)** | | **0 (Vehicle)** | | **5** | | **15** | | **50[a]** | |
| **Number of Animals**<br>**Main Recovery** | | **M: 4**<br>**M: 2** | **F: 4**<br>**F: 2** | **M: 4**<br>**M: 0** | **F: 4**<br>**F: 0** | **M: 4**<br>**M: 0** | **F: 4**<br>**F: 0** | **M: 4**<br>**M: 2** | **F: 4**<br>**F: 2** |
| **Toxicokinetics [b]:** | Day 29 | | | | | | | | |
| | $AUC_{(0\text{-}24h)}$ (µg.h/mL) | | | 4350 | 4900 | 5840 | 10,500 | 36,900 | 41,800 |
| | $C_{max}$ (µg/mL) | | | 221 | 247 | 431 | 579 | 1920 | 2140 |
| | Day 176 | | | | | | | | |
| | $AUC_{(0\text{-}24h)}$ (µg.h/mL) | | | 5040 | 2700 | 3860 | 11,800 | | |
| | $C_{max}$ (µg/mL) | | | 247 | 137 | 309 | 579 | | |
| **Noteworthy Findings** | **Died or Sacrificed Moribund** | 0 | 0 | 1 [c] | 1 [c] | 0 | 0 | 4 [d] | 4 [d] |
| **Clinical Observations**[e] | | + | + | + | + | + | + | +++ | +++ |
| **Haematology (Day 15)** | Lymphocytes ($10^3$/µL) | 6.763 | 5.233 | 7.423 | 6.908 | 8.848* | 7.793 | 11.512* | 9.455** |
| | (% change from control) | | | (+9.8) | (+32.0) | (+30.8) | (+48.9) | (+70.2) | (+80.7) |
| | WBCs ($10^3$/µL) | 11.000 | 8.517 | 10.805 | 11.563 | 13.000* | 11.900* | 17.400** | 15.000** |
| | (% change from control) | | | (-1.8) | (+35.8) | (+18.2) | (+39.7) | (+58.2) | (+76.1) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Immunophenotyping (Day 15)** | CD3+ ($10^3$/µL) | 4.392 | 3.585 | 4.940 | 4.543 | 6.263* | 5.790* | 9.072** | 6.887** |
| | (% change from control) | | | (+12.5) | (+26.7) | (+42.6) | (+61.5) | (+107) | (+92.1) |
| | CD3+CD4+ ($10^3$/µL) | 2.428 | 1.990 | 3.085 | 2.548 | 3.768* | 3.280 | 6.445* | 5.057** |
| | (% change from control) | | | (+27.1) | (+28.0) | (+55.2) | (+64.8) | (+65.4) | (+154) |
| | CD3+CD8+ ($10^3$/µL) | 1.453 | 1.242 | 1.553 | 1.690 | 1.890 | 2.123* | 1.660 | 1.490 |
| | (% change from control) | | | (+6.9) | (+36.1) | (+30.1) | (+70.9) | (+14.2) | (+20.0) |
| **Serum Chemistry** | **Day 15** | | | | | | | | |
| | A/G ratio | 1.20 | 1.17 | 1.20 | 1.13 | 1.20 | 1.00* | 1.13 | 1.10 |
| | (% change from control) | | | (0) | (-3.4) | (0) | (-14.5) | (-5.8) | (-6.0) |
| | Albumin (g/dL) | 4.10 | 4.07 | 4.05 | 3.98 | 4.15 | 3.95 | 4.12 | 4.02 |
| | (% change from control) | | | (-1.2) | (-2.2) | (+1.2) | (-2.9) | (+0.5) | (-1.2) |
| | Globulin (g/dL) | 3.48 | 3.53 | 3.35 | 3.55 | 3.53 | 4.03 | 3.67 | 3.77 |
| | (% change from control) | | | (-3.7) | (+0.6) | (-1.4) | (+14.2) | (+5.5) | (+6.8) |
| | **Day 170** | | | | | | | | |
| | Thyroid stimulating hormone (UIU/mL) | 0.5398 | 0.9055 | 0.3543 | 0.6443 | 0.8783 | 39.0393 | ND | ND |
| | (% change from control) | | | (-34.4) | (-28.8) | (+62.7) | (+4211) | | |
| | Thyroxine (ng/dL) | 6.23 | 8.88 | 5.97 | 6.40 | 9.45** | <6.20 | | |
| | (% change from control) | | | (-4.2) | (-27.9) | (+51.7) | (30.2+) | | |
| | Total triiodothyronine (ng/dL) | 199.0 | 194.8 | 207.0 | 236.0 | 203.0 | 125.5 | | |
| | (% change from control) | | | (+4.0) | (+21.1) | (+2.0) | (-35.6) | | |
| **Organ Weights (g)** [f] | Brain | 75.83 | 67.73 | 76.03 | 65.87 | 70.90 | 59.98* | ND | ND |
| | (% change from control) | | | (+0.3) | (-2.7) | (-6.5) | (-11.4) | | |
| | Liver | 74.58 | 59.80 | 88.17 | 74.07** | 81.23 | 66.83 | | |
| | (% change from control) | | | (+18.2) | (+23.9) | (+8.9) | (+11.8) | | |
| **Histopathology Number examined** | | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| **Cecum** | Inflammation | | | | | | | | |
| | Minimal | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 2 |
| | Mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Colon** | Inflammation | | | | | | | | |
| | Minimal | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 0 |
| | Mild | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| | Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Duodenum** | Inflammation | | | | | | | | |
| | Mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Kidney** | Infiltration, mononuclear cells | | | | | | | | |
| | Minimal | 2 | 1 | 1 | 2 | 1 | 1 | 0 | 2 |
| | Mild | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Inflammation, mononuclear cells | 1 | 0 | 2 | 1 | 2 | 1 | 2 | 1 |
| | Minimal | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 |
| | Mild | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | Moderate | | | | | | | | |
| **Liver** | Infiltration, mononuclear cells | | | | | | | | |
| | Minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Infiltration, mononuclear cells, periportal | | | | | | | | |
| | Minimal | 3 | 2 | 3 | 3 | 4 | 3 | 0 | 2 |
| | Mild | 0 | 0 | 1 | 1 | 0 | 0 | 2 | 1 |
| | Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| **Lymph node, axillary** | Lymphoid hyperplasia | | | | | | | | |
| | Minimal | 0 | 0 | 0 | 1 | 1 | 2 | 0 | 1 |
| | Mild | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| | Moderate | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| **Lymph node, mesenteric** | Lymphoid hyperplasia | | | | | | | | |
| | Minimal | 0 | 0 | 1 | 2 | 0 | 1 | 0 | 0 |
| | Mild | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Pancreas** | Atrophy, acinar | | | | | | | | |
| | Mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Infiltration, mononuclear cells | | | | | | | | |
| | Minimal | 1 | 0 | 0 | 2 | 1 | 2 | 3 | 1 |
| | Mild | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | Inflammation, mononuclear cells | | | | | | | | |
| | Minimal | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | Mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Parathyroid** | Infiltration, mononuclear cells | | | | | | | | |
| | Minimal | 0 | 0 | 2 | 1 | 2 | 1 | 1 | 0 |
| | Mild | 1 | 1 | 1 | 0 | 0 | 1 | 2 | 0 |
| **Salivary gland** | Infiltration, mononuclear cells | | | | | | | | |
| | Minimal | 0 | 1 | 2 | 1 | 1 | 0 | 2 | 1 |
| | Mild | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| | Inflammation, mononuclear cells | | | | | | | | |
| | Minimal | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 0 |
| | Mild | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 1 |
| | Moderate | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| | Marked | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| **Skin** | Atrophy, follicular | | | | | | | | |
| | Moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Infiltration, mononuclear cells | | | | | | | | |
| | Minimal | 2 | 3 | 3 | 3 | 0 | 4 | 0 | 3 |
| | Mild | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 |
| | Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| | Marked | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| **Spleen** | Lymphoid hyperplasia | | | | | | | | |
| | Minimal | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 3 |
| | Mild | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Stomach** | Inflammation | | | | | | | | |
| | Minimal | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | Mild | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 |
| | Inflammation, mononuclear cells | | | | | | | | |
| | Minimal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | Mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Thyroid** | Atrophy | | | | | | | | |
| | Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | Marked | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | Infiltration, mononuclear cells | | | | | | | | |
| | Minimal | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| | Mild | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| | Moderate | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | Inflammation, mononuclear cells | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Mild | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | Moderate | | | | | | | | |
| **Post-dose Evaluation:** | **Number Evaluated** | 2 | 2 | 0 | 0 | 0 | 0 | 2 | 2 |
| **Noteworthy findings Histopathology** | **Number examined** | 2 | 2 | | | | | 2 | 2 |
| **Salivary gland** | Infiltration, mononuclear cells | | | | | | | | |
| | Minimal | 0 | 0 | | | | | 1 | 1 |
| | Inflammation, mononuclear cells | | | | | | | | |
| | Minimal | 0 | 0 | | | | | 1 | 0 |
| **Skin** | Inflammation, mononuclear cells | | | | | | | | |
| | Minimal | 1 | 0 | | | | | 1 | 2 |

[a] Due to the development of severe adverse effects, 50 mg/kg/week group monkeys only received 6 or 7 weekly doses (1 male was last dosed on Day 37 and the rest of the group was last dosed on Days 43/44 for females and males, respectively) with dosing being suspended to see if the animals would improve.

[b] The plasma concentration of tremelimumab collected from the control group animals (0 mg/kg) at 0.5 hour postdose on treatment Days 1, 29, and 176 and recovery Day 99 were less than the LLOQ (0.156 µg/mL).

[c] Male 9 from the 5 mg/kg/week group was found dead on Day 52 due to severe, peracute diarrhea. Because the microscopic changes in the intestine of this animal were those of acute suppurative inflammation with ulcerations typical of an infectious process, instead of the chronic inflammation typically observed in other monkeys dosed with tremelimumab, the diarrhea and mortality of this animal were not considered directly related to treatment. In addition, Female 27 of the 5 mg/kg/week group was euthanized on Day 94 due to a non-treatment-olrelated compound fracture of the arm.

[d] After approximately 5 weeks of dose cessation and administration of palliative treatment, the 50 mg/kg/week animals failed to improve and several of these monkeys were euthanized due to poor condition. At this point, it was decided to begin the recovery phase early, beginning on Day 79, for the surviving high-dose monkeys along with the control monkeys originally designated as recovery monkeys (for comparison purposes).

[e] Adverse clinical observations included diarrhea in 5/12, 4/8, 6/8, and 10/12 animals of the control, 5, 15, and 50 mg/kg groups 1/4 M and 1/4 F in 5 mg/kg group and 3/6 M and 3/6 F in 50 mg/kg group required supportive care; dose-dependent decrease in appetite in 1/12, 3/8, 4/8, and 8/12 animals in the control, 5, 15, and 50 mg/kg groups; treatment-related adverse skin conditions in 1/8, 1/8, and 9/12 animals in 5, 15, and 50 mg/kg groups; skin conditions in animals in 5 and 15 mg/kg groups appeared during second half of dosing phase, and lasted for approximately 2 months; incidence and severity of skin conditions were less severe (small bumps and scabs on all the limbs, pruritus, wrinkled skin, and generalized scabbing) than those observed in the animals in the 50 mg/kg group; animals in 50 mg/kg group developed open sores along with lower incidences of swollen eyelids; dry, cracked, scaly, or crusty skin; rash or reddened skin; scabbed areas; and yellowish skin; skin findings in 50 mg/kg group first manifested on Day 33 (after the fifth dose), several other animals in the same group developed adverse skin observations by the seventh dose leading to discontinuation of dosing; palliative treatment did not improve diarrhea/skin conditions but affected recovery animals appeared normal by the end of the recovery period; dose-related enlarged lymph nodes in axillary and/or inguinal areas in 1/12, 6/8, 7/8, and 11/12 animals in the control, 5, 15 and 50 mg/kg group, respectively; affected animals were clinically normal at the end of the recovery period.

[f] Both absolute and relative weights differed from controls in the direction indicated. Displayed figures are for the absolute organ weight effects.

-, No noteworthy findings; +, Mild; ++, Moderate; +++, Marked; * $p<0.05$; ** $p<0.01$.

The FDA's Assessment:
The FDA generally agrees with the Applicant's summaries of the repeat-dose toxicology studies in monkeys. Findings described by the Applicant were generally present in both the 1-month and 6-month toxicology studies. In the 6-month toxicology study, tremors occurred in one female at 15 mg/kg and one female at 50 mg/kg. One female at 5 mg/kg had moderate focal liver mineralization characterized by an encapsulated mass composed of mineralized, necrotic debris. The toxicological significance is not clear. Liver weights were increased in treated animals. Females at 5 mg/kg had increased AST levels (+255%) on Day 30 that improved by Day 92; this was driven by one female.

Hematologic changes were observed at Day 30 in the six-month study.

| Test | Study Day | Male | | | Female | | |
|---|---|---|---|---|---|---|---|
| | | 5 mg/kg | 15 mg/kg | 50 mg/kg | 5 mg/kg | 15 mg/kg | 50 mg/kg |
| RBCs | 30 | -0.95% | -7.75% | -5.23% | -0.04% | -12.00% | -0.04% |
| Hematocrit | 30 | -0.39% | -3.25% | -5.92% | -2.38% | -14.73% | -3.00% |
| Hemoglobin | 30 | 0.82% | -4.11% | -5.42% | -2.37% | -15.09% | -3.68% |
| Leukocytes | 30 | 14.89% | -6.77% | ***56.74%*** | 25.09% | 11.97% | ***85.46%*** |
| Lymphocytes | 30 | 5.67% | -6.71% | ***56.78%*** | 26.16% | 29.53% | ***94.64%*** |
| Monocytes | 30 | -15.93% | **-37.44%** | 33.92% | 43.26% | 22.64% | 103.77% |
| Neutrophils | 30 | 39.97% | -5.04% | 54.46% | 23.38% | -2.04% | 77.99% |
| Eosinophils | 30 | -49.49% | 108.59% | 179.29% | -34.13% | 22.75% | 22.75% |
| Basophils | 30 | 2.70% | 43.24% | 197.30% | **220.00%** | 133.33% | **366.67%** |

There were no notable findings in reproductive organs in either the 1-month or 6-month repeat-dose toxicology studies in monkeys.

### 5.5.2. Genetic Toxicology

The Applicant's Position:
No studies were conducted in accordance with ICH S6(R1).

The FDA's Assessment:
The FDA agrees.

### 5.5.3. Carcinogenicity

The Applicant's Position:
No studies were conducted in accordance with ICH S6(R1).

The FDA's Assessment:
The FDA agrees.

### 5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Assessment of embryofetal development with tremelimumab was performed following IV treatment of pregnant cynomolgus monkeys (Study No. 2501-001) during the period of organogenesis (from confirmation of pregnancy on GD20 to GD50) at dose levels of 0 (vehicle), 5, 15, or 30 mg/kg/wk. After the final dose on GD48, animals were maintained until GD100 ± 1, when caesarean sections were carried out and fetuses assessed. There were no unscheduled deaths during the course of the study and no tremelimumab-mediated effects on clinical signs, body weights, vaginal smears, placental weights and appearance, or abortion rates/prenatal losses in the pregnant dams. No effects of tremelimumab were observed on fetal weights, or external, visceral and skeletal abnormalities, or weights of selected organs. Therefore, tremelimumab did not elicit maternal toxicity, developmental toxicity, or teratogenicity and the NOAEL was considered to be 30 mg/kg.

**Table 5: Design of Study 2501-001, Endpoints Evaluated, and Noteworthy Findings**

| | | | | | |
|---|---|---|---|---|---|
| **Study Number:** 2501-001 | | **Test Article:** Tremelimumab | | **Test Article Lot:** E 5 644 LO 05 (61002D) | **Number of Doses:** 5 |
| **Control Article** (b) (4)histidine ((b) (4) %), L-histidine HCl (b) (4) %), trehalose (b) (4) %), polysorbate 80 (b) (4) %) | | | | | **Species:** Cynomolgus monkey |
| **Route of Administration:** Intravenous bolus | | **Duration of Post-dose Treatment-free Period:** 52 days | | | **GLP Compliance:** Yes |
| **Study Type:** Reproductive toxicity/embryo-fetal development | | | | | **eCTD Location:** Module 4.2.3.5.2 |
| **Study Objective:** To investigate the embryonic and teratogenic effects when administered to pregnant cynomolgus monkey during the period of organogenesis | | | | | |
| **GRP** | **Test Article** | **Number of Pregnant Females** | **Dose Level (mg/kg)** | | **Number of Animals with Cesarean section on GD100** |
| 1 | Vehicle | 16 | 0 | | 13 |
| 2 | Tremelimumab | 16 | 5 | | 12 |
| 3 | Tremelimumab | 16 | 15 | | 14 |
| 4 | Tremelimumab | 16 | 30 | | 12 |
| **Toxicokinetics (group mean value)** | | | | | |
| **Dose Level (mg/kg)** | | **0** | **5** | **15** | **30** |
| $AUC_{0-24}$ (µg.h/mL) | GD20 | NA | 2830 ± 530 | 9050 ± 1190 | 18600 ± 6540 |
| | GD48 | NA | 3680 ± 977 | 12,900 ± 3750 | 23,800 ± 4720 |
| $AUC_{Days\ 20-49}$ (µg.h/mL) | | NA | 76,800 ± 17200 | 208,000 ± 59900 | 454,000 ± 75,000 |
| $C_{max}$ (µg/mL) | GD20 | NA | 154 ± 32.2 | 498 ± 78.4 | 954 ± 345 |
| | GD48 | NA | 187 ± 42.8 | 707 ± 144 | 1230 ± 210 |
| ADA incidence (number of M/F) and percentage positive | | NA | NA | NA | NA |
| **Endpoints Evaluated (Dams)**: mortality, clinical signs, body weight, food consumption, pregnancy outcome (pre-implantation loss/abortions, fetal/embryonic death, placental weights).<br>**Endpoints Evaluated (Fetuses)**: mortality, body weight, fetal body measurements, organ weights, and external, visceral, and skeletal examinations. | | | | | |
| **Noteworthy Findings:** There were no noteworthy tremelimumab-related findings. | | | | | |

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusion. Tremelimumab did not induce embryo-fetal mortality or increase the incidence of fetal variations or malformations at dose levels ≤30 mg/kg administered once weekly during the period of organogenesis from GD20 to GD48 in an embryo-fetal toxicity study in cynomolgus monkeys (approximately 31 times the exposure based on AUC at the human dose of 300 mg IV on Cycle 1/Day 1).

There were no effects on maternal toxicity or effects on embryo-fetal development at tremelimumab doses up to 30 mg/kg administered once weekly during the period of organogenesis from GD20 to GD48 in an embryo-fetal toxicity study in cynomolgus monkeys.

Tremelimumab is an IgG2 antibody and is anticipated to be transferred across the placenta; however, it is difficult to assess the potential risk to the fetus resulting from in-utero exposure to tremelimumab in this study given that tremelimumab was administered to pregnant cynomolgus monkeys only during the period of organogenesis. In humans and monkeys, transfer of IgG antibodies from mother to fetus across the placenta is mediated by the neonatal Fc receptor (FcRn) and FcRn expression in the placenta is highest during the second and third trimesters in humans and during approximately the last 50 days of pregnancy in cynomolgus monkeys; thus, IgG transfer is highest after the period of organogenesis in both species (Cauvin et al., 2015; Pentsuk and van der Laan, 2009).

Maternal immune tolerance of the semi-allogeneic fetus is critical for maintenance of pregnancy. CTLA-4 regulates immune responses by controlling T cell activation and contributing to the immunosuppressive effects of Tregs. CTLA-4 may also contribute to immune tolerance in pregnancy considering Tregs constitutively expressing CTLA-4 are essential for regulating immune responses at the maternal-fetal interface by maintaining an anti-inflammatory environment necessary for implantation and placental development (Robertson et al., 2018).

Given that disruption of CTLA-4-mediated immunosuppression may abrogate maternal immune tolerance to fetal antigens, the FDA performed a literature-based assessment (reviewed by Dr. Melissa A. Pegues and Dr. Brian Christmas) of the potential for blockade of CTLA-4 to cause reproductive and embryofetal toxicity. Administration of an anti-mouse CTLA-4 antibody to pregnant CBA/J female mice on GD 4.5, 6.5, and 8.5 resulted in lower maternal body weight gain, increased resorptions, and reduced number of live fetuses compared to mice administered an isotype control antibody (Wang et al., 2019). Additionally, analysis of decidual CD4 T cells from these mice demonstrated that treatment with an anti-CTLA-4 antibody resulted in an increase in the percentage of cells expressing the Th1 associated cytokines TNF-α and IFNγ and a decrease in the percentage of cells expressing the Th2 associated cytokines IL-4 and IL-10 compared to controls (Wang et al., 2019). In humans, CTLA-4 expression positively correlated with production of Th2 cytokines, IL-4 and IL-10, and negatively correlated with expression of Th1 cytokines, IL-2 and IFNγ, in samples from normal pregnancies. CTLA-4 expression was lower on decidual T cells from miscarriages and was associated with lower frequency of cells expressing IL-4 or IL-2 and an increase in cells expressing IL-2 or IFNγ, suggesting a shift towards a pro-inflammatory Th1 expression profile (Jin et al., 2011). Taken together, these findings suggest that disruption of CTLA-4 signaling may lead to alterations in tolerogenic T cell responses, which in turn may be associated with pregnancy loss.

Further, studies using genetically engineered mice suggest that CTLA-4 may be important for the development of neonatal immune tolerance. Homozygous CTLA-4 deficient (CTLA-$4^{-/-}$) mice resulting from mating mice heterozygous for CTLA-4 (CTLA-$4^{+/-}$) develop a lymphoproliferative disorder characterized by a systemic accumulation of T cell blasts in multiple organs, including liver, heart, lungs, and lymphoid organs, that results in death due to heart failure 3 to 4 weeks after birth (Waterhouse et al., 1995; Tivol et al., 1995; Araki et al., 1998). These findings suggest that fetal exposure to a CTLA-4 blocking antibody may increase the risk of developing immune-mediated disorders or of altering normal immune responses.

The proposed indication for tremelimumab is in combination with durvalumab, an anti-PD-L1 antibody, and platinum-based chemotherapy; both durvalumab and the referenced chemotherapy regimen can also cause fetal harm. Based on the mechanism of action of tremelimumab and nonclinical findings from animal models, FDA recommends advising females of reproductive potential to use effective contraception during treatment with tremelimumab and for 3 months after the last dose.

### 5.5.5. Other Toxicology Studies

The Applicant's Position:

In vitro tissue cross-reactivity studies were conducted in both monkey (IM645; ) and human (IM676). Tremelimumab bound only to cells in tissues expected to contain CTLA-4 expressing cells and were considered similar between species. In cynomolgus monkey tissues, positive staining was specific for lymphocytes in lymphoid tissues including tonsil, lymph node, spleen, and thymus. Positive staining was noted on rare to occasional lymphocytes in mucosa-associated lymphoid tissue in stomach and colon. In human tissues, positive staining was specific for lymphocytes in lymphoid tissues including tonsil, lymph node, spleen, and non-involuted thymus. Positive staining was noted on rare to occasional lymphocytes in mucosa-associated lymphoid tissue in the small intestine and colon, and rare lymphocytes in lymphoid nodules of 1 thyroid gland.

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusion. The placenta was noted for positive staining in humans, but not monkeys.

X X

Primary Reviewer Supervisor

# 6. Clinical Pharmacology

## 6.1.Executive Summary

The FDA's Assessment:

Tremelimumab is a human IgG2 mAb directed against CTLA-4. The Combination of tremelimumab and durvalumab targets PD-L1 and CTLA-4 to block complementary immunosuppressive pathways acting at initial T-cell priming and activation and later at the effector T-cell response.

The Applicant seeks the approval of 1 dose tremelimumab 300 mg in combination with durvalumab 1500 mg at Cycle 1, followed by durvalumab 1500 mg every 4 weeks (Q4W) as monotherapy (T300+D) for the treatment of patients with unresectable hepatocellular carcinoma(uHCC).

The proposed dosage regimen of tremelimumab in combination with durvalumab (T300+D) achieved a statistically and clinically significant 2.7-months longer median survival (the primary endpoint) over sorafenib (the standard of care) in the pivotal trial, Study D419CC00002 (HIMALAYA) and supported by Study D4190C00022 (Study 22). Incidence of adverse events (AEs) in T300+D arms appeared generally comparable to the control arm (76 vs 85 %), Grade 3 or 4 (50% vs 52%), and discontinuation of study treatment (8 % vs 11%). The incidence of any serious AEs including events with outcome of death was higher in T300+D compared to the control arm (18% vs 9.4%).

In support of this BLA, the Applicant submitted reports of the population pharmacokinetic (PPK) and exposure-response (E-R) analyses, and immunogenicity evaluation. The PPK analyses showed that the following covariates had no clinically significant effects on the PK of tremelimumab: body weight (34 to 149 kg), age (18 to 87 years), sex, race (White, Black, Asian, Native Hawaiian, Pacific Islander, or American Indian), serum albumin levels (0.3 to 396 g/L), lactate dehydrogenase levels (12 to 5570 U/L), soluble PD-L1 (67 to 349 pg/mL), varying degrees of organ dysfunctions including mild to moderate renal impairment (CLcr 30 to 89 mL/min), and mild to moderate hepatic impairment (bilirubin <3x ULN and any AST). The E-R analyses found no evidence indicative of relationship for safety or efficacy.

In the HIMALAYA study, patients who received the T300+D regimen and who were evaluable for the presence of anti-drug-antibodies (ADA) against tremelimumab, 11 % (20/182) patients tested positive for ADAs; neutralizing antibodies against tremelimumab were detected in 40% (8/20) of patients. In patients who received the T300+D regimen and who were evaluable for presence of ADA against durvalumab, 3.1 % (9/294) patients tested positive for anti-durvalumab antibodies and 56% (5/9) of them test positive for neutralizing antibodies against durvalumab. The presence of ADAs against tremelimumab had no apparent effect on tremelimumab exposure; however, geometric mean concentrations of durvalumab at week 12 predose decreased in patients who tested positive for anti-durvalumab antibodies. There is no observed impact of ADA against durvalumab or tremelimumab on safety. The effect of ADA on efficacy is unknown due to low occurrence of ADA incidents.

| REVIEW ISSUES | RECOMMENDATIONS/COMMENTS |
|---|---|
| Pivotal or supportive evidence of effectiveness | The effectiveness of tremelimumab and durvalumab for the proposed indication was established in study HIMALAYA (pivotal trial). The T300+D arm demonstrated a statistically significant OS compared to sorafenib arm with a stratified hazard ratio of 0.78 (95% CI: 0.66, 0.93; p = 0.0035). Median OS was 16.4 months in the T300+D and 13.8 months in the sorafenib arm; this represents an estimated 2.6-month difference in median values.<br><br>E-R analyses suggest flat relationships for both efficacy and safety with either tremelimumab or durvalumab PK exposures at the recommended dosing regimen.<br>Study 22 further provides safety, efficacy and PK and PD supportive evidence for selection of the T300+D regimen. |
| General dosing instructions | The recommended dosing regimens:<br>For patients ≥30 kg:<br>• a single dose of tremelimumab 300 mg in combination with durvalumab 1500 mg administered Q4W<br>For patients <30 kg:<br>• a single dose of tremelimumab 4 mg/kg in combination with durvalumab 20 mg/kg administered Q4W |
| Dosing in patient subgroups (intrinsic and extrinsic factors) | *Dose based on 30 kg body weight cutpoint*<br><br>Body weight ≥ 30kg: The proposed adult flat dosing regimen is acceptable given (1) the minimal impact of body weight on tremelimumab exposure in the range of 34 to 149 kg, and (2) flat E-R relationships for both efficacy and safety at the recommended dosing regimen.<br><br>Body weight < 30 kg: Although no clinical data are available to support dosing for patients <30 kg, the proposed weight-based dosing regimen is appropriate. The approved durvalumab regimen had a body weight dosing cutoff at 30 kg. It is an acceptable general approach to prevent overexposure in patients with lower body weight. |
| Immunogenicity | *ADA against tremelimumab*<br><br>In the HIMALAYA study, in patients who were treated with T300+D and who were evaluable for the presence of |

| | |
|---|---|
| | ADAs against tremelimumab, 11% (20/182) patients tested positive for ADAs. Neutralizing antibodies against tremelimumab were detected in 40% (8/20) of them.<br><br>The presence of ADAs against tremelimumab had no apparent effect on PK or safety. Due to the low occurrence of ADA, the impact of ADA on overall survival (OS) is inconclusive.<br><br>*ADA against durvalumab*<br>During the initial 12 weeks of treatment in study HIMALAYA with T300+D, 3.1% (9/294) patients tested positive for ADAs against durvalumab and, neutralizing antibodies were detected in 55.6% (5/9) of them.<br><br>The presence of durvalumab ADA reduced durvalumab concentrations; geometric mean of durvalumab serum trough concentrations in patients with ADA positive was 33 mcg/mL compared to 86 mcg/mL in patients with ADA negative after 3 months of Q4W dosing.<br>Based on the data provided, the presence of ADA does not appear to impact safety. Because of the low occurrence of anti-durvalumab antibodies, the effect of these antibodies on OS is unknown. |
| Labeling | The proposed labeling is acceptable upon the Applicant and FDA reaching agreements to the FDA recommended labeling revisions. |

## 6.2.Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:
The PK of durvalumab have been well characterized and are summarized in the current prescribing information for IMFINZI. This submission provides the updated PK, PPK, and ER analyses for durvalumab and tremelimumab to support this application. The clinical pharmacological data are derived from 1 pivotal study (HIMALAYA), 20 supportive durvalumab studies, and 17 supportive tremelimumab studies.

A durvalumab PPK model was updated based on data from 5 previous studies (ie, Studies 1108, ATLANTIC, PACIFIC, CASPIAN, and POSEIDON), with additional data from a pool of data from 2 HCC studies (HIMALAYA and Study 22), where patients received durvalumab 1500 mg Q4W, were combined for the analysis. Details of the model are provided in Section 19.4.1.2.

For tremelimumab, a PPK model was updated based on 6 previous studies (Japan Study 02, Study 06, Study 10, DETERMINE, Study D4884C00001, and POSEIDON; Table 12) with additional data from a pool of data from HCC studies (comprising Arms B and C of HIMALAYA and Parts 1, 2, and 3 of Study 22), where patients received tremelimumab 75 mg × 4 doses, 300 mg × 1 dose, and 750 mg Q4W. Details of the model are provided in Section 19.4.1.2.

An ER efficacy analysis was conducted using exposure data (durvalumab: $C_{max}$, $C_{min}$, and AUC at Cycle 1 and steady state; tremelimumab: $C_{max}$, $C_{min}$, and AUC at Cycle 1 and $AUC_{0\text{-}inf}$) and OS and PFS data for patients who had received T300+D in the HIMALAYA study. There were no significant exposure ($C_{max}$, $C_{min}$, AUC, and $AUC_{0\text{-}inf}$)-efficacy (OS and PFS) relationships identified for durvalumab or tremelimumab (T300+D). Details of the ER efficacy analysis are provided in Section 19.4.2.2.

An ER safety analysis was performed for the same patient population evaluating exposure data (durvalumab: $C_{max}$, $C_{min}$, and AUC at Cycle 1 and steady state; tremelimumab: $C_{max}$, $C_{min}$, and AUC at Cycle 1 and $AUC_{0\text{-}inf}$) of durvalumab and tremelimumab , against data on Grade 3, 4, and 5 drug-related AEs, Grade 3, 4, and 5 drug-related AESIs, and all Aes leading to treatment discontinuation. No significant exposure-safety relationships were identified for durvalumab or tremelimumab. Data from Study 06 demonstrated that there was no risk of QT prolongation related to exposure of tremelimumab. Details of the ER safety analysis are provided in Section 19.4.2.4.

The Applicant's Position:

The updated PPK models of durvalumab and tremelimumab, as well as data from the HIMALAYA CSR, adequately described the PK data of both compounds at the dose regimens evaluated in HIMALAYA as indicated in the following:

- The PK of durvalumab in the HIMALAYA study/pooled HCC studies (HIMALAYA and Study 22) is similar to the established PK of durvalumab 1500 mg Q4W.
- The PK of tremelimumab was as expected (ie, dose proportional [$C_{max}$] based on comparisons of T75, T300, and T750).
- The $C_{min,1}$ for tremelimumab was 3.3 times higher in the T300+D arm than in the T75+D arm.
- There is no clinically meaningful change in the PK of the individual durvalumab and tremelimumab components when they are given in combination together.
- The PPK indicated that there is no need for dose adjustment for durvalumab or tremelimumab in special populations, based on baseline patient characteristics (clinically relevant change was defined as ≥ 30% change).
- Anti-drug antibody status did not have an effect on durvalumab or tremelimumab PK.

There was no clear relationship between body weight and efficacy (OS and PFS) or any safety endpoints evaluated in patients treated with durvalumab and tremelimumab in HIMALAYA. Overall, there was no evidence that decreased body weight led to increased efficacy or safety risk, or vice versa. Given that body weight is the most influential factor on the PK of durvalumab and tremelimumab, the lack of a relationship between body weight and efficacy/safety endpoints further confirms that there was no causal relationship between variation in exposure and efficacy or safety outcomes in HIMALAYA.

The FDA's Assessment:

- FDA agrees with the Applicant's position that based on PPK model assessment there is no need for dose adjustment for durvalumab or tremelimumab in special populations.
- FDA agrees with the Applicant's position that the fixed dose regimen and the BW-based dose

have similar exposures of durvalumab and tremelimumab. This conclusion is supportive by Study 22, where similar $C_{max}$ and $C_{trough}$ were observed following the weight-based and the equivalent fixed dosing regimen of durvalumab and tremelimumab.

- FDA agrees with the Applicant's position that tremelimumab ADA has no impact on its PK, or safety. The data showed no difference for tremelimumab concentrations and no identifiable trend of infusion related reaction (IRR) between patients who tested ADA positive vs ADA negative. See Table 8 in section 6.3 for additional details
- FDA disagrees with the Applicant's position that there is no impact of ADA against durvalumab on pharmacokinetic of durvalumab. Reduction of durvalumab geometric mean concentrations at week 12 predose was observed in patients who developed ADA. See Figure 5 in section 6.3 for additional details

### 6.2.2. General Dosing and Therapeutic Individualization

#### 6.2.2.1. General Dosing

Data:

The approved durvalumab dose regimen in locally advanced, unresectable Stage III NSCLC is 10 mg/kg Q2W or 1500 mg Q4W, and the approved durvalumab dose regimen in ES-SCLC is 1500 mg Q3W in combination with etoposide and either carboplatin or cisplatin for 4 cycles followed by 1500 mg Q4W monotherapy for patients with body weight greater than 30 kg and 20 mg/kg Q3W in combination with etoposide and either carboplatin or cisplatin for 4 cycles followed by 20 mg/kg Q4W monotherapy for patients with a body weight of 30 kg or less. HIMALAYA and Study 22 results confirmed that durvalumab 1500 mg in combination with 1 dose of tremelimumab 300 mg at Cycle 1, followed by durvalumab 1500 mg Q4W as monotherapy is an appropriate dose regimen for patients with HCC.

Based on PK simulations, the predicted $C_{max}$ for a single dose of tremelimumab 4 mg/kg was approximately 3- to 4-fold higher than the predicted $C_{max}$ for tremelimumab 1 mg/kg (compared to any of the 4 tremelimumab doses in the T75+D regimen). A fixed dose of T300 mg was considered equivalent to tremelimumab 4 mg/kg. Thus, the T300+D dosing regimen (T300 mg + D 1500 mg for 1 dose, followed by D 1500 mg monotherapy Q4W) was selected for Study 22 and HIMALAYA.

The Applicant's Position:

PPK data for durvalumab and tremelimumab indicate that there is no need for dose adjustment of durvalumab 1500 mg Q4W or tremelimumab 300 mg in special populations (including patients with mild or moderate hepatic impairment; clinically relevant change was defined as ≥ 30% change) (Sections 6.2.1 and 6.2.2.2). Taken together, the observed clinical benefits and the manageable safety profile, as well as the PK and ER data, support the proposed dose of durvalumab 1500 mg Q4W plus tremelimumab 300 mg to be the appropriate dose regimen for the proposed population (with a body weight greater than 30 kg).

It is to be noted that since the body weight of all the patients in the HIMALAYA study and in Study 22 was above 30 kg, no data are available on safety and tolerability of this dose regimen in patients with extremely low body weight (≤ 30 kg). Therefore, in order to prevent over exposure in these patients, it is recommended that patients with a body weight of ≤ 30 kg at the start of treatment should receive a weight-based dosing of tremelimumab 4 mg/kg and durvalumab 20 mg/kg for the combination dose at

cycle 1. If a patient's weight is or decreases to 30 kg or below at any point after first dose at cycle 1, the patient should receive a weight based dosing of durvalumab 20 mg/kg Q4W until the weight increases to > 30 kg, at which point the patient should receive the original assigned fixed dose of durvalumab 1500 mg Q4W.

The FDA's Assessment:
The effectiveness of the current regimen tremelimumab 300 mg at Cycle 1 in combination with 1500mg durvalumab followed by durvalumab 1500 mg monotherapy Q4W (T300+ D) is supported by the dose finding Study 06 and Study 22, and pivotal Study HIMALAYA. FDA agrees with the Applicant's position on dose selection based on efficacy, safety, and pharmacodynamic (PD) data from these studies. See section 6.3 for justification on dose selection.

#### 6.2.2.2. Therapeutic Individualization

Data:
The effect of intrinsic factors (ie, race, age, renal impairment, hepatic impairment, sex, and body weight) on the PK of durvalumab or tremelimumab have been evaluated in the previous PPK analysis and reconfirmed in current PPK analysis. The final PPK modeling indicated that the baseline patient characteristics of age, race, renal function, and hepatic function had no effect on the PK of durvalumab or tremelimumab. While the PPK analysis identified a few statistically significant covariates, none had a clinically relevant impact on key PK exposure metrics of durvalumab or tremelimumab.

The impact of intrinsic and extrinsic factors on the PK of durvalumab and tremelimumab in HIMALAYA and Study 22 following durvalumab or durvalumab plus tremelimumab administration was further evaluated using the updated PPK models, including HIMALAYA and Study 22 data. The results indicated that none of the intrinsic or extrinsic factors evaluated had a clinically meaningful impact on the PK of durvalumab or tremelimumab in HIMALAYA and Study 22.

The Applicant's Position:
The PPK analysis supports the conclusion that there is no need for dose adjustment for durvalumab or tremelimumab based on these intrinsic and extrinsic factors.

The FDA's Assessment:
FDA agrees with the Applicant's position that there is no need for dose adjustment for tremelimumab or durvalumab for the following intrinsic and extrinsic factors, body weight, age, sex, race, serum albumin level, lactate dehydrogenase level, soluble PD-L1, mild to moderate renal impairment, and mild to moderate hepatic impairment , as the PPK analyses showed no effect of these covariates on the PK of both tremelimumab and durvalumab and flat E-R relationships were observed for both efficacy and safety at the recommended dosing regimen.

#### 6.2.2.3. Outstanding Issues

Data: None.

The Applicant's Position: There are no outstanding issues to report.

The FDA's Assessment:

FDA agrees with the Applicant's position that there are no outstanding issues from the clinical pharmacology perspective.

## 6.3.Comprehensive Clinical Pharmacology Review

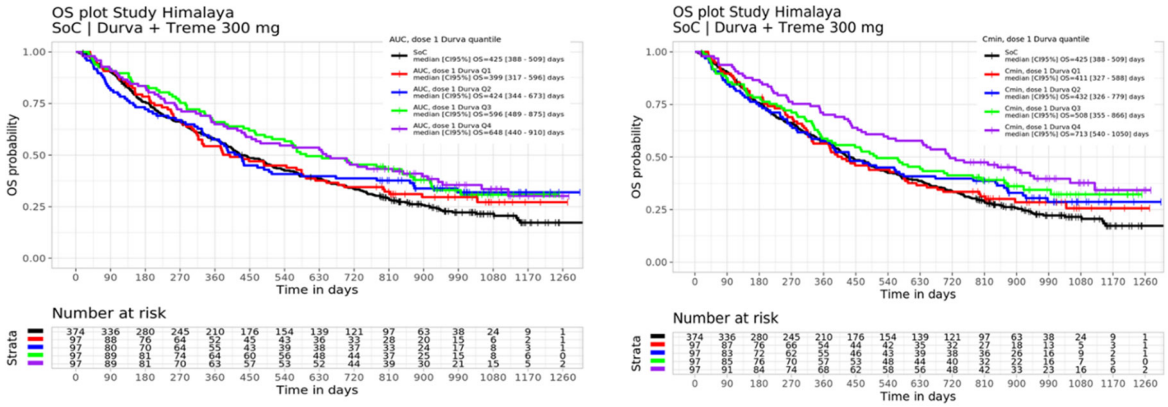
### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

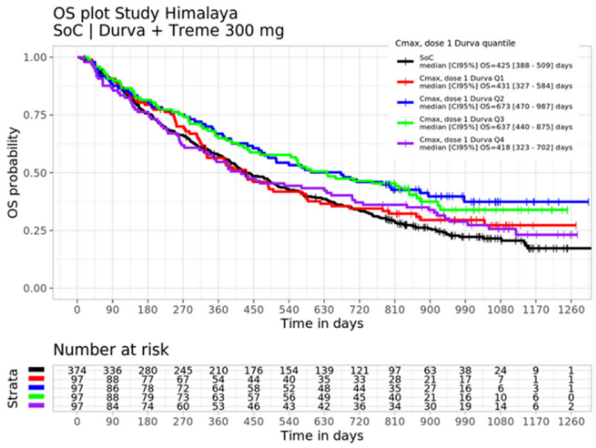
Data:
Pharmacology and clinical PK of tremelimumab and durvalumab was summarized in Section 6.2.1.

Figure 1 and Figure 2 are representative ER efficacy analyses in the T300+D cohort of HIMALAYA. Figure 3 is representative of the ER safety analysis results in the T300+D cohort of HIMALAYA. The immunogenicity data of tremelimumab and durvalumab for HIMALAYA study are summarized in Table 6.

In addition, the concentration-QTc analysis were performed on ECG data from 379 patients who received at least 1 dose of tremelimumab in combination with durvalumab in Study 06.

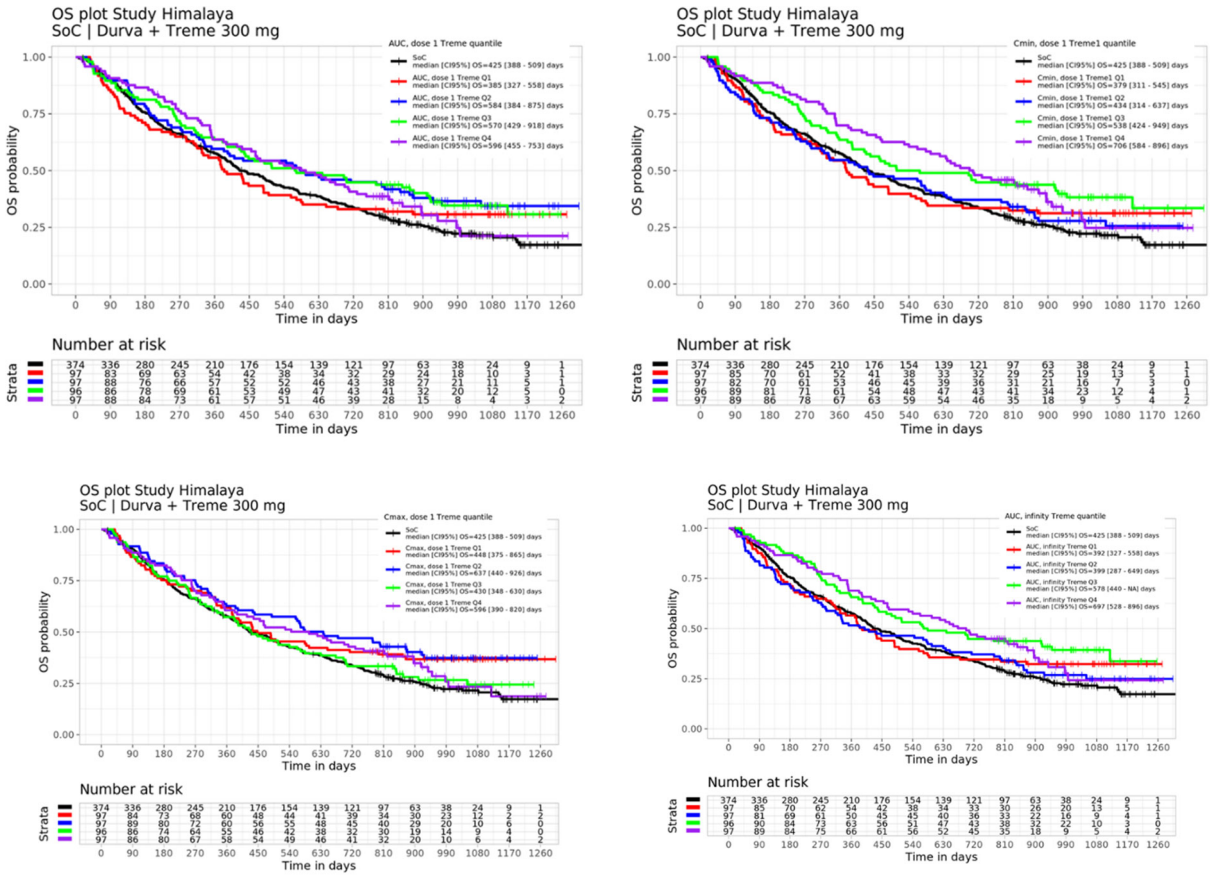
**Figure 1 OS Kaplan-Meier Plots for Durvalumab Exposure Metrics by Quartiles at Dose 1**






Source: Figure 13 in Population PK and Exposure-Response Report, Module 5.3.3.5

**Figure 2 OS Kaplan-Meier Plots for Tremelimumab Exposure Metrics by Quartiles at Dose 1**

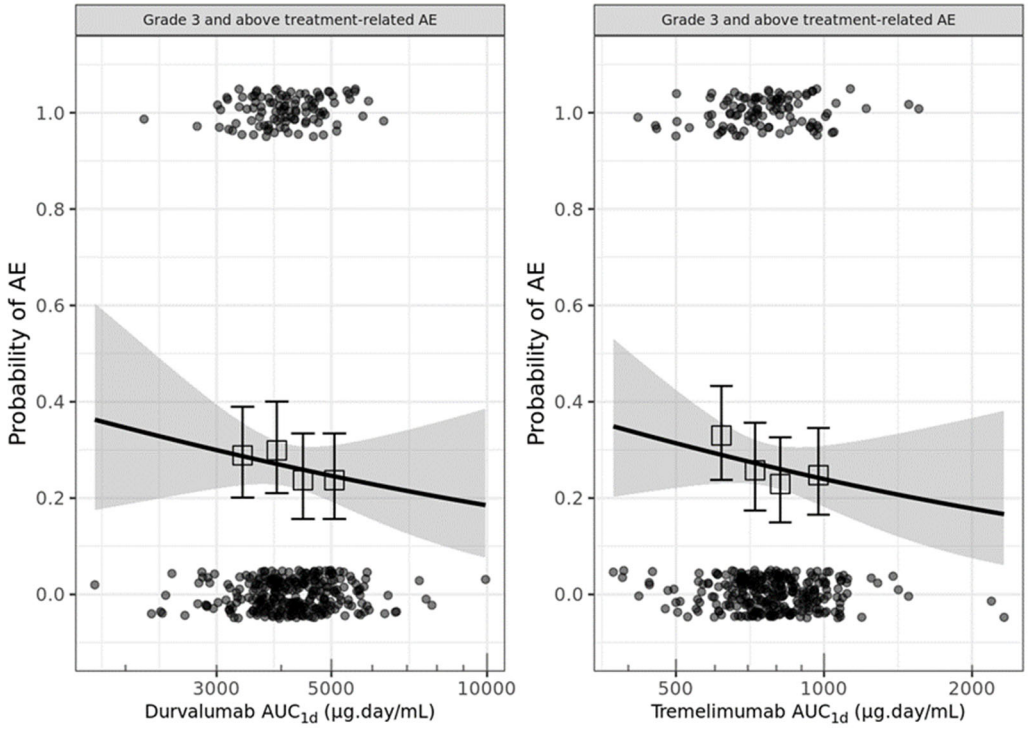



Source: Figure 15 in Population PK and Exposure-Response Report, Module 5.3.3.5



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

**Figure 3** **Relationship Between the Probability of Having Grade 3 and Above Treatment-related Aes and $AUC_{dose\ 1}$ for Durvalumab and Tremelimumab**




Note: The black solid circles are the observed AE, and the open squares with error bars are the observed probability of response at each exposure quartile. The black lines are the logistic regression between 2 variables, and the gray area represents the associated confidence interval.
Source: Figure 23 in Population PK and Exposure-Response Report, Module 5.3.3.5

**Table 6: Summary of ADA Responses to Tremelimumab and Durvalumab**

| ADA category | HIMALAYA T300+D | |
|---|---|---|
| | ADA to Tremelimumab (N = 388) n (%) | ADA to Durvalumab (N = 388) n (%) |
| ADA-evaluable patients | 182 (46.9%) | 294 (75.8%) |
| ADA prevalence[a] | 29 (15.9%) | 24 (8.2%) |
| ADA incidence[b] | 20 (11.0%) | 9 (3.1%) |
| Treatment-boosted ADA[c] | 0 | 0 |
| Treatment-induced ADA (positive post-baseline only) | 20 (11.0%) | 9 (3.1%) |
| ADA positive at baseline only | 6 (3.3%) | 13 (4.4%) |
| ADA positive post-baseline and positive at baseline | 3 (1.6%) | 2 (0.7%) |
| Persistently positive [d] | 23 (12.6%) | 9 (3.1%) |
| Transiently positive [e] | 0 | 2 (0.7%) |

| ADA category | HIMALAYA T300+D | |
|---|---|---|
| | ADA to Tremelimumab (N = 388) n (%) | ADA to Durvalumab (N = 388) n (%) |
| nAb positive at any time | 8 (4.4%) | 5 (1.7%) |

[a] ADA prevalence is defined as the proportion of patients with a positive ADA result at any time, baseline, or post-baseline in the ADA-evaluable population.
[b] ADA incidence is the proportion of treatment-emergent patients (sum of treatment-induced ADA and treatment-boosted ADA) in the ADA-evaluable population.
[c] Treatment-boosted ADA is defined as baseline positive ADA titer that was boosted to ≥ 4-fold during the study period.
[d] Persistently positive is having at least 2 post-baseline ADA-positive measurements with at least 16 weeks (112 days) between the first and last positive measurements or an ADA-positive result at the last available assessment. The category may include patients meeting these criteria who were ADA positive at baseline.
[e] Transiently positive is ADA positive as baseline and having at least 1 post-baseline ADA-positive measurement and not fulfilling the conditions for persistently positive.
If a subject has more than 1 titer result, the maximum titer result is used whether it is baseline or post-baseline.
Source: Tables 39 and 40 in D419CC00002 CSR, Module 5.3.5.1

***Pharmacodynamics***

Pharmacodynamic data from Study 22 demonstrated that T300+D increases both CD4+ and CD8+ T cells compared with D alone. The proportion of patients with expanded T-cell clones was greater for the T300+D and T arms compared to D monotherapy, demonstrating that addition of T to D monotherapy drives early immune activation. Finally, the T300+D is capable of expanding a functionally distinct immune cell subset compared to D or T alone providing the biologic rationale supporting the differentiated clinical activity.

The Applicant's Position:

An ER efficacy analysis was conducted using exposure data (durvalumab: $C_{max}$, $C_{min}$, and AUC at Cycle 1 and steady state; tremelimumab: $C_{max}$, $C_{min}$, and AUC at Cycle 1 and $AUC_{0\text{-}inf}$) and OS and PFS data for patients who had received T300+D in the HIMALAYA study. There were no significant exposure ($C_{max}$, $C_{min}$, AUC, and $AUC_{0\text{-}inf}$)-efficacy (OS and PFS) relationships identified for durvalumab or tremelimumab (T300+D).

An ER safety analysis was performed for the same patient population evaluating exposure data (durvalumab: $C_{max}$, $C_{min}$, and AUC at Cycle 1 and steady state; tremelimumab: $C_{max}$, $C_{min}$, and AUC at Cycle 1 and $AUC_{0\text{-}inf}$) of durvalumab and tremelimumab, against data on Grade 3, 4, and 5 drug-related Aes, Grade 3, 4, and 5 drug-related AESIs, and all Aes leading to treatment discontinuation. No significant exposure-safety relationships were identified for durvalumab or tremelimumab. Data from Study 06 demonstrated that there was no risk of QT prolongation related to exposure of tremelimumab.

There was no clear relationship between body weight and efficacy (OS and PFS) or any safety endpoints evaluated in patients treated with durvalumab and tremelimumab in HIMALAYA. Overall, there was no evidence that decreased body weight led to increased efficacy or safety risk, or vice versa. Given that body weight is the most influential factor on the PK of durvalumab and tremelimumab, the lack of a relationship between body weight and efficacy/safety endpoints further confirms that there was no causal relationship between variation in exposure and efficacy or safety outcomes in HIMALAYA.

Both ADA incidence and nAb prevalence to durvalumab were consistently low across all treatment

regimens in HIMALAYA and in the HCC tumor and Pan-tumor pools. Similarly, the median of maximum durvalumab ADA titer of patients with treatment-emergent ADA were numerically similar and consistently low across all treatment regimens in HIMALAYA and in pools. The prevalence and incidence of ADA to tremelimumab based on results from HIMALAYA and from pooled datasets ranged from 12.3% to 29.4% and 8.0% to 22.5%, respectively. The majority of tremelimumab-treated patients who had positive ADA results were classified as treatment-emergent ADA positive and persistently ADA positive. In treatment-emergent ADA-positive patients, the median of maximum tremelimumab ADA titer was low in pooled datasets. Anti-drug antibody status did not have an effect on durvalumab PK or the PK of tremelimumab based on observed data and PPK analysis. There was no apparent effect of durvalumab or tremelimumab ADA on the safety or efficacy of durvalumab or tremelimumab. Overall, these results support a low immunogenicity risk of durvalumab and tremelimumab.

The concentration-QTc modeling results did not identify a significant linear relationship between tremelimumab or durvalumab serum concentrations and ΔQTcF.

The FDA's Assessment:

FDA's assessment of general pharmacology and pharmacokinetic characteristics of tremelimumab is summarized in the Table 7 below.

**Table 7 General pharmacology and pharmacokinetic characteristic of tremelimumab**

| | |
|---|---|
| **Physicochemical Properties** | |
| Chemical structure and molecular weight | 149,145 Da |
| Administration, formulation type, strengths | Strength includes 25 mg/1.25 mL (20 mg/mL) and 300 mg/15 mL (20 mg/mL) solution:<br>Administration: IV over 60 minutes. |
| **Pharmacology** | |
| Mechanism of Action | human immunoglobulin G2 (IgG2) kappa monoclonal antibody (mAb) directly blocked CTLA-4. |
| QT/QTc Prolongation | As monoclonal antibody, tremelimumab is not expected to cause QT/QTc prolongation. There is no relationship between tremelimumab serum concentrations and ΔQTcF. |
| **General Information** | |
| Bioanalysis | Bioanalysis of tremelimumab utilized an indirect enzyme-linked immunosorbent assay (ELISA) to quantify tremelimumab concentrations. The presence of durvalumab 600 µg/mL did not affect quantitation of tremelimumab.<br>Bioanalysis of durvalumab utilized electrochemiluminescent (ECL) assay to measure the concentrations of durvalumab in human serum samples. |

<table>
<tr><td>Dose or exposure range tested in clinical trials</td><td>The pharmacokinetics of tremelimumab as a single agent was studied in patients who received the following doses: 1mg/kg or 75 mg, 3mg/kg or 750 mg or 10 mg/kg administered Q4W or Q4W x 7 then every 12 weeks, or at a single dose of 300 mg.</td></tr>
<tr><td>Exposures at Proposed Dose Regimen</td><td>Exposures to tremelimumab following a single dose of tremelimumab 300 mg plus durvalumab Q4W were simulated based on the pooled data from 9 studies (N=2406) including the HIMALAYA trial. Table below shows the predicted exposures after a single dose of 300 mg.
<table>
<tr><th></th><th colspan="3">300 mg</th></tr>
<tr><th></th><th>Cmin,dose1 (µg/mL)</th><th>Cmax,dose1 (µg/mL)</th><th>AUCdose1 (µg•day/mL)</th></tr>
<tr><td>Geometric Mean (CV%)</td><td>11.9 (40.4)</td><td>86.5 (23.9)</td><td>763 (28.0)</td></tr>
<tr><td>Mean (SD)</td><td>12.9 (6.70)</td><td>89.7 (51.0)</td><td>801 (528)</td></tr>
<tr><td>Median (Min-Max)</td><td>12.2 (2.00-196)</td><td>85.1 (37.0-2330)</td><td>756 (295-23700)</td></tr>
</table>
CV=Coefficient of variation; SD=Standard Deviation<br>
* Parameters were estimated at 28 days cycle<br>
Source: sponsor's IR</td></tr>
<tr><td>Dose Proportionality</td><td>A dose-proportional increase in PK exposure (Cmax and $AUC_{0-28D}$) of tremelimumab was observed with the dose of 1, 3 and 10 mg/kg tremelimumab Q4W.
<table>
<tr><th rowspan="2">Dose level</th><th colspan="2">Tremelimumab geometric mean (n, geometric %CV)</th></tr>
<tr><th>$C_{max}$ (µg/mL/mg)</th><th>$AUC_{0-28D}$ (µg·day/mL/mg)</th></tr>
<tr><td>T1 Q4W Escalation (N = 59)</td><td>0.319 (55, 37.8)</td><td>2.82 (36, 39.3)</td></tr>
<tr><td>T3 Q4W Escalation (N = 34)</td><td>0.258 (32, 60.7)</td><td>2.83 (17, 21.1)</td></tr>
<tr><td>T10 Q4W Escalation</td><td>0.261</td><td>2.45</td></tr>
</table></td></tr>
</table>

| | |
|---|---|
| | (N = 9) \| (9, 26.1) \| (9, 32.2)<br>Source: Table 53, Study 06 CSR, Module 5.3.5.2. |
| **Accumulation** | The recommended dose is a single dose of 300 mg.<br>There is little to no accumulation of tremelimumab (Cmax or trough serum concentration [Ctrough]) on week 13 following Q4W dosing. Accumulation ratio ranged from 0.949 to 1.17. |
| **Distribution** | From a final two-compartmental tremelimumab population PK model, the geometric mean (% coefficient of variation [CV%]) for central (V1) and peripheral (V2) volume of distribution was 3.45 (27%) and 2.47 (43%) L, respectively. |
| **Metabolism** | Tremelimumab and durvalumab are mAbs that are expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. |
| **Elimination**: Terminal half-life and CL | Tremelimumab clearance decreases over time, with a mean maximal reduction (CV%) from baseline values of approximately 22.7% (26.1%) resulting in a geometric mean (CV%) steady state clearance (CLss) of 0.202 L/day (19.2%); the decrease in CLss is not considered clinically relevant. The geometric mean (CV%) terminal half-life at steady state was approximately 20.4 (34.7%) days. |
| **Immunogenicity** | The solution phase, bridging, ECL immunoassay was validated for the measurement of ADA and neutralizing antibody (nAb) to tremelimumab in serum samples. ADA immunocomplexes were captured on streptavidin-coated standard 96-well MSD plates. ECL signal intensity was proportional to the levels of ADA present in the sample. For detection of nAb, ADA contained serum samples were incubated with ruthenium-conjugated tremelimumab and then added to CTLA-4 coated standard 96-well MSD plate. Nab bound to tremelimumab and decreased ruthenium-conjugated tremelimumab association with CTLA-4 in the wells. ECL signal intensity was inversely proportional to the level of nAb present in the sample.<br><br>The solution phase, bridging, ECL immunoassay was validated for the measurement of ADA and neutralizing antibody (nAb) to durvalumab in serum samples. ADA immunocomplexes were captured on streptavidin-coated standard 96-well MSD plates. For nAb detection, ADA contained serum samples were incubated with durvalumab and sPD-L1 in an anti-PD-L1 coated standard 96-well MSD plate. Nab bound to durvalumab and increased sPD-L1 binding to anti-PD-L1. ECL signal intensity was proportional to the level of ADA and nAb present |

in the sample.

The 20 patients with treatment emergent ADA against tremelimumab in T300 +D arm were all classified as persistently ADA positive and none were transiently positive. The 9 patients with treatment emergent ADA against durvalumab in T300 +D arm were all classified as persistently ADA positive. The median of maximum tremelimumab and durvalumab ADA titers were low (ranges 1-16) from HIMALAYA study.

| Summary of ADA Responses (HIMALAYA) | | | |
|---|---|---|---|
| Parameter | D (N = 388) | T300 + D (N = 388) | T75 + D (N = 152) |
| Durvalumab | | | |
| Treatment-emergent ADA positive | 2.8% (8/282) | 3.1% (9/294) | 4.6 % (5/108) |
| Median of Maximum Titer | 2 | 4 | 2 |
| Persistently Positive | 2.8% (8/282) | 3.1% (9/294) | 3.7% (4/108) |
| Median of Maximum Titer | 2 | 8 | 2 |
| Transiently Positive | 0 | 0 | 0.9% (1/108) |
| Median of Maximum Titer | N/A | NA | 1 |
| nAb positive at any time | 25% (2/8) | 56% (5/9) | 0 |
| Tremelimumab | | | |
| Treatment-emergent ADA positive | | 11% (20/182) | 22.5% (23/102) |
| Median of Maximum Titer | | 8 | 8 |

| | | | |
|---|---|---|---|
| Persistently Positive | | 12.6% (23/182) | 19.6% (20/102) |
| Median of Maximum Titer | | 8 | 16 |
| Transiently Positive | | 0 | 4.9 % (5/102) |
| Median of Maximum Titer | | N//A | 2 |
| nAb positive at any time | | 40% (8/20) | 70% (16/23) |

Source: Tables 39 and 40 in D419CC00002 CSR, Module 5.3.5.1

ADA assessment

- FDA agrees with Applicant's position that ADA of tremelimumab has no impact on its PK, or safety. Table 8 below shows that there is no impact of ADA on PPK model predicted $AUC_{0\text{-}INF}$ or CL,ss. FDA also compared tremelimumab's concentrations at the timepoint around the ADA sampling (predose at wk4). Figure 4 shows PK concentrations at week 4 predose of ADA positive patients coincide with the concentration of ADA negative patients. 90% confidence interval (CI) of geometric mean ratio (GMR) of tremelimumab concentration in ADA positive vs ADA negative mostly ranges between 0.75 and 1, which is closed to 1. The result showed no difference for tremelimumab concentrations in patients who tested ADA positive vs ADA negative. For safety, there is also no identifiable trend of IRR occurrence vs ADA incidence (Table 9Table 8). Due to the low occurrence of ADA, there is no formal analysis done to assess the impact of ADA on effectiveness of tremelimumab.

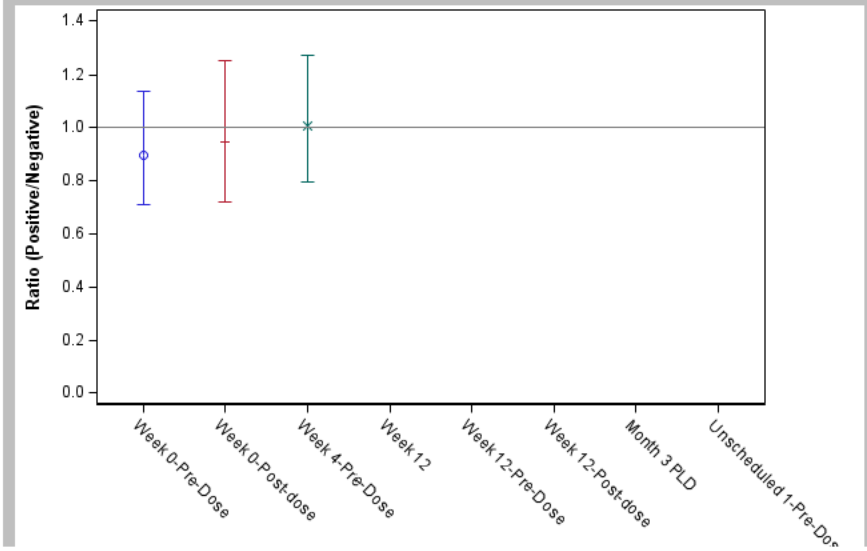
**Table 8 $CL_{ss}$ and $AUC_{0\text{-}INF}$ derived from tremelimumab PPK models for ADA positive and ADA negative individuals who received a single dose of tremelimumab 300 mg**

| Parameter Geometric Mean | Number of observations (N) | Mean of Predicted $AUC_{0\text{-}INF}$ (μg/mL*day) | Mean of CLss (L/day) |
|---|---|---|---|
| **ADA+ tremelimumab** | **20** | **1147** | **0.26** |

| | | | |
|---|---|---|---|
| **ADA- tremelimumab** | **153** | **1105** | **0.25** |

Data Source: FDA analysis

**Figure 4 By sample analysis for ratio of tremelimumab concentrations in patients who tested ADA positive vs who tested ADA negative.**




Data Source: FDA analysis

**Table 9 Infusion reaction in patients with tremelimumab ADA positive vs ADA negative.**

| **Patient # (%)** | **Treme 300 mg x1 dose + Durva 1500 mg Q4W** | |
|---|---|---|
| | ADA + (N=20) | ADA- (N=153) |
| IRR Aes | 2(10%) | 10 (7.3%) |
| ≥ grade 3 IRR | 0 | 1 (0.7%) |

Source: BLA table 14.3.9.2

- FDA disagrees with the Applicant's position that there is no impact of ADA against durvalumab on the PK of durvalumab. Reduction of geometric mean durvalumab concentrations at week 12 predose was observed in patients who developed ADA with 90% CI of GMR of durvalumab median concentration of 0.1 and 0.4 (Figure 5). Due to low ADA incidence of 3.2% (9/279), the

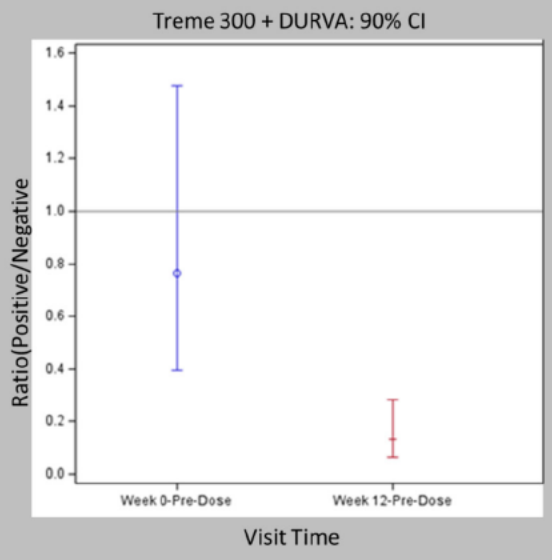
insufficient data prevent the assessment whether observed the ADA-associated exposure decrease reduced effectiveness. There were no infusion reactions of any grade observed in ADA positive patients (Table 10).

**Table 10 Infusion reaction in durvalumab's ADA positive vs ADA negative patients.**

| Patient # (%) | Treme 300 mg x1 dose + Durva 1500 mg | |
|---|---|---|
| | ADA + (N=9) | ADA- (N=270) |
| IRR Aes | 0 | 16 (5.9) |

Data Source: BLA table 14.3.9.2

**Figure 5 Reduction of durvalumab concentrations on week 12 pre-dose in patients with ADA positive status compared to patients with ADA negative status**




Data Source: FDA analysis

### 6.3.2. Clinical Pharmacology Questions

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

Data:
See Section 8.1.2 efficacy results and Section 6.3.1 general pharmacology and pharmacokinetics.

The Applicant's Position:
The clinical pharmacology program provides evidence that the selected dose and schedule of tremelimumab 300 mg as a single priming dose in combination with durvalumab 1500 mg at Cycle 1/Day 1, followed by durvalumab as monotherapy Q4W offers benefit for patients with uHCC based on a statistically significant and clinically meaningful OS benefit vs sorafenib (HR: 0.78 [96.02% CI: 0.65, 0.93]) in the HIMALAYA study.

The PPK indicated that there is no need for dose adjustment for durvalumab or tremelimumab in special populations, based on baseline patient characteristics (clinically relevant change was defined as ≥ 30% change).

The ER efficacy analysis showed there was no clear relationship between body weight and efficacy (OS and PFS) or any safety endpoints evaluated in patients treated with durvalumab and tremelimumab in HIMALAYA.

The FDA's Assessment:

- FDA agrees with Applicant's position that for efficacy, ER analysis showed no significant relationship between durvalumab or tremelimumab exposures and efficacy (OS and PFS). For safety, no significant correlation between durvalumab or tremelimumab PK exposures and safety events was found, including treatment-related AEs, Grade 3+ AEOSI, and treatment discontinuation.
- FDA agrees with Applicant's position that fixed dose regimen and BW-based dose have similar exposures of durvalumab and tremelimumab. This conclusion is supported by study 22, where similar Cmax and Ctrough were observed following the weight-based and the equivalent fixed dosing regimen of durvalumab and tremelimumab.

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

Data:
See Section 6.2.2.1 general dosing and Section 6.3.1 general pharmacology and pharmacokinetics.

The Applicant's Position:
The dosing regimen of T 300 mg as a single priming dose in combination with durvalumab 1500 mg at Cycle 1/Day 1, followed by durvalumab as monotherapy Q4W is appropriate as 1L treatment of patients with uHCC, the indication being sought for this submission. This dosing regimen was supported by the clinical efficacy and safety data from patients with uHCC in HIMALAYA, and PPK and ER analyses that included data from HIMALAYA.

The FDA's Assessment:
FDA agrees with Applicant's position that the dosing regimen of T300 +D was also supported by

pharmacodynamic, clinical efficacy and safety data from dose finding study 06 and study 22.

Regarding tremelimumab dose selection

- In Study 06, tremelimumab was studied in patients with metastatic NSCLC following doses 1 mg/kg, 3 mg/kg, and 10 mg/kg administered once every 4 weeks (Q4W). Dose level 1mg/kg or 75 mg tremelimumab in combination with durvalumab Q4W (T75 +D) was selected in the dose finding Study 06 as tremelimumab 3 mg/kg Q4W exceeded MTD.

- Based on results from Study 06, Study 22 further evaluated the dose level of T75+D and a single higher dose of tremelimumab 300 mg in combination with durvalumab (T300+D) in patients with advanced HCC. Applicant predicted a single higher dose instead of four repeated doses might provide a higher PD effect with a reduced toxicity. In addition to evaluation of combination arms, Study 22 included two monotherapy arms: durvalumab monotherapy 1500 mg Q4W(D) and tremelimumab monotherapy 10 mg/kg or 750 mg every 12 weeks (Q12W) for 7 doses(T750).

- T300+D arm was selected from study 22 because it has the highest confirmed ORR (24.0%). A benefit-risk assessment based on results from Study 22 showed that the efficacy of both T75+D and T750 was not superior to the durvalumab arm. Patients in the T300+D arm showed the highest confirmed ORR (Table 11).

**Table 11 Study 22 –tremelimumab summary of clinical activity**

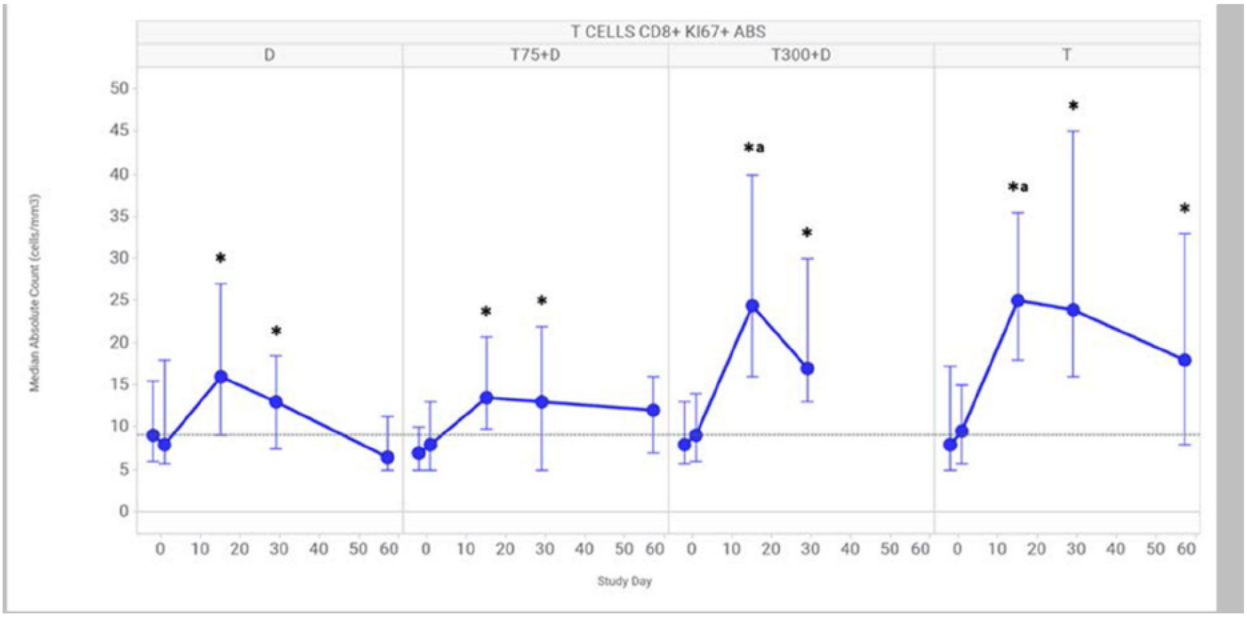
| **Study**<br>**Analysis set** | | **Study 22 (Parts 2 and 3)** | | |
|---|---|---|---|---|
| | **T300+D (N=75)** | **D (N=104)** | **T75+D (N=84)** | **T750 (N=69)** |
| **Tumor response assessment** | | BICR per RECIST 1.1 | | |
| **Confirmed ORR, N (%)** | 18 (24.0) | 12(11.9) | 8 (9.5) | 5 (7.2) |
| **Complete Response** | 1 (1.3) | 0 | 2 (2.4) | 0 |
| **Median DoR from onset of response (months)** [a] | 18.43 | 11.17 | 13.21 | 23.95 |

Data source: BLA Table 14.2.6.7.4

- T300+D also showed more robust PD activities. Across treatments, median CD8+Ki67+ T cells

were statistically elevated above median baseline values with peak increases on Day 15. In Figure 6, median CD8+Ki67+ T cells on Day 15 for treatment arm T300+D were statistically greater than those observed in patients receiving D or T75+D. T300+D reached a potential saturable PD effect on median CD8+ as treatment arms T300+D and T750 had comparable median CD8+ counts.

**Figure 6 Median CD8+Ki67+ T cell absolute counts (cells/mm$^3$) over time across treatment arms**

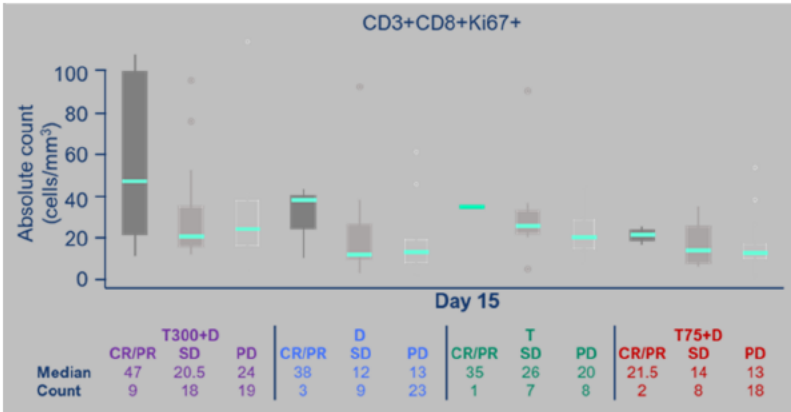



* Denotes statistically significant elevations above median baseline value ($p < 0.01$ by Wilcoxon Signed-Rank test); ** denotes values statistically significantly elevated ($p < 0.01$) above that of patients receiving D or T75+D by Wilcoxon pairwise comparisons.

Source: Appendix 16.1.15, Bioanalytical Report G-BI-0188, Figure 6.2-2.

- T300+D pool was enriched in CD8+ cells, which correlated with ORR. Associations were observed between median CD8+Ki67+ T cell counts and patients stratified by BOR categories of CR/PR. Noted that median CD8+Ki67+ T cell counts from patients with CR/PR were elevated at the highest levels above those of stable disease(SD) and partial disease(PD) (Figure 7Figure 7).The proliferating CD8+Ki67+ T cell counts were associated with response in all 4 treatment arms supporting that the proposed mechanism of enhanced immune activation of CD8 may lead to a better response rate in patients. Most importantly, there is a higher count of CR/ PR (9 patients) in the T300+D arm coupled with highest median CD8+Ki67+ T cells (47 cell/mm$^3$). This result suggests that the robust PD activity in T300+D arm may correlate with higher response rate.

**Figure 7 CD8+Ki67+ T Cell absolute counts (cells/mm$^3$) on day 15 in patients stratified by response category across treatments**




| | T300+D | | | D | | | T | | | T75+D | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CR/PR | SD | PD | CR/PR | SD | PD | CR/PR | SD | PD | CR/PR | SD | PD |
| Median | 47 | 20.5 | 24 | 38 | 12 | 13 | 35 | 26 | 20 | 21.5 | 14 | 13 |
| Count | 9 | 18 | 19 | 3 | 9 | 23 | 1 | 7 | 8 | 2 | 8 | 18 |

Elevated CD8+Ki67+ T cells on day 15 are associated with CR/PR

Highest median CD8+Ki67+ T cells occurred in CR/PR in T300+D arm

Data source: Applicant's AOM

- Overall results supported the hypothesis that tremelimumab's PD and efficacy response may associate with the first dosing cycle. A single dose of tremelimumab of 300 mg has accomplished a better PD effects and efficacy outcome compared to multiple doses of tremelimumab 75 mg Q4W x4.

Regarding durvalumab dose selection
FDA agrees with Applicant's position based on the following efficacy, safety, and PD evidence. The effectiveness of durvalumab 1500 mg Q4W is supported by Study 06, study 22 and HIMALAYA.

- Study 06 showed that a complete sPD-L1 suppression was maintained in all patients who received durvalumab 20 mg/kg Q4W.
- Study 22 showed Cmax and Ctrough values of durvalumab following dosing with 20 mg/kg Q4W and fixed 1500 mg dose Q4W were similar.
- Current dose selection of durvalumab in combination with tremelimumab is in agreement with the previous approved dosage of durvalumab monotherapy in Stage III NSCLC, which is a weight based dosing of 10 mg/kg Q2W or a fixed regimen 1500 mg Q4W.

FDA also agrees with Applicant's proposed body weight based dose selection for patients with body weight less than 30 kg to receive equivalent of durvalumab 20 mg/kg Q4W with a single tremelimumab 3 mg/kg dose based on the following rationales:

- No patients **<30 kg** included in study 22 or HIMALAYA. The safety profile of the fixed dose regimen in patients with extremely low body weight (less than 30 kg) is unknown. Body weight based dosing is an acceptable approach to prevent over-exposure in these patients.
- It was also justified from the approval durvalumab dosing regimen, which has a body weight cutoff at 30 kg as BW-based dosing for < 30 kg and flat dosing for ≥ 30 kg.

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

Data:
See Section 6.2.2.2 therapeutic individualization.

The Applicant's Position:
The PPK analysis supports the conclusion that there is no need for dose adjustment for durvalumab or tremelimumab based on these intrinsic and extrinsic factors.

The FDA's Assessment:
FDA agrees with Applicant's position.

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

Data:
No food-drug or drug-drug interaction studies have been conducted for tremelimumab or durvalumab. PK drug-drug interaction of durvalumab or tremelimumab with other therapeutics is not anticipated given that durvalumab and tremelimumab are not primarily cleared via hepatic or renal pathways; instead, the primary elimination pathways are protein catabolism via reticuloendothelial system or target-mediated disposition. Durvalumab and tremelimumab are not expected to induce or inhibit the major drug metabolizing cytochrome P450 pathways.

The Applicant's Position:
There are no clinically relevant food-drug or drug-drug interactions with durvalumab in combination with tremelimumab in patients with uHCC.

The FDA's Assessment:
FDA agrees with Applicant's position.

X X

Primary Reviewer Team Leader

# 7. Sources of Clinical Data

## 7.1.Table of Clinical Studies

Data:
An overview of the clinical studies supporting the efficacy and safety of the submission is in Table 12.

**Table 12 Summary of Clinical Studies Included in the Submission Package**

| **Study Name (Study Number) Status DCO** | **Phase Study Design** | **Patient Population** | **No. of Patients Assigned and Treated (Treatment Group)** |
|---|---|---|---|
| **Studies in HCC** | | | |
| **HIMALAYA (D419CC00002)** Ongoing 27 Aug 2021 | Phase III Randomized, open-label, comparative, multicenter | Advanced HCC with no prior systemic therapy for HCC | 1324 (total) 393 (T300+D) 389 (D) 389 (Sorafenib) 153 (T75+D) |
| **Study 22 (D4190C00022)** Complete 06 Nov 2020 | Phase II Randomized, open-label, comparative, multicenter | Advanced unresectable HCC | 326 (total) 74 (T300+D) 101 (D) 82 (T75+D) 69 (T) |
| **Studies in other cancer types** | | | |
| **Study 1108 (D4190C00001)** Complete 16 Oct 2017 | Phase I Open-label, dose-escalation, dose-expansion | Advanced solid tumors, including NSCLC, UC, and SCCHN | 1022 D (total) 27 in dose-escalation 995 in dose-expansion |
| **Study 06 (D4190C00006)** Complete 19 Nov 2017 | Phase Ib Open-label, dose-escalation, dose-expansion | Advanced NSCLC | 379 D + T (total) 102 in dose-escalation 277 in dose-expansion |
| **Study 10 (D4190C00010)** Complete 11 Apr 2018 | Phase I Open-label, dose-escalation, dose-expansion | Advanced solid tumors | 379 D + T (total) 20 in dose-exploration 359 in dose-expansion |
| **Japan Study 02 (D4190C00002)** Complete 31 Mar 2018 | Phase I Open-label, multicenter | Advanced solid tumors | 140 (D) 124 (D + T) |

**Table 12 Summary of Clinical Studies Included in the Submission Package**

| Study Name (Study Number) Status DCO | Phase Study Design | Patient Population | No. of Patients Assigned and Treated (Treatment Group) |
|---|---|---|---|
| **ARCTIC (D4191C00004)** Complete 09 Feb 2018 | Phase III Randomized, open-label, multicenter | Locally advanced or metastatic NSCLC | 595 (total)<br>126 (Substudy A)<br>62 (D)<br>63 (SoC)<br>460 (Substudy B)<br>117 (D)<br>173 (D + T)<br>110 (SoC)<br>60 (T) |
| **MYSTIC (D419AC00001)** Ongoing 04 Oct 2018 | Phase III Randomized, open-label, multicenter | Advanced or metastatic NSCLC | 1092 (total)<br>369 (D)<br>371 (D + T)<br>352 (SoC) |
| **CONDOR (D4193C00003)** Complete 27 Aug 2018 | Phase II Randomized, open-label, multicenter | Recurrent or metastatic SCCHN not amenable to therapy with curative intent | 267 (total)<br>67 (D)<br>67 (T)<br>133 (D + T) |
| **EAGLE (D4193C00002)** Complete 10 Sep 2018 | Phase III Randomized, open-label, multicenter | Recurrent or metastatic SCCHN not amenable to therapy with curative intent | 723 (total)<br>237 (D)<br>246 (D + T)<br>240 (SoC) |
| **HAWK (D4193C00001)** Complete 05 Oct 2018 | Phase II Single arm, open-label, multicenter | Recurrent or metastatic SCCHN | 112 D (total) |
| **PACIFIC (D4191C00001)** Complete 22 Mar 2018 | Phase III Randomized, Double-blind, multicenter | Locally advanced or metastatic NSCLC | 713 (total)<br>476 (D)<br>237 (placebo) |
| **ATLANTIC (D4191C00003)** Complete 03 June 2016 | Phase II Non-comparative, open-label, multicenter | Locally advanced or metastatic NSCLC | 444 D (total) |
| **NEPTUNE (D419AC00003)** Ongoing 24 June 2019 | Phase III Randomized, open-label, multicenter | Advanced or metastatic NSCLC | 809 (total)<br>410 (D + T)<br>399 (SoC) |
| **DETERMINE (D4880C00003)** Complete 24 Jan 2016 | Phase II Randomized, double-blind, placebo-controlled | Unresectable pleural or peritoneal malignant mesothelioma | 569 (total)<br>380 (T)<br>189 (placebo) |

**Table 12 Summary of Clinical Studies Included in the Submission Package**

| Study Name (Study Number) Status DCO | Phase Study Design | Patient Population | No. of Patients Assigned and Treated (Treatment Group) |
|---|---|---|---|
| **D4884C00001** Complete 31 Dec 2018 | Phase II Open-label, multicentre | Advanced and metastatic solid tumors including urothelial bladder cancer, pancreatic ductal adenocarcinoma, and triple-negative breast cancer | 64 (Total) 64 (T) |
| **Study 11 (D4190C00011)** Complete 08 Nov 2017 | Phase I Open-label, multicenter | Recurrent or metastatic SCCHN | 71 (D+T) |
| **Study 21 (D4190C00021)** Complete, 18 Oct 2019 | Phase Ib/II Multicenter | Metastatic or recurrent gastric or gastroesophageal junction adenocarcinoma, gastric adenocarcinoma | 113 (total) 77 (D+T) 24 (D) 12 (T) |
| **DANUBE (D419BC00001)** Complete 27 Jan 2020 | Phase III Randomized, open-label, multicenter | Unresectable urothelial carcinoma | 1032 (total) 346 (D) 342 (D+T) 344 (SoC) |
| **KESTREL (D419LC00001)** Complete 06 Jul 2020 | Phase 3 Randomized, open-label, multicenter | Recurrent or metastatic SCCHN | 823 (total) 202 (D) 408 (D+T) 206 (SoC) |

Abbreviations: D, durvalumab monotherapy given at a dose of either 10 mg/kg Q2W IV (or equivalent) or 20 mg/kg Q4W IV (or equivalent) for any line of therapy (across tumor types); DCO, data cutoff; HCC, hepatocellular carcinoma; NSCLC, non-small-cell lung cancer; Q4W, every 4 weeks; SCCHN, squamous cell carcinoma of the head and neck; SoC, standard of care; T, tremelimumab; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, tremelimumab 75 mg for 4 doses in combination with durvalumab 1500 mg Q4W; UC, urothelial carcinoma.

The Applicant's Position:

The primary evidence supporting the efficacy and safety claims in the proposed indication is based on the final analysis of the HIMALAYA study. Study 22 provides supportive efficacy and safety in the proposed indication. All other studies in Table 12 were included in safety pools as described in Section 8.2.

The FDA's Assessment:

FDA agrees with the Applicant's description of the HIMALAYA trial (D419CC00002) and Study 22 (D4190C00022). The clinical data supporting the FDA's assessment of efficacy and safety were based primarily on the results of the HIMALAYA trial (D419CC00002). FDA agreed that the additional clinical studies listed in Table 7 were acceptable to be submitted as pooled data to support the safety evaluaton of the T300+D regimen.

# 8. Statistical and Clinical Evaluation

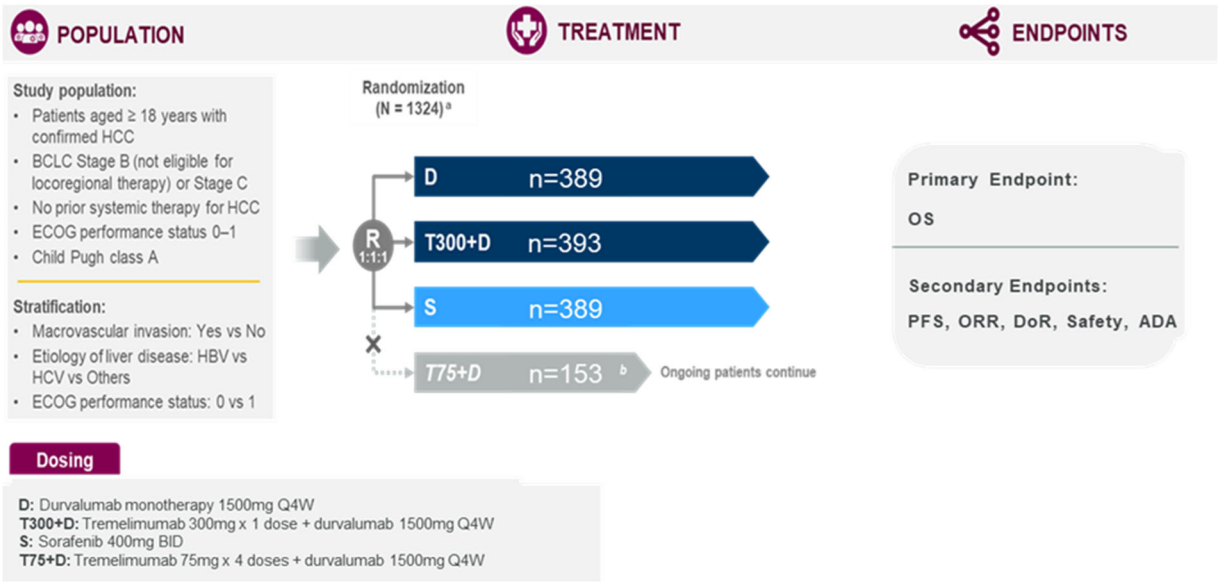
## 8.1.Review of Relevant Individual Trials Used to Support Efficacy

### 8.1.1. Pivotal HIMALAYA study (D419CC00002)

**Trial Design**

The Applicant's Description:
HIMALAYA is a randomized, open-label, sponsor-blind, multicenter, global, Phase III study to assess the efficacy and safety of T300+D and of D vs S in the treatment of patients with uHCC who are not eligible for locoregional therapy and have not received prior systemic therapy for HCC. The study was planned to randomize approximately 1310 patients in a 1:1:1:1 ratio to 4 treatment arms: D, T75+D, and T300+D and S; however, enrollment into the T75+D arm was closed after a total of 155 patients were enrolled following a benefit-risk assessment based on results from a pre-planned IA of Study 22. This analysis showed that while both the tremelimumab-containing regimens were tolerable, the efficacy of the T75+D arm did not meaningfully differentiate from the D arm. Patients already randomized and receiving treatment with T75+D could continue assigned study treatment, provided the Investigator and patient agreed it was in the best interest of the patient. The patients enrolled after T75+D arm closure were randomized in a 1:1:1 ratio to the D, T300+D, and S arms. Figure 8 shows the design of the study.

**Figure 8 HIMALAYA: Study Design**




a Patient numbers shown correspond to the actual enrollment.
B Enrollment into the T75+D arm was closed following protocol edition 4.0 (29 November 2018). Patients randomized to T75+D prior to protocol amendment 3 could continue on their assigned study treatment, provided the Investigator and patient agreed this was in the patient's best interest. Patients randomized to T75+D arm who had not completed or started all 4 doses of tremelimumab could either complete the full schedule or continue with durvalumab monotherapy only .

**Trial location:** Europe, Russia, Asia Pacific, US/Canada, Brazil

**Choice of control group:** Sorafenib, an oral multi-kinase inhibitor that suppresses tumor neo-angiogenesis and proliferation, is the SoC in uHCC. Sorafenib at a dose of 400 mg BID (orally) was chosen as the comparator arm in the HIMALAYA study.

**Key inclusion/exclusion criteria:** Eligible patients were adults (≥ 18 years) with histologically confirmed HCC who had not received prior systemic therapy for HCC and were not eligible for locoregional therapy for uHCC. At enrollment, patients were required to have an ECOG PS of 0 or 1 with a life expectancy of at least 12 weeks. In addition, patients were also required to have at least 1 target lesion per RECIST 1.1. Key exclusion criteria included patients co-infected with HBV and HCV, patients with main portal vein thrombosis on baseline imaging, active/prior documented gastrointestinal bleeding within 12 months, and use of any concurrent chemotherapy, study drug, or biologic or hormonal therapy for cancer treatment.

**Dose selection and regimens:** Assuming an average body weight of 75 kg, the following dose regimens were selected for HIMALAYA: Durvalumab monotherapy = durvalumab 1500 mg Q4W (equivalent to 20 mg/kg Q4W); T75+D = durvalumab 1500 mg Q4W + tremelimumab 75 mg Q4W for 4 doses; T300+D = durvalumab 1500 mg + tremelimumab 300 mg for 1 dose, followed by durvalumab 1500 mg monotherapy Q4W. S 400 mg orally BID was based on the approved product label.

**Assignment to treatment and blinding:** HIMALAYA is a randomized, open-label study. Eligible patients were centrally randomized to treatment using the interactive voice response system. Patients were stratified according to MVI (yes vs no), etiology of liver disease (confirmed HBV vs confirmed HCV vs others), and PS (ECOG 0 vs 1). Patients and investigators were not blinded to the study treatments, due to the unique safety profile differences between durvalumab and tremelimumab compared with sorafenib, and the different routes of administration (IV for durvalumab and tremelimumab, oral for sorafenib), which would cause undue burden to patients if given in a blinded manner. The Sponsor, however, was blinded to treatment assignment and did not have access to any aggregate summaries by treatment arm during the study.

**Dose modification and discontinuation:** Weight-based dosing modifications were applied for durvalumab (20 mg/kg Q4W) and tremelimumab (1 mg/kg Q4W for T75+D and 4 mg/kg for T300+D) if a patient's weight decreased to ≤ 30 kg, and after consultation between the Investigator and the study physician. Once the patient's weight increased to > 30 kg, the patient was to receive the original assigned fixed dose of durvalumab 1500 mg Q4W with or without tremelimumab. Suspected sorafenib-related toxicities were managed based on the approved product label for each country. Treatment through progression was allowed at the Investigator's discretion for all arms if patients were considered to still be receiving benefit.

**Administrative structure:** An IDMC was established to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in this study, to ensure the integrity of the study, and to oversee the 2 planned interim analyses. The IDMC is composed of individuals external to the Sponsor.

**Procedures and schedule:** The tumor assessments were to be performed at screening as baseline, with follow-up at Week 8 ± 1 week from the date of randomization, at Week 12 ± 1 week from the date of randomization, and then every 8 weeks ± 1 week until confirmed objective disease progression.

**Concurrent medications:** Concomitant medications or treatments deemed necessary to provide adequate prophylactic or supportive care could be prescribed by the Investigator (unless identified as

"prohibited" in the CSP). Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc.]) was provided as necessary for all patients.

**Subject completion, discontinuation, or withdrawal:** Patients could voluntarily discontinue study treatment or withdraw from the study at any time. Survival follow-up was to continue until the end of the study unless the patient expressly withdrew their consent.

The FDA's Assessment:
FDA generally agrees with the Applicant's description of the HIMALAYA study design. Although sorafenib is approved for the first-line treatment of unresectable HCC, patients may also receive atezolizumab in combination with bevacizumab, which demonstrated an overall survival and progression-free survival improvement compared to sorafenib (HR for OS = 0.58; 95% CI: 0.42, 0.79; p=0.0006 and HR for PFS = 0.59; 95% CI: 0.47, 0.76; p=<0.0001), provided treatment with bevacizumab is appropriate. FDA notes that the HIMALAYA trial allowed enrollment of patients with esophageal varices unless there had been active or prior documented gastrointestinal bleeding within 12 months of study enrollment. Esophagogastroduodenoscopy was not mandated prior to enrollment but adequate endoscopic therapy, according to institutional standards, was required for patients with a history of esophageal variceal bleeding or those assessed at high risk for esophageal variceal bleeding as determined by the treating physician. No conclusions can be made regarding the benefit of treatment beyond progression as no formal analysis was conducted.

**Study Endpoints**

**The Applicant's Description:**

The primary efficacy endpoint is OS defined as the time from the date of randomization until death due to any cause. For the primary endpoint, OS is to be compared between the T300+D and S alone groups for superiority. For the key secondary endpoints, OS is to be compared between the D and S groups first for NI and then for superiority.

Objective response rate, landmark analyses of OS and PFS, DoR, TTP, DCR, PK parameters, assessments of HRQoL by PROs, and immunogenicity by presence of ADAs are other secondary endpoints.

The FDA's Assessment:
FDA agrees with the Applicant's description of the study endpoints.

**Statistical Analysis Plan and Amendments**

The Applicant's Description:
The formal statistical analysis of OS (primary endpoint) was performed for the following efficacy test hypotheses (alternative hypotheses):

- H1 (primary): Difference between T300+D and S arms (for superiority).
- H2 (key secondary): D is not inferior to S with NI margin of 1.08.
- H3 (key secondary): Difference between D and S (for superiority).

If all the OS analyses were considered successful (ie, superiority tests were statistically significant and non-inferiority was achieved), the 4.9% alpha level would be passed to test the difference in the 3-year survival rates (OS36) between T300+D and S.

No formal statistical analysis was conducted for the T75+D arm since it was closed for enrollment with protocol amendment 3.

**Analysis Sets**

All efficacy analyses were performed on the FAS (intent-to-treat population), which includes all randomized patients, including patients who were randomized in error.

The SAS consists of all patients who received any amount of IP(s) (durvalumab, tremelimumab, or sorafenib), including patients who were randomized in error or not randomized and still started on treatment.

The PK analysis set included all patients who received at least 1 dose of IP(s) for whom any PK post-dose data were available.

The durvalumab ADA evaluable set consists of all patients in the SAS who have a non missing baseline durvalumab ADA and at least 1 non-missing post-baseline durvalumab ADA result.

**Multiple Testing Strategy**

There were 2 interim analyses and a final analysis planned for this study. To strongly control the family-wise error rate at the 5% level (2-sided), an alpha level of 0.1% was spent on the interim ORR and DoR analysis (IA1), while the remaining 4.9% alpha level was spent on all OS analyses. The primary objective of OS was tested (H1: T300+D vs S) with 4.9% for this comparison.

**Interim Analyses of OS**

One interim analysis for ORR was planned after a minimum of 100 subjects in the T300+D and D arms had the opportunity for 32 weeks of follow-up and not prior to the last patient enrolled (IA1). When the IA1 DCO was declared (02 September 2019), a total of 470 patients in the T300+D and D arms combined had reached 32 weeks of follow-up.

An OS interim analysis was planned when approximately 404 OS events occurred in the T300+D and S combined (~52% maturity), approximately 30 months after the first subject was randomized (IA2). When the IA2 DCO was declared (22 May 2020), 415 OS events had occurred in the T300+D and S arms combined.

**Final Analysis**

The final analysis was to be performed when there had been approximately 515 OS events in the T300+D and S arms combined (~67% maturity), approximately 37.5 months after the first patient was randomized. The DCO date for the final analysis was 27 August 2021, 46 months after the first patient was randomized. At the DCO, there had been 555 OS events in the T300+D and S arms combined (71% maturity).

**Subgroup Analyses**

Efficacy subgroup analyses were conducted comparing OS between T300+D vs S, D vs S, and T300+D vs D for the following subgroups of the FAS, as defined prior to database lock: etiology of liver disease

(confirmed HBV, confirmed HCV, others), as determined by virology laboratory assessments conducted at screening; serum AFP level (< 400 ng/mL, ≥ 400 ng/mL); MVI (yes, no), defined as tumoral MVI of hepatic and/or portal vein branches; EHS (yes, no), defined as distant metastases on pathology at screening; MVI = yes and/or EHS = yes; MVI = no and EHS = no; PD-L1 expression level (TIP ≥ 1% [positive], TIP < 1% [negative]; ECOG PS at screening (0, 1); BCLC score at study entry (B, C); sex (M, F); age at randomization (< 65 years, ≥ 65 years); and region (Asia excluding Japan, Rest of World including Japan).

The FDA's Assessment:

FDA agrees with the Applicant's description of the statistical analysis plan (SAP). OS was analyzed using stratified log-rank test and hazard ratio (HR) was estimated using stratified Cox proportional hazard model, with stratification factors of etiology of liver disease, ECOG Performance status and macrovascular invasion collected at randomization. The original SAP (version date: 25 October 2017) was amended 3 times with key changes summarized below:

Amendment 1 (version date: 23 August 2019)

- Updated protocol deviations list.
- Defined prior and concomitant medications.
- Added a clarification that p-value for survival will be obtained from log-rank test.
- Added timing and statistical analysis details for IA1.
- Specified ORR analyses at different timepoints.
- Updated best objective response (BoR) definition to reflect study schedule.
- Added Cochran–Mantel–Haenszel (CMH) analysis as requested by FDA.
- Added details about patient reported outcomes (PRO) plots and compliance tables.
- Removed Arm T75+D from formal comparisons and including for descriptive purposes.
- Changed study objective to compare Arm T300+D vs. D from secondary objectives to exploratory objectives.
- Added max-combo test to OS sensitivity analyses.
- Corrected incomplete dates imputation rules.
- Corrected disease control rate (DCR) definition.
- Added new secondary and exploratory endpoints.

Amendment 2 (version date: 15 May 2020)

- Added ECOG 0/1 to the target patient population criteria.
- Added power calculations and design assumptions for the noninferiority analysis.
- Clarified multiple testing procedure and alpha recycling. Clarified that adjusted alpha levels for OS analyses will be performed using Lan and DeMets approach that approximates the O'Brien Fleming spending function for both the primary and key secondary analyses.
- Clarified that ORR and DoR for both confirmed and unconfirmed responses will be analyzed at IA2 and final analysis (FA) according to Investigators' assessments per RECIST 1.1. Removed BICR RECIST 1.1 and BICR mRECIST 1.1 ORR analyses at IA2 and FA.
- Added the anticipated number of events across Arms D and S, significance levels for H2 and H3 at the time of IA2 and FA, and confidence interval levels to be applied for the non-inferiority comparisons at IA2 and FA based on the anticipated number of events.
- Clarified that for subgroup analyses, stratification factor values collected from the eCRF will be

used to define subgroups.
- Added additional details of the non-inferiority analysis.
- Removed PRO endpoints of EORTC QLQ C30 time to deterioration (TTD) in physical functioning, EORTC QLQ C30 TTD in fatigue, EORTC QLQ C30 TTD in appetite loss, EORTC QLQ C30 TTD in nausea, and EORTC QLQ HCC18 TTD in abdominal pain from the multiple testing plan. Clarified that the analysis set for EORTC QLQ-C30 time to symptom deterioration will consist of a subset of FAS patients who have a baseline symptom score ≤90.
- Added additional details for mixed model repeated measures (MMRM) model. Clarified that MMRM estimates should only be summarized for visits where scores for at least 25% of patients in both treatment arms are available.
- Clarified that safety and PRO visit windows should be applied until the last dose of study treatment + 90 days rather than until PD.
- Clarified that the primary PRO comparisons will be between immunotherapy arms (Arm D, Arm T300+D) and Arm S.
- Added additional subgroup analysis.
- Changed the max-combo test from a sensitivity analysis for OS to an exploratory analysis.
- Updated cutoff for the summaries of most common AEs to be 10%.
- Updated imputations of completely missing end dates for AEs and concomitant medications.

Amendment 3 (version date: 30 July 2021)

- Added the statistical margin for the non-inferiority comparison and clarified that 1.08 is the clinical non-inferiority margin.
- Added analyses for ORR subgroups at IA1, IA2, and FA. Clarified that the ORR subgroup analysis at IA1 will use BICR data.
- Added a summary to compare BoR by Investigator assessment to BoR by BICR assessment for the FAS-32w. FAS-32w is defined as an analysis set for the subset of subjects randomized >= 32 weeks prior to IA1 DCO.
- Clarified multiple testing procedure and alpha recycling.
- Added OS sensitivity analysis for assessing the impact of COVID-19.
- Added a test of OS at 36 months.
- Clarified the two stage-method (Latimer 2018) will be the primary method for the treatment switch analysis and that a Weibull mixture cure model will be fit to adjust for subsequent therapy initiation.
- Changed the region group to (Asia (except Japan) versus Rest of World (includes Japan)).
- Clarified that subjects who are unable to read PRO questionnaires will be excluded from compliance calculations.
- Added additional secondary and exploratory endpoints.

In addition, based on the final SAP (version date: 30 July 2021), FDA adds the following details regarding the proposed analyses:

- OS was analyzed using a stratified log-rank tests adjusting for etiology of liver disease (confirmed HBV vs. confirmed HCV vs. others), ECOG (0 vs. 1), and macrovascular invasion (yes vs. no). Hazard ratio (HR) and the corresponding confidence intervals (Cis) were estimated from stratified Cox proportional hazards model using the same stratification variables as stratified

log-rank test. The stratification variables used were the values recorded in the randomization system (IWRS).

- At IA1, only descriptive summaries of ORR by investigator assessment (per RECIST 1.1) and BICR (per RECIST 1.1 and mRECIST) including exact 95% Cis were presented for each of the four treatment arms for FAS-32w. At IA2 and FA, the investigator assessed ORR per RECIST 1.1 was compared between Arms T300+D vs. S and Arms D vs. S in the FAS. Logistic regression models adjusting for the randomization stratification factors would be presented to calculate odds ratio together with its associated profile likelihood 95% CI. A Cochran Mantel–Haenszel (CMH) test stratified by randomization stratification factors would also be employed to calculate odds ratios and p-values.
- The clinical noninferiority margin of HR 1.08 was determined using 95%-95% fixed margin approach (FDA Guidance 2016; EMEA Guideline 2005) based on two phase 3 trials of sorafenib (Llovet 2008 and Cheng 2009) in first-line HCC and assuming conservative 60% retention. Given that the Applicant is not seeking an indication for durvalumab monotherapy, FDA did not conduct a detailed assessment of the appropriateness of a non-inferiority claim based on this margin.

**Protocol Amendments**

The Applicant's Description:

The original CSP, dated 09 August 2017, was subject to 6 global amendments. Important amendments to the original study protocol, including those amendments that came into effect with respect to the recruitment of patients, and other significant changes to study conduct are summarized in Table 13. None of the modifications to the protocol had any impact on the integrity of the trial or interpretations of the results.

**Table 13: Protocol Amendments and Other Significant Changes to Study Conduct**

| Amendment Number/ Date | Key Details of Amendment |
|---|---|
| Amendment 1<br>Protocol version 2.0<br>20 December 2017 | • Updated descriptions of risks for durvalumab, tremelimumab, and the combination of durvalumab with tremelimumab. Toxicity Management Guidelines replaced with new version from 01 November 2017.<br>• Inclusion of the exploratory objective: to assess PFS from rechallenge in the durvalumab plus tremelimumab combination arms only, and to assess PFS from the first post IP discontinuation therapy in all arms<br>• Updated inclusion and exclusion criteria to ensure patients received antiviral medication as clinically indicated, for compliance with new CSP template, to clarify protocol definition of clinically meaningful ascites, to exclude a history of or current brain metastases<br>• Updated AEOSI terminology |
| Amendment 2<br>Protocol version 3.0<br>23 January 2018 | • No major updates – released to correct errors noted in CSP version 2.0 |

| Amendment Number/ Date | Key Details of Amendment |
|---|---|
| Amendment 3<br>Protocol version 4.0<br>29 November 2018 | • Enrollment into the T75+D arm was closed based on results from a pre-planned IA evaluating tolerability and clinical activity in Study D419CC00022. All other arms were unchanged.<br>• Subsequent updates to primary and secondary objectives, the multiple testing procedure strategy, and sample size based on closeout of T75+D arm<br>• Update such that IA1 was performed after approximately 100 patients per treatment arm had the opportunity for 32 rather than 24 weeks of follow-up<br>• Amended exclusion of patients with inferior vena cava thrombosis |
| Amendment 4<br>Protocol version 5.0<br>17 December 2018 | • No major updates – released to correct errors noted in CSP version 4.0 |
| Amendment 5<br>Protocol version 6.0<br>20 August 2019 | • The primary analysis was revised to change the dual primary objectives to a hierarchical approach with a single primary objective (T300+D vs S for superiority) and 2 key secondary objectives (D vs S for NI, then D vs S for superiority) of OS based on an IA of the ongoing Study 22<br>• Subsequent updates to efficacy assessments in IA1 and the order of hypotheses for superiority were changed based on the revision to the primary analysis.<br>• Added an exploratory objective relating to patients with early mortality risk |
| US Edition 1.0<br>21 February 2020 | • Changes made to address FDA comments received for global Protocol version 6.0 (20 August 2019) regarding non-inferiority analysis<br>• Added details for NI margin determination<br>• Added specifications for non inferiority and superiority analyses (target HR, anticipated OS events, estimated significance levels and estimated CI)<br>• Added clarification of alpha spending<br>• Added non-proportional hazard assumption will be assessed |
| Amendment 6<br>Protocol version 7.0<br>22 September 2021 | • OS at 36 months was added to the secondary objectives.<br>• Clarified that patients in all treatment arms, not just durvalumab, may continue to receive treatment following the final primary analysis DCO.<br>• Added that long-term follow-up data may be collected in eCRFs post final primary analysis for approximately 3 years and defined end of study, if long-term follow-up is collected post final primary analysis, as the last visit of the last patient in the study. |
| US Edition 2<br>09 November 2021 | • Changes made to US Protocol to align with global protocol version 7.0 |

**Changes to Planned Analyses**

All major changes to the planned analyses were made prior to the database lock for the final analysis (DCO: 27 August 2021) and were detailed in Section 6 of the SAP. Minor changes to the algorithms for counting the number of dose delays for sorafenib and for determination of analysis windows for tremelimumab and durvalumab were made after the SAP was finalized.

The FDA's Assessment:

FDA agrees with the Applicant's description of key protocol changes and adds the following:

- In the original CSP, the primary efficacy endpoint is to compare OS of T75+D vs. S at 2-sided alpha of 4.9%. An alpha level of 0.1% was spent on the interim ORR and DoR analysis to strongly control the

type-1 error rate. The two key secondary endpoints, comparing OS of T300+D vs. S and OS of D vs. S, were tested at 2-sided alpha of 4.9% with Dunnett and Tamhane's step-up procedure to control the overall type-1 error rate. Following Amendment 4, enrollment into T75+D arm was discontinued based on interim analysis results regarding tolerability and clinical activity obtained from another ongoing study, Study 22 (D419CC00022). The primary efficacy endpoints were updated to comparing OS of T300+D vs. S and comparing OS of D vs. S as dual primary endpoints. Given there was no interim efficacy analysis conducted when dropping the T75+D arm in the HIMALAYA study, no alpha adjustment was needed to control the overall type-1 error rate.

### 8.1.2. Study Results: HIMALAYA

**Compliance with Good Clinical Practices**

Data: Not applicable

The Applicant's Position:
The Sponsor's procedures, internal quality control measures, and audit program provide reassurance that the durvalumab and tremelimumab clinical development program is being conducted in accordance with GCP, as documented by the ICH.

The FDA's Assessment:
FDA agrees with the Applicant's position. There is no evidence that compliance with good clinical practices was violated during the conduct of the HIMALAYA trial.

**Financial Disclosure**

Data:
Financial disclosures for HIMALAYA are addressed in Section 19.2 of this assessment aid.

The Applicant's Position:
The integrity of HIMALAYA data was not affected by the financial interest of the investigators.

The FDA's Assessment:
The Applicant provided financial disclosure information for the HIMALAYA trial and Study 22. There were no investigators associated with Study 22 who reported financial disclosures. There were 3 investigators for which a certificate of due diligence was submitted.

There was a total of 18 investigators or sub-investigators at one site who disclosed financial interests or arrangements for the HIMALAYA trial. This site has a financial agreement with MedImmune that includes financial support for research, therefore all investigators at this site were reported as having financial disclosures. One investigator at this site enrolled 2 patients of which 1 was randomized to study treatment (T300+D). A total of 8 investigators were associated with the HIMALAYA trial; certificates of due diligence were submitted for these investigators.

FDA has determined that the impact of financial bias on the outcome analyses in the HIMALAYA trial is minimized by the following and is unlikely to have significantly biased the interpretation of study results:

- Overall survival, which is unlikely to be affected by bias, served as the primary study endpoint.
- The number of patients enrolled by investigators who reported financial disclosures (1 patient

randomized out of a total of 1324 randomized patients in the HIMALAYA trial) was low.
- The investigators at this site enrolled less than 1% of the HIMALAYA study population and therefore it is unlikely that this investigator would have a meaningful impact on study results.

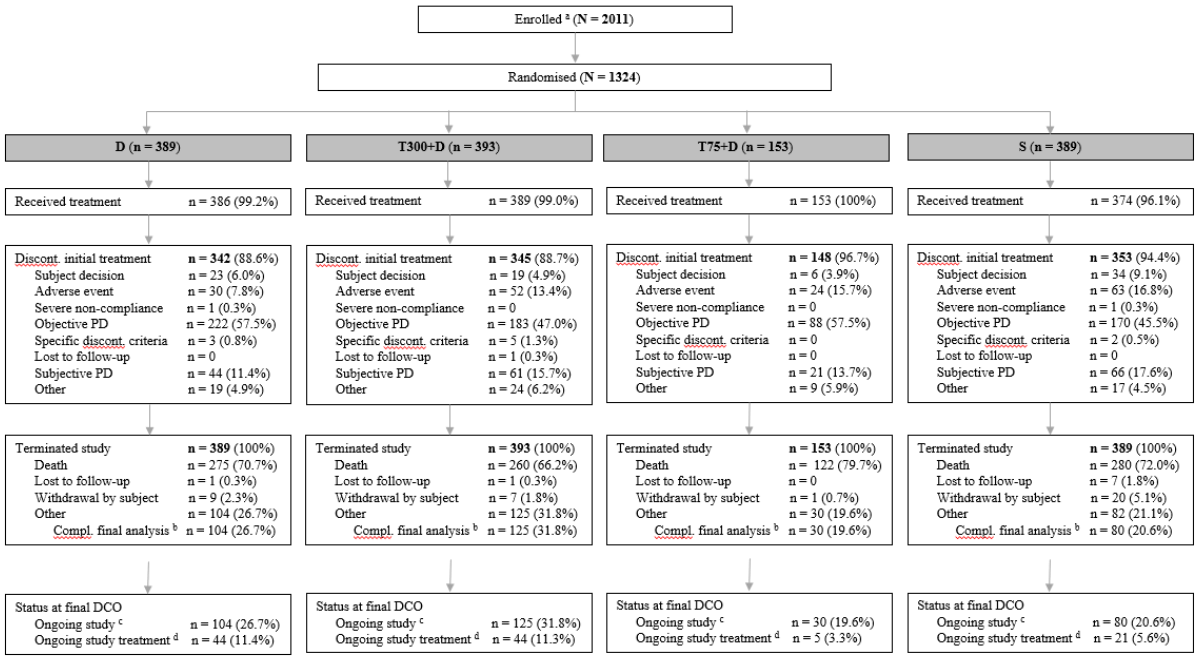
The FDA concludes that it is unlikely that the reported financial disclosures led to significant bias in the conduct of this study. Additional information is provided in Section 19.

**Patient Disposition**

Data:

A total of 1324 patients were randomized into 1 of the 4 original treatment arms: 389 patients randomized to D, 393 patients randomized to T300+D, 153 patients randomized to T75+D, and 389 patients randomized to S at 170 study centers in 16 countries in North and South America, Europe, and Asia Pacific. The disposition of patients in the global cohort is summarized in Figure 9.

**Figure 9 HIMALAYA: Summary of Patient Disposition**




[a] Informed consent received. The reported value of 2011 includes 61 rescreened subjects who each received a new subject ID code during the rescreening phase per protocol. The actual number of subjects enrolled was 1950.

[b] Patients confirmed alive in follow-up or on active study treatment at the time of final analysis reported 'study completion' on the disposition eCRF.

[c] Patients ongoing in study are the same as patients who completed the final analysis.

[d] Percentages are calculated from the number of patients who received treatment in the Global Study. For combination therapy patients, durvalumab reason is reported.

Source: Table 14.1.1 HIMALAYA CSR, Module 5.3.5.1

The Applicant's Position:

The disposition of patients in HIMALAYA is summarized in Figure 9.

The FDA's Assessment:

FDA agrees with the Applicant's description of patient disposition. Overall, the reasons for treatment discontinuation appear similar across treatment arms. Overall, the reasons for treatment discontinuation appear similar across treatment arms.

**Protocol Violations/Deviations**

Data:
The number of patients with important protocol deviations with the potential to affect study analyses was low (36 patients overall [2.7%]). Important protocol deviations were numerically higher in the S arm than in the D and T300+D arms, mainly driven by nonreceipt of study treatment: 3 patients (0.8%) in the D arm, 4 (1.0%) in the T300+D arm, and 15 (3.9%) in the S arm.

A total of 107 patients had 281 protocol deviations resulting from the impact of the COVID-19 pandemic.

The Applicant's Position:
There were no important protocol deviations relating to the pandemic. The protocol deviations observed in the study do not raise any concerns regarding the overall conduct or quality of the study, or the clinical interpretation of data within the patient population enrolled.

The FDA's Assessment:
The Applicant reported 9 patients who had 11 important protocol deviations in the T300+D arm (2.3%) and 21 patients with one important deviation each in the S arm (5.4%). Important protocol deviations were described in the SAP as follows:

1. Subjects randomized but who did not receive study treatment.
2. Subjects who deviate from key entry criteria per the Clinical Study Protocol (CSP).
   a) Inclusion criteria:
      7. Barcelona Clinic Liver Cancer (BCLC) stage B (that is not eligible for locoregional therapy) or stage C.
      8. Child-Pugh Score class A.
      9. ECOG performance status of 0 or 1 at enrollment.
   b) Exclusion criteria:
      11. History of hepatic encephalopathy within past 12 months or requirement for medications to prevent or control encephalopathy (e.g., no lactulose, rifaximin, etc. if used for purposes of hepatic encephalopathy).
      13. Patients with main portal vein thrombosis (i.e., thrombosis in the main trunk of the portal vein, with or without blood flow) on baseline imaging.
      14. Active or prior documented GI bleeding (e.g., esophageal varices or ulcer bleeding) within 12 months.
      (Note: For patients with a history of GI bleeding for more than 12 months or assessed as high risk for esophageal variceal by the Investigator, adequate endoscopic therapy according to institutional standards is required.)
      17. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). Patients without active disease in the last 5 years are excluded unless discussed with the Study Physician and

considered appropriate for study participation. (Exceptions included patients with vitiligo, alopecia, hypothyroidism on stable hormone replacement, any chronic skin condition that does not require systemic therapy, and celiac disease controlled by diet alone.)
18. Patients co-infected with HBV and HCV, or co-infected with HBV and hepatitis D virus (HDV). HBV positive (presence of HbsAg and/or anti-HbcAb with detectable HBV DNA); HCV positive (presence of anti-HCV antibodies); HDV positive (presence of anti-HDV antibodies).
19. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, ILD, serious chronic GI conditions associated with diarrhea, inferior vena cava thrombosis, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase the risk of incurring AEs, or compromise the ability of the patient to give written informed consent.

3. Baseline RECIST scan > 42 days before randomization.
4. No baseline RECIST 1.1 assessment on or before date of randomization.
5. Received prohibited systemic anti-cancer agents. Please refer to the CSP section 7.7 for the systemic anti-cancer agents that are detailed as being 'excluded' from permitted use during the study. This will be used as a guiding principle for the physician review of all medications prior to database lock.
6. Subjects randomized who received their randomized study treatment at an incorrect dose or received an alternative study treatment to that which they were randomized.
7. Did not have the intended disease or indication 1L HCC. ("Subjects have confirmed HCC based on histopathological findings from tumor tissues and must not have received prior systemic therapy for HCC.")

In the T300+D arm the protocol deviations included the following:

- patient randomized but did not receive study treatment (n=4),
- patient received/used incorrect medication (n=2),
- additional investigational systemic anticancer therapy concurrent with those under investigation in this study (n=1),
- Child-Pugh score was not class A (n=1),
- concurrent chemotherapy, radiotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment other than those under investigation in this study while patient is on study treatment (n=1), patient co-infected with HBV and HCV (n=1), and,
- patient with main portal vein tumor thrombosis (n=1).

The higher number of protocol deviations in the S arm was due to more patients who were randomized but did not receive study treatment (n=15). Other protocol deviations in the S arm include Child-Pugh score not class A (n=3), baseline tumor assessment performed more than 28 days before first dose of study medication (n=2), and active or prior documented autoimmune or inflammatory disorders, systemic (n=1).

Protocol deviations relating to the pandemic included:

- Visits not performed or performed outside the visit window (visit delayed)
- Visits performed by phone (telemedicine) instead of on site or forms signed electronically (using DocuSign)
- Protocol-defined procedures or laboratory assessments not performed or completed

FDA has concluded that these protocol deviations are unlikely to alter the results of the primary OS analysis or to have had an impact on the accuracy or reliability of the study data. During the review cycle data anomalies for the OS endpoint were reported at one study site (#6208). Refer to the FDA Assessment of Data Quality and Integrity for further discussion and FDA sensitivity analyses of OS to assess impact of these data anomalies.

Data:

**Table 14: Demographic Characteristics of HIMALAYA**

| | N (%) of Patients | | | | |
|---|---|---|---|---|---|
| | **D (N = 389)** | **T300+D (N = 393)** | **T75+D (N = 153)** | **S (N = 389)** | **Total (N = 1324)** |
| Age (years) | | | | | |
| n | 389 | 393 | 153 | 389 | 1324 |
| Mean | 62.6 | 63.0 | 63.4 | 63.5 | 63.1 |
| SD | 11.47 | 11.65 | 12.03 | 11.12 | 11.48 |
| Median | 64.0 | 65.0 | 65.0 | 64.0 | 64.0 |
| Min | 20 | 22 | 18 | 18 | 18 |
| Max | 86 | 86 | 85 | 88 | 88 |
| Age group (years,) n (%) | | | | | |
| < 65 | 203 (52.2) | 195 (49.6) | 74 (48.4) | 195 (50.1) | 667 (50.4) |
| ≥ 65 to < 75 | 130 (33.4) | 145 (36.9) | 55 (35.9) | 137 (35.2) | 467 (35.3) |
| ≥ 75 | 56 (14.4) | 53 (13.5) | 24 (15.7) | 57 (14.7) | 190 (14.4) |
| Sex, n (%) | | | | | |
| Male | 323 (83.0) | 327 (83.2) | 121 (79.1) | 337 (86.6) | 1108 (83.7) |
| Female | 66 (17.0) | 66 (16.8) | 32 (20.9) | 52 (13.4) | 216 (16.3) |
| Race, n (%) | | | | | |
| White | 160 (41.1) | 182 (46.3) | 70 (45.8) | 179 (46.0) | 591 (44.6) |
| Black or African American | 2 (0.5) | 7 (1.8) | 4 (2.6) | 10 (2.6) | 23 (1.7) |
| Asian | 212 (54.5) | 195 (49.6) | 75 (49.0) | 189 (48.6) | 671 (50.7) |
| Native Hawaiian or other Pacific Islander | 0 | 1 (0.3) | 0 | 0 | 1 (0.1) |
| American Indian or Alaska Native | 0 | 0 | 0 | 0 | 0 |
| Other | 15 (3.9) | 7 (1.8) | 4 (2.6) | 5 (1.3) | 31 (2.3) |
| Missing | 0 | 1 (0.3) | 0 | 6 (1.5) | 7 (0.5) |
| Ethnic group, n (%) | | | | | |
| Hispanic or Latino | 13 (3.3) | 21 (5.3) | 11 (7.2) | 21 (5.4) | 66 (5.0) |
| Not Hispanic or Latino | 376 (96.7) | 372 (94.7) | 142 (92.8) | 362 (93.1) | 1252 (94.6) |
| Missing | 0 | 0 | 0 | 6 (1.5) | 6 (0.5) |
| Region group, n (%) | | | | | |
| Asia (except Japan) | 167 (42.9) | 156 (39.7) | 60 (39.2) | 156 (40.1) | 539 (40.7) |
| Rest of world (includes Japan) | 222 (57.1) | 237 (60.3) | 93 (60.8) | 233 (59.9) | 785 (59.3) |

| | N (%) of Patients | | | | |
|---|---|---|---|---|---|
| | D (N = 389) | T300+D (N = 393) | T75+D (N = 153) | S (N = 389) | Total (N = 1324) |
| Weight group (kg), n (%) | | | | | |
| < 70 | 218 (56.0) | 190 (48.3) | 82 (53.6) | 202 (51.9) | 692 (52.3) |
| ≥ 70 – < 90 | 130 (33.4) | 158 (40.2) | 56 (36.6) | 137 (35.2) | 481 (36.3) |
| ≥ 90 | 41 (10.5) | 45 (11.5) | 15 (9.8) | 50 (12.9) | 151 (11.4) |
| BMI group (kg/m$^2$) | | | | | |
| < 18.5 | 15 (3.9) | 19 (4.8) | 5 (3.3) | 17 (4.4) | 56 (4.2) |
| ≥ 18.5 – < 25.0 | 210 (54.0) | 188 (47.8) | 78 (51.0) | 195 (50.1) | 671 (50.7) |
| ≥ 25.0 – < 30.0 | 114 (29.3) | 128 (32.6) | 51 (33.3) | 125 (32.1) | 418 (31.6) |
| ≥ 30.0 | 47 (12.1) | 56 (14.2) | 19 (12.4) | 48 (12.3) | 170 (12.8) |
| PD-L1 status [a] | | | | | |
| Positive | 154 (39.6) | 148 (37.7) | 65 (42.5) | 148 (38.0) | 515 (38.9) |
| Negative | 190 (48.8) | 189 (48.1) | 79 (51.6) | 181 (46.5) | 639 (48.3) |
| Randomized but not treated [b] | 3 (0.8) | 4 (1.0) | 0 | 15 (3.9) | 22 (1.7) |
| Missing [c] | 42 (10.8) | 52 (13.2) | 9 (5.9) | 45 (11.6) | 148 (11.2) |

[a] PD-L1 expression level is based on the TIP score method as: PD-L1 positive (TIP ≥ 1%) or PD-L1 negative (TIP < 1%).

[b] Baseline PD-L1 results are not available for patients who were randomized but not treated.

[c] Missing PD-L1 may be due to the following reasons: screening sample not tested, screening sample not evaluable for TIP score, or screening sample not provided by site.

Baseline is the last assessment prior to the intake of the first dose of any study treatment.
Source: Tables 14.1.4, 14.1.5 HIMALAYA CSR, Module 5.3.5.1

The Applicant's Position:

The treatment arms were balanced in terms of demographic and baseline characteristics. Overall, the patient population was representative of the target population of patients with uHCC. The median age at study entry was 64.0 years (range: 18 to 88 years), 83.7% of patients were male, and 40.7% were from the Asian region (excluding Japan). PD-L1 status was balanced across treatment arms, with 38.9% of patients having positive PD-L1 expression (TIP ≥ 1%).

The FDA's Assessment:

FDA agrees with the Applicant's summary of patient demographic characteristics. Key demographic characteristics were generally well balanced across treatment arms. The median age of patients randomized to the T300+D, durvalumab and sorafenib arms was 64 years, slightly lower than the median age at diagnosis (66 years) reported in the SEER registry. While the proportion of patients enrolled in HIMALAYA by race and geographic region is comparable to enrollment by race in other trials designed to support the approval of drugs for the first-line treatment of HCC, very few patients randomized to the T300+D, durvalumab and sorafenib arms were of Black/African American (n=19) or Native Hawaiian/Pacific Islander (n=1) race and no patients of American Indian/Alaskan Native race, which may lead to limited generalizability of the study results to these populations.

For patients randomized to the T300+D, durvalumab and sorafenib arms, FDA notes that 40.9% (n=479) were enrolled in Asia excluding Japan, 9.2% (n=108) in Japan, 42.2% (n=494) in rest of the world, and only 7.7% (n=90) of randomized patients were enrolled in the United States, with 7.9% (n=31) in the T300+D arm, and 10.3% (n=40) in the S arm.

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Data:
At screening, 30.6% of patients were HBV positive, 27.2% were HCV positive, and 42.2% were uninfected. A total of 99.5% of patients were Child-Pugh Class A. At study entry, 19.2% of patients were BCLC Stage B, and 80.8% were BCLC Stage C.

The Applicant's Position:
Patients' disease characteristics at screening were generally balanced across the treatment arms and representative of the intended target population with uHCC. Importantly, stratification factors comprising etiology of liver disease (determined by virology laboratory assessments at screening), MVI, and ECOG PS were balanced across treatment arms.

The FDA's Assessment:
FDA agrees with the Applicant's summary of patient baseline disease characteristics. Baseline disease characteristics were generally balanced across treatment arms. Baseline characteristics were also comparable to those observed in studies for other approved therapies for the first-line treatment of HCC.

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

Data:
The administration of all study drugs (including study treatment) was recorded in the appropriate sections of the eCRF. The most commonly used concomitant medications (≥ 10% of patients in all treatment arms) were nucleoside and nucleotide reverse transcriptase inhibitors (17.9%) and proton pump inhibitors (10.6%). In total, 3 patients (0.8%) in the D monotherapy arm received prohibited concomitant medications. The use of prohibited concomitant medication did not raise concerns about the conduct of the study.

The Applicant's Position:
Durvalumab and tremelimumab were administered by study site personnel, who monitored compliance. For patients randomized to the S arm, treatment compliance was assured through reconciliation of site drug accountability logs. Concomitant treatments administered prior to randomization were generally balanced across treatment arms and were representative of those commonly prescribed to patients in the target population.

The FDA's Assessment:
FDA agrees that the types and frequencies of comorboidities and drugs to treat those are expected for this patient population. FDA agrees that concomitant treatments were generally balanced between the two treatment arms.

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

Data:

***Primary endpoint analysis***

HIMALAYA met its primary objective: treatment with T300+D demonstrated a statistically significant, clinically meaningful, and sustained improvement in OS compared with S. The HR for T300+D vs S was

0.78 (96.02% CI: 0.65, 0.92; stratified log-rank 2-sided p-value = 0.0035). The Kaplan-Meier estimate of mOS was 16.43 months in the T300+D arm, which was approximately 2.7 months longer than mOS in the S arm (13.77 months) (Table 15). At the time of Final Analysis (DCO: 27 August 2021), the maturity of the OS curves for T300+D and S was 71%, with a median duration of follow-up for patients in T300+D and S arms of 33.18 months and 32.23 months, respectively.

The OS benefit in the T300+D arm was sustained over time, as supported by the greater proportion of patients treated with T300+D that were alive at 12, 18, 24, and 36 months compared to patients treated with S (Table 15). While not formally tested due to its position in the MTP, the 36-month OS rate demonstrated a nominally statistically significant improvement in T300+D compared to S ($p < 0.0029$).

The separation of OS curves between T300+D and S occurred approximately 4 months after randomization and remained separated through the remainder of patient follow-up (Figure 10). A post-hoc analysis calculating piecewise constant treatment effects for the T300+D vs S comparison shows there was no initial detriment in OS for T300+D prior to the separation from S observed at 4 months from randomization (Table 16). Subsequently, the observed treatment effect of T300+D vs S led to a statistically significant OS benefit when accounting for the totality of the data.

**Table 15 Overall Survival in HIMALAYA (Pivotal Study)**

| | HIMALAYA FAS (Final Analysis) | | |
|---|---|---|---|
| | **D (N = 389)** | **T300+D (N = 393)** | **S (N = 389)** |
| HR (compared to sorafenib) [a] | 0.86 | 0.78 | - |
| 95% CI [a] | 0.73 – 1.02 | 0.66 – 0.92 | - |
| 96.02% CI for HR (T300+D vs S) [a, b] | - | 0.65 – 0.93 | - |
| 2-sided p-value (T300+D vs S) | - | 0.0035 | - |
| 95.67% CI for HR (D vs S) [a, c] | 0.73 – 1.03 | - | - |
| 2-sided p-value (D vs S) [d] | 0.0674 | - | - |
| Median OS (months) [e] | 16.56 | 16.43 | 13.77 |
| 95% CI for median OS [e] | 14.06 – 19.12 | 14.16 – 19.58 | 12.25 – 16.13 |
| OS rate at 12 months, % [e] | 59.3 | 60.2 | 56.2 |
| OS rate at 18 months, % [e] | 47.4 | 48.7 | 41.5 |
| OS rate at 24 months, % [e] | 39.6 | 40.5 | 32.6 |
| OS rate at 36 months, % [e] | 24.7 | 30.7 | 20.2 |
| Deaths, n (%) | 280 (72.0) | 262 (66.7) | 293 (75.3) |
| Censored patients, n (%) | 109 (28.0) | 131 (33.3) | 96 (24.7) |
| Still in survival follow-up at DCO [f] | 104 (26.7) | 125 (31.8) | 79 (20.3) |
| Terminated prior to death [g] | 109 (28.0) | 131 (33.3) | 96 (24.7) |
| Lost to follow-up | 1 (0.3) | 1 (0.3) | 7 (1.8) |
| Withdrawn consent | 4 (1.0) | 5 (1.3) | 10 (2.6) |

**Table 15 Overall Survival in HIMALAYA (Pivotal Study)**

| | HIMALAYA FAS (Final Analysis) | | |
|---|---|---|---|
| | D (N = 389) | T300+D (N = 393) | S (N = 389) |
| Median (range) duration of follow-up in censored patients (months) [h] | 31.61 (1.91 – 45.70) | 32.36 (6.18 – 42.84) | 30.36 (0.03 – 43.60) |
| Median (95% CI) duration of follow-up in all patients (months) [i] | 32.56 (31.57 – 33.71) | 33.18 (31.74 – 34.53) | 32.23 (30.42 – 33.71) |

[a] The HR was calculated using a CPH model adjusting for treatment arm, etiology of liver disease (HBV vs HCV vs all others), ECOG (0 vs 1), and MVI (yes vs no). An HR < 1 favors either the T300+D arm or the D arm compared with the S arm in terms of being associated with a longer OS.

[b] T300+D vs S (primary objective in HIMALAYA). Statistical significance for T300+D vs S was based on a 2-sided interim $p < 0.0419$ (overall alpha 4.9%), as defined in the MTP.

[c] D vs S (key secondary objective in HIMALAYA). The noninferiority margin for D vs S was 1.08, as defined in the MTP.

[d] The analysis was performed using a stratified log-rank test adjusting for treatment arm, etiology of liver disease (HBV vs HCV vs all others), ECOG (0 vs 1), and MVI (yes vs no).

[e] Calculated using the Kaplan-Meier method.

[f] Patients confirmed alive in follow-up or on active study treatment at the time of final analysis reported "study completion" on the disposition CRF.

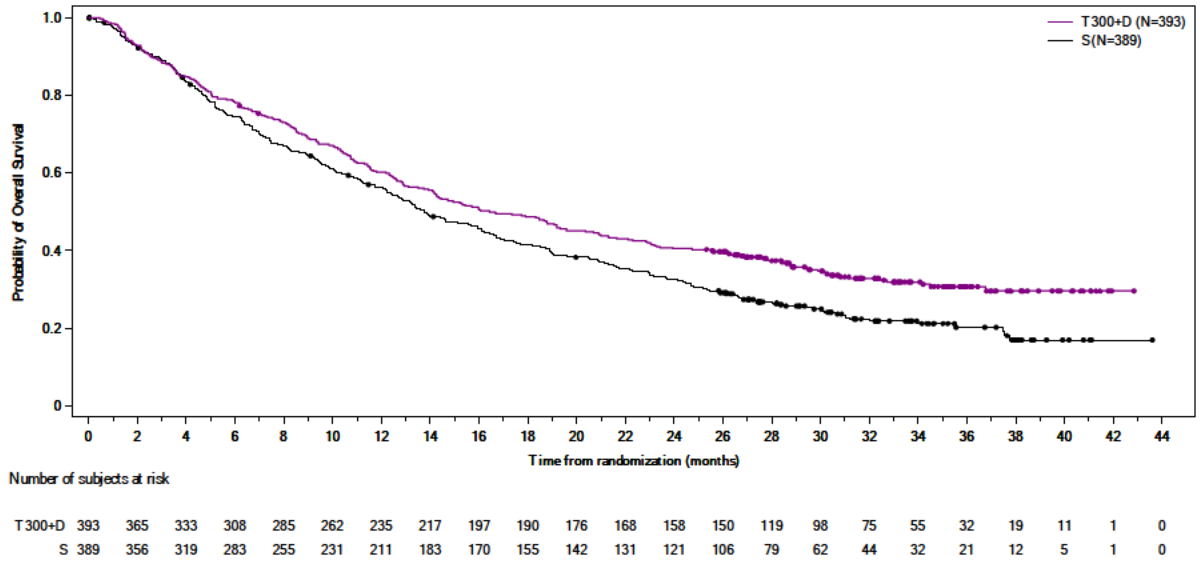
[g] Includes patients with unknown survival status or patients who were lost to follow-up.

[h] Median for duration of follow-up is the arithmetic median.

[i] Calculated using reverse the KM technique (with censor indicator reversed).

Source: Table 14.2.1.1, Table 14.2.1.1.4, HIMALAYA CSR, Module 5.3.5.1

**Figure 10 Kaplan-Meier Plot of Overall Survival in the T300+D and S Arms in HIMALAYA, FAS (Final Analysis)**




Source: Figure 14.2.1.3, HIMALAYA CSR, Module 5.3.5.1

***Sensitivity analysis***

***Non-proportional Hazards***

The shape of the OS curves for T300+D and D showed an initial delay in separation from the OS curve for S (separation at 4 months for T300+D and at 9 months for D, as described above). This is expected as IO agents have illustrated delayed treatment effects in clinical settings. Given the delay in OS curve separation, which suggests non-proportional hazards, the OS HRs for T300+D vs S and D vs S should be interpreted as an average estimate of the observed benefit over the observed period. Additional measures such as landmark OS rates at 24 and 36 months should be considered alongside the survival curves to better understand the treatment effect over time.

To assess the assumption of proportionality of hazards for OS, a complementary plot of log (-log [Survival]) against log (time from randomization to death) was examined. This showed some evidence of delayed treatment effects as illustrated by the lack of parallel lines of log (-log [survival])(Survival) against log (time from randomization to death) for the individual treatment arms. This is consistent with the observed delay in separation of OS curves (4 months for T300+D vs S and 9 months for D vs S).

The assumption of non-proportionality was further assessed with a post-hoc analysis performed to test the linear interaction between treatment and time. No significant linear interaction was found for either T300+D vs. S (nominal p = 0.094) or D vs. S (nominal p = 0.35). Although the study was not statistically powered to detect such interactions, the signal strength of non-proportionality was not evident when testing this hypothesis.

A post-hoc analysis calculating piecewise constant treatment effects for the T300+D vs S comparison shows there was no initial detriment in OS for T300+D prior to the separation from S observed at 4 months from randomization. Subsequently, the observed treatment effect of T300+D vs S led to a statistically significant OS benefit when accounting for the totality of the data (Table 16).

**Table 16 Piecewise Constant HRs for the T300+D vs S and D vs S Comparisons of Overall Survival in HIMALAYA, FAS (Final Analysis)**

| Time interval post-randomization | Piecewise HRs (95% CI) [a, b] | |
|---|---|---|
| | T300+D vs S [c] | D vs S [c] |
| 0–4 months | 0.93 (0.65, 1.33) | 0.94 (0.66, 1.34) |
| 4–9 months | 0.81 (0.57, 1.14) | 1.01 (0.73, 1.40) |
| 0–9 months | 0.87 (0.68, 1.11) | 0.98 (0.77, 1.24) |
| > 9 months | 0.70 (0.56, 0.89) | 0.77 (0.61, 0.97) |

[a] Hazard function was assumed to be constant within the time interval. Only subjects who were alive and not censored at the beginning of the time interval were included and any of them with data beyond the time interval were censored at the end of the interval.

[b] The analysis was performed using a Cox proportional hazards model adjusting for treatment, etiology of liver disease (HBV versus HCV versus others), ECOG (0 versus 1), and macro-vascular invasion (yes versus no). Values of the variables used for adjustment were obtained from IVRS.

[c] A HR < 1 favors IO treatment arms to be associated with a longer overall survival than sorafenib.

Source: Table 14.2.1.1.6, HIMALAYA CSR, Module 5.3.5.1

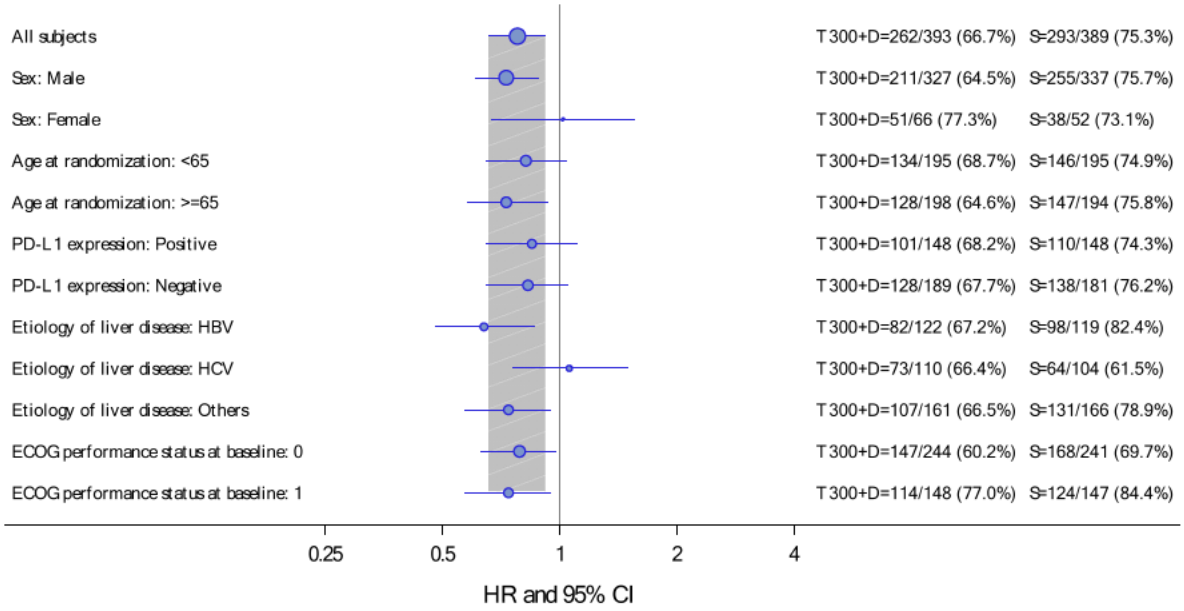
***Inversed Censoring***

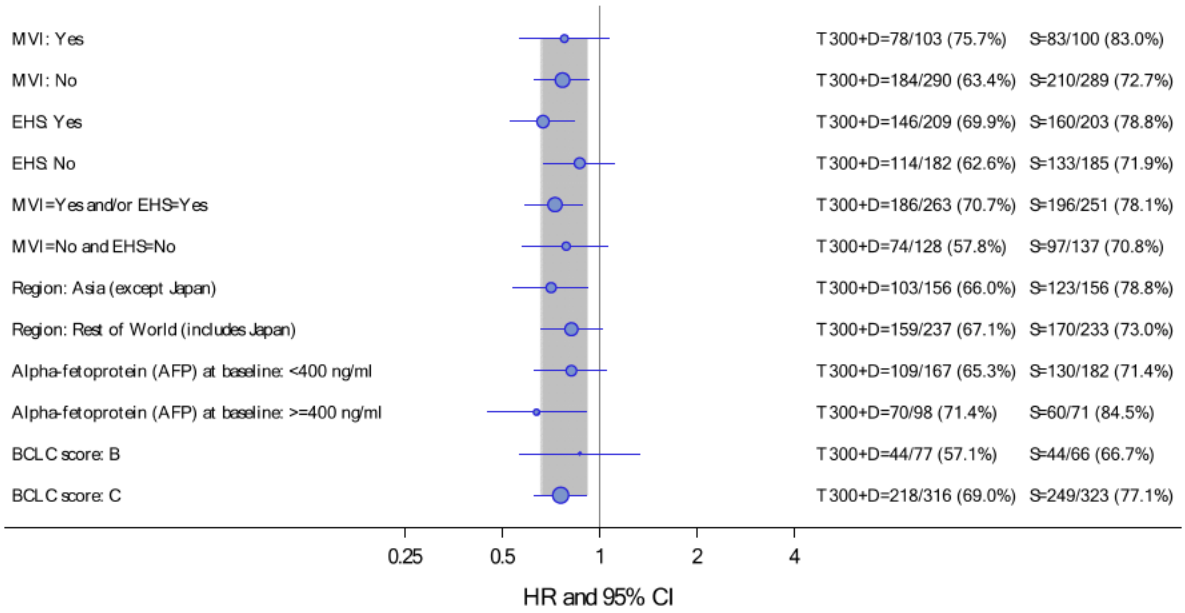
A reverse Kaplan-Meier survival curve showed that the curves for T300+D, D, and S remain close to 1 for the first 26 months post-randomization, indicating nearly complete follow-up for this period of time. No meaningful difference in the length of follow-up among D, T300 +D, and S was observed, as evidenced by similar median follow-up times in censored patients in Table 15 (D: 31.61 months, T300+D: 32.36 months, and S: 30.36 months).

***Subgroup analyses***

In HIMALAYA, prespecified subgroup analyses of OS were performed in the FAS to investigate the consistency of treatment effect across prespecified stratification factors and subgroups based on demographics, geographical region, and disease characteristics. All predefined subgroup HRs were in favor of T300+D vs S (HR < 1), consistent with the overall OS analysis, with the exception of females (HR = 1.02; 95% CI: 0.67, 1.56) and HCV-positive patients (HR = 1.06; 95% CI: 0.76, 1.49) (Figure 11). A post-hoc analysis of baseline covariates within the HCV subgroup identified imbalances in prognostic factors known for patients with HCC (EHS and serum albumin-bilirubin); when controlling for these imbalances, the HR favored T300+D (HR = 0.89).

**Figure 11 Forest Plots of Overall Survival by Subgroup for T300+D vs Sorafenib in HIMALAYA (FAS)**






An HR < 1 implies a lower risk of death for T300+D.
Size of circle is proportional to the number of events. Gray band represents the 95% CI for the overall (all subjects) HR.
Source: Figure 14.2.1.2, HIMALAYA CSR, Module 5.3.5.1

The Applicant's Position:

HIMALAYA met the primary objective of superiority of T300+D over S in patients with 1L uHCC. Additionally, when controlling for imbalances in key prognostic factors, the OS benefit favoring T300+D treatment vs S was consistent across all prespecified subgroups.

The FDA's Assessment:

FDA agrees that based on the results of the HIMILAYA trial, treatment with T300+D in patients with 1L uHCC provides a statistically significant and clinically meaningful improvement in OS compared to sorafenib. FDA provides the following additional notes:

- The stratified OS HRs for T300+D vs. sorafenib and for durvalumab vs. sorafenib reported by the Applicant were calculated using a stratified Cox proportional hazard model with patients from all three arms. FDA conducted separate sensitivity analyses using stratified Cox proportional hazard models with patients only from the T300+D and S arms. This analysis showed an OS HR of 0.78 (95% CI: 0.66, 0.92), and with patients only from the durvalumab and sorafenib arms that resulted in an OS HR of 0.86 (95% CI: 0.73, 1.01), which are consistent with the Applicant's results.
- On August 9, 2022, FDA sent an Information Request (IR) to the Applicant requesting clarification of the alpha boundaries used for the Applicant's primary and key secondary endpoints. FDA noted an inconsistency regarding the 96.02% CI of HR comparing T300+D to sorafenib, with the significance level of 0.0419 in footnote b of Table 15. The Applicant responded on August 15, 2022 and stated that the footnote is an error. The correct alpha level applied at final analysis was 0.0398 accounting for the 555 observed OS events in contrast to the planned 515 OS events at final analysis. In addition, FDA conducted a sensitivity analysis based on the first 515 OS events observed. The estimated median OS was 16.4 months for patients treated with T300+D vs. 13.8 months for patients treated with sorafenib, and the estimated stratified OS HR was 0.80 (95% CI: 0.67, 0.95) in

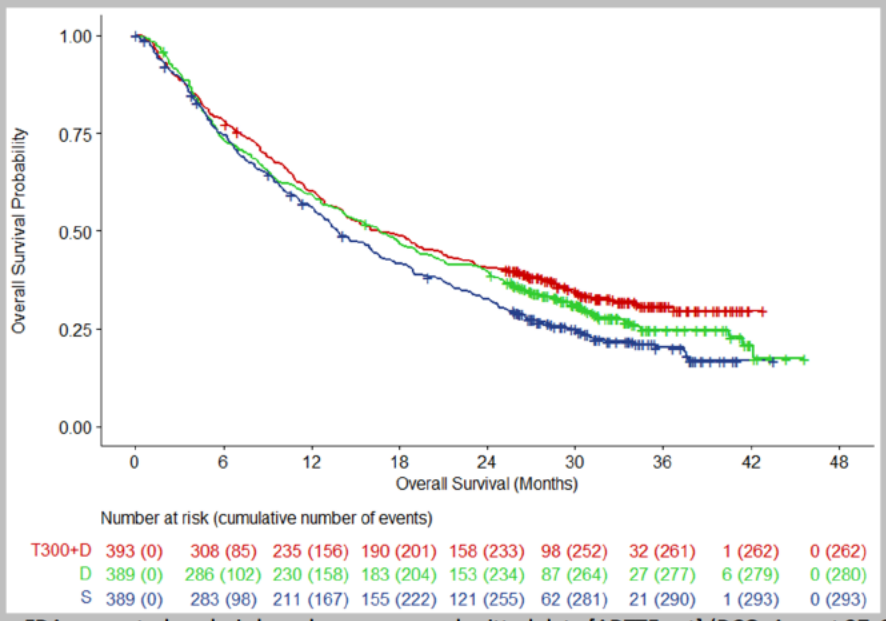
favor of the T300+D arm, which was consistent with the primary OS analysis.

- In CSR Addendum 1, the Applicant stated that a discrepancy in the survival information for subject (b) (6) was noted on February 8, 2022. To assess the impact of this discrepancy, FDA conducted a sensitivity analysis repeating the primary analysis by updating the date of death for this subject. The median OS, hazard ratios with Cis, and p-value were unchanged up to rounding error.
- The Kaplan-Meier curves indicate non-proportional hazards and can limit the interpretation of treatment effects based on the OS HR estimate alone. FDA considers the landmark OS estimates by treatment arms presented by the Applicant to be exploratory analyses only. The point estimate of event rates at a fixed time point for a time-to-event endpoint can be misleading because it does not represent the entire effect size of treatment and the chosen landmark time is arbitrary. FDA also considers the Applicant's additional sensitivity analyses to examine the proportional hazard assumption be exploratory only. The chosen cutoff times for calculating piecewise constant treatment effects are arbitrary and hinders the interpretability of the results. FDA performed an additional exploratory test to evaluate whether the proportional hazard assumption was violated, although there was low power to detect violation of non-proportionality with the available sample size. This test failed to detect evidence of non-proportionality.
- FDA agrees with the subgroup analyses results presented by the Applicant. Overall, the subgroup analyses comparing T300+D vs sorafenib showed that there were no outlier subgroups and the treatment effect was generally consistent with that of the all-randomized patients, with the exception of females and HCV-positive patients. Per the Applicant, the subgroup analysis of Etiology of liver disease was based on value collected at screening. Based on value collected at randomization, the estimated HR for HCV-positive patients was 1.03 (95%: 0.73, 1.45). Among the subgroup of patients enrolled in the United States (n=71), the HR was 0.82 (95% CI: 0.47, 1.43). FDA considers the results of subgroup analyses to be exploratory and should be interpreted with caution.

Although the comparison of T300+D vs. sorafenib will serve as the basis for approval, FDA notes that the SAP pre-specified a testing hierarchy such that when the OS superiority test for T300+D vs. sorafenib was statistically significant, an OS non-inferiority test for D vs. S would be conducted, followed by an OS superiority test for durvalumab vs. sorafenib. At the time of final OS analysis (T300+D vs. sorafenib), 573 events were observed in the durvalumab and sorafenib arms combined. Durvalumab achieved statistical non-inferiority to sorafenib based on the Applicant's pre-specified non-inferiority margin of 1.08. Given that the Applicant is not seeking an indication for durvalumab monotherapy, FDA did not conduct a detailed assessment of the appropriateness of a non-inferiority claim. Notably, durvalumab did not achieve superiority over sorafenib with a 2-sided p-value of 0.0674, which was greater than the pre-specified alpha level of 0.0433. FDA sent an IR on August 9, 2022 requesting clarification on how the 0.0433 alpha boundary was calculated. In response, the Applicant stated that they took a more conservative approach towards alpha allocation for the durvalumab vs. sorafenib OS comparisons; they treated the type-1 error that would have been allocated to the interim and final analyses of the non-inferiority and superiority hypotheses as spent even though OS for durvalumab vs. sorafenib was only to be tested at the final analysis per the multiple testing procedure. FDA notes that even with an alpha boundary of 0.049 (without accounting for the interim analyses) the superiority test for OS for durvalumab vs. sorafenib would have failed. This provided supportive evidence that both components of the T300+D combination regimen were needed to achieve a statistically significant OS effect over sorafenib.

As an additional exploratory analysis to evaluate the contribution of components, FDA compared the OS for T300+D arm to the OS for durvalumab arm. The estimated stratified OS HR was 0.90 (95% CI: 0.76, 1.07). The estimated median OS was 16.4 months (95% CI: 14.2, 19.6) for the T300+D arm compared to 16.6 months (95% CI: 14.1, 19.1) for the durvalumab arm. The Kaplan-Meier plot comparing OS for all 3 arms is presented in Figure 12.

**Figure 12 Kaplan-Meier Plot of Overall Survival in All 3 Arms in HIMALAYA, FAS**




Source: FDA generated analysis based on sponsor submitted data [ADTTE.xpt] (DCO: August 27, 2021).

**Data Quality and Integrity**

Data: Not applicable

The Applicant's Position:
No quality or integrity issues were identified for HIMALAYA.

The FDA's Assessment:

On August 24, 2022, the Applicant notified the FDA regarding data anomalies at clinical site #6208 in Russia. This site randomized 14 patients into the HIMALAYA trial between December 2017 and July 2019 (4 to durvalumab arm, 2 to T300+D arm, 2 to T75+D arm and 6 to sorafenib arm). The Applicant conducted an onsite investigation which included a comprehensive review of survival data and medical records/source documents for the 14 patients. Discrepancies in death dates between the CRF/source documents vs local oncology registry/death certificates were identified for 4 patients (1 in durvalumab arm, 1 in T300+D arm and 2 in sorafenib arm), among which 3 patients had significant data anomalies with differences in the date reported by the sub-Investigator and the death certificate ranging from 11 to 275 days. These 3 patients were treated by the same sub-Investigator, who was reported as having

limited experience with clinical trials and was reported to no longer be at the site. No clear pattern was identified in the data anomaly to suggest the motive for the data discrepancies.

FDA performed additional sensitivity analyses to investigate the impact of these data anomalies on the primary analysis results of OS for the HIMALAYA study. These sensitivity analyses included updating the survival data for the 4 patients with data anomalies from clinical site 6208 in the FAS population and excluding all patients from site 6208 in the FAS population. FDA also conducted additional sensitivity analyses excluding all patients from Russian sites in the FAS population and excluding all patients from both Russian and Ukraine sites in the FAS population as site inspections to these geographic regions is prohibited by the ongoing military crisis. Median OS and stratified HR of the T300+D and sorafenib arms for these sensitivity analyses were consistent with the median OS and stratified HR for the original FAS population with only decimal differences (Table 17).

**Table 17 Sensitivity Analyses Evaluating Data Anomalies**

| Analysis population | Number of patients | | Median OS (95% CI)[a], months | | HR[b] (95% CI) |
|---|---|---|---|---|---|
| | T300+D | S | T300+D | S | |
| FAS | 393 | 389 | 16.4 (14.2, 19.6) | 13.8 (12.3, 16.1) | 0.78 (0.66, 0.92) |
| FAS with updated survival data for the 4 patients with data anomalies | 393 | 389 | 16.4 (14.2, 19.6) | 13.8 (12.3, 16.1) | 0.78 (0.66, 0.92) |
| FAS excludes patients from site 6208 | 391 | 383 | 16.7 (14.2, 20.4) | 13.8 (12.3, 16.1) | 0.77 (0.65, 0.91) |
| FAS excludes patients from Russia | 377 | 366 | 16.7 (14.2, 20.4) | 13.6 (12.2, 16.1) | 0.77 (0.65, 0.92) |
| FAS excludes patients from Russia and Ukraine | 358 | 347 | 16.7 (14.1, 20.4) | 13.6 (12.1, 16.2) | 0.78 (0.65, 0.94) |

a. Calculated using the Kaplan-Meier method.
b. Calculated using a stratified Cox proportional hazard model with stratification factors of etiology of liver disease (HBV vs HCV vs all others), ECOG (0 vs 1), and MVI (yes vs no). An HR < 1 favors the T300+D arm compared with the S arm in terms of being associated with a longer OS.

Source: FDA generated analysis based on Applicant submitted data [ADTTE.xpt] (DCO: August 27, 2021).

**Efficacy Results – Secondary and Other Relevant Endpoints**

Data:

***ORR***

At the final DCO, the ORR based on Investigator assessment according to RECIST 1.1 for confirmed responses was 17.0% for the D arm, 20.1% for the T300+D arm, and 5.1% for the S arm (Table 18). Treatment with T300+D or D had a higher likelihood of response when compared with S. The odds ratio for the comparison of T300+D vs S was 4.69 (95% CI: 2.85, 8.04; nominal p < 0.0001) in favor of the T300+D arm. In the comparison of D vs S, the odds ratio was 3.80 (95% CI: 2.29, 6.57; nominal p < 0.0001) in favor of the D arm. Of note, the study was not sized for this comparison and no multiplicity adjustments were made. Overall, the data support that patients who received T300+D or D were more likely to have a response than patients who received S.

**Table 18 Objective Response Rate Based on Investigator Assessment (Confirmed Responses) According to RECIST 1.1 (FAS)**

| Treatment Arm | N | Number of Patients with Response [a] | Response Rate (%) | Comparison Between Arms | | |
|---|---|---|---|---|---|---|
| | | | | Odds Ratio | 95% CI | 2-sided p-value |
| D | 389 | 66 (17.0) | 17.0 | 3.80 | 2.29, 6.57 | <0.0001 |
| T300+D | 393 | 79 (20.1) | 20.1 | 4.69 | 2.85, 8.04 | <0.0001 |
| T75+D | 153 | 26 (17.0) | 17.0 | - | - | - |
| S [b] | 389 | 20 (5.1) | 5.1 | - | - | - |

[a] Responses include only confirmed responses.

[b] Comparator arm for the odds ratio is S.

The analysis was performed using a logistic regression model adjusted for treatment with factors for etiology of liver disease, ECOG PS, and MVI.

An odds ratio > 1 favors IO treatment arms.

Source: Table 14.2.4.1.1.2 HIMALAYA CSR

***Best Objective Response (BOR)***

In the FAS, 20.1% of patients in the T300+D arm, 17.0% in the D arm, and 5.1% in the S arm achieved a BOR of either CR or PR based on Investigator assessment (confirmed responses only). Complete responses were only observed in the D containing arms: 6 patients (1.5%) in the D arm and 12 patients (3.1%) in the T300+D arm. Among patients who had a response, the rate of PR was numerically higher in patients in the T300+D and D arms when compared with S, namely 67 patients in the T300+D arm (17.0%) and 60 patients in the D arm (15.4%) compared with 20 patients in the S arm (5.1%) (Table 19). Importantly, approximately 4 times as many patients receiving T300+D (n = 79) had a BOR of CR or PR compared with S (n = 20).

**Table 19 Best Objective Response Based on Investigator Assessment (Confirmed Response) According to RECIST 1.1 (FAS)**

| Response status | BOR | Number (%) of patients | | |
|---|---|---|---|---|
| | | D (N = 389) | T300+D (N = 393) | S (N = 389) |
| Response | Total | 66 (17.0) | 79 (20.1) | 20 (5.1) |
| | Complete response | 6 (1.5) | 12 (3.1) | 0 |
| | Partial response | 60 (15.4) | 67 (17.0) | 20 (5.1) |
| Non-response | Total | 323 (83.0) | 314 (79.9) | 369 (94.9) |
| | Stable disease | 147 (37.8) | 157 (39.9) | 216 (55.5) |
| | Progression | 160 (41.1) | 141 (35.9) | 118 (30.3) |
| | RECIST progression | 143 (36.8) | 117 (29.8) | 91 (23.4) |
| | Death | 17 (4.4) | 24 (6.1) | 27 (6.9) |
| | Not evaluable | 16 (4.1) | 16 (4.1) | 35 (9.0) |

Source: Table 14.2.5.1.9, HIMALAYA CSR, Module 5.3.5.1.

***Progression-free Survival***

The Kaplan-Meier estimate for median PFS in the HIMALAYA study (investigator assessment according to RECIST 1.1) was similar in the T300+D (3.78 months) and S (4.07 months) arms (HR = 0.90 [95% CI: 0.77, 1.05]) with the curves separating in favor of T300+D. Consistent with the tail effect in the OS curve, more patients receiving T300+D remained progression-free at the final DCO (12.5%) compared to those

in the S arm (4.9%).

Overall, almost 50% of patients in the HIMALAYA IO arms continued to receive treatment after RECIST 1.1 progression, indicating that patients were receiving clinical benefit per Investigator assessment and suggesting that progression did not imply treatment resistance. Importantly, patients with BOR of PD in the T300+D arm experienced a better OS outcome when compared with the same group of patients in the S arm further supporting that PFS is not a direct measure of clinical benefit.

***Time to Progression***

At the final DCO, the Kaplan-Meier estimate of median TTP (RECIST 1.1 progression based on Investigator assessment) was 3.75 months in the D arm, 5.42 months in the T300+D and 5.55 months in the S arm.

***Disease Control Rate***

The proportion of patients in the FAS who achieved overall controlled disease based on RECIST 1.1 Investigator assessment (ie, patients achieving either CR, PR, or stable disease) was similar in all treatment arms (DCR was 54.8% in the D arm, 60.1% in the T300+D arm, and 60.7% in the S arm).

The Applicant's Position:

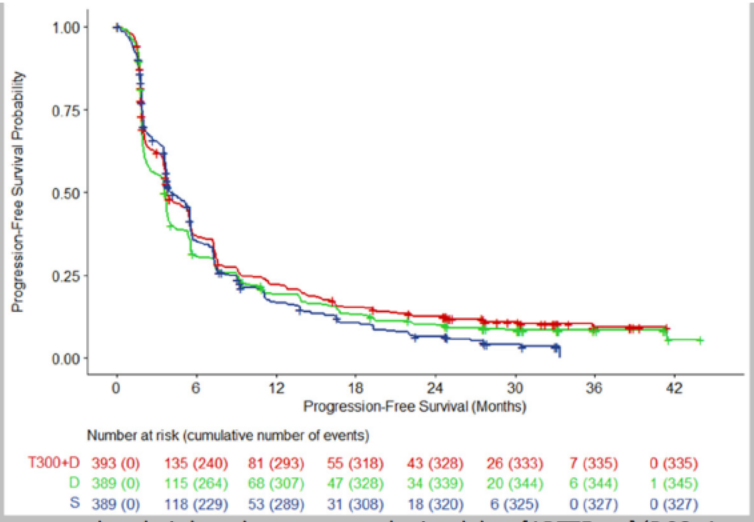
The benefit of T300+D was also observed across other secondary endpoints in HIMALAYA, including ORR. The Kaplan-Meier estimate for median PFS was similar in the HIMALAYA T300+D and S arms (HR = 0.90) with the curves separating in favor of T300+D. Overall, almost 50% of patients in the HIMALAYA IO arms continued to receive treatment after RECIST 1.1 progression, indicating that patients were receiving clinical benefit per Investigator assessment and suggesting that progression did not imply treatment resistance.

The FDA's Assessment:

FDA agrees with the results of the Applicant's analyses presented above. FDA provides the following additional assessment:

- The Kaplan-Meier estimate for median PFS per investigator assessment was 3.8 months (95% CI: 3.7, 5.3) in the T300+D arm, 3.6 months (95% CI: 3.2, 3.7) in the D arm, and 4.1 months (95% CI: 3.7, 5.5) in the S arm. The Kaplan-Meier plot for PFS for all 3 arms is presented in Figure 13. The stratified HR was 0.9 (95% CI: 0.77, 1.05) comparing T300+D arm vs. S arm, 1.02 (95% CI: 0.88, 1.20) comparing D arm vs. S arm, and 0.89 (95% CI: 0.76, 1.04) comparing T300+D arm vs. D arm.

**Figure 13 Kaplan-Meier Plot of Progression-Free Survival in All 3 Arms in HIMALAYA, FAS**




Source: FDA generated analysis based on sponsor submitted data [ADTTE.xpt] (DCO: August 27, 2021).

According to the SAP, PFS was censored for 2 or more consecutive missed visits but not censored for new anticancer therapy prior to progression. FDA repeated the PFS analysis where PFS was censored both for missed visits and for new anticancer therapy. The Kaplan-Meier estimate for median PFS was 3.8 months (95% CI: 3.7, 5.4) in the T300+D arm, 3.6 months (95% CI: 3.1, 3.7) in the D arm, and 4.0 months (95% CI: 3.7, 5.5) in the S arm, consistent with the results of the Applicant's analysis.

- The endpoints of PFS, ORR, TTP and DCR were not adjusted for multiplicity. The analyses of these endpoints are considered exploratory and the reported p-values for ORR odds ratios are nominal.

**Dose/Dose Response**

Data: See Section 6.3.2.

The Applicant's Position:
No clinically meaningful exposure-efficacy relationships were identified for this dose regimen, indicating that no dose optimization for uHCC is necessary. No dose adjustment is necessary based on body weight (> 30 kg) or other intrinsic or extrinsic factors based on covariate analysis in the PPK modeling. No apparent relationship between body weight and efficacy was observed, suggesting that the fixed dosing regimen used in the study was appropriate. For additional details, see Section 6.

The FDA's Assessment:
FDA agrees with the Applicant's position.

**Durability of Response**

Data:
In the FAS, median DoR from onset of objective response based on Investigator assessment per RECIST 1.1 was greater for patients in the T300+D arm (22.34 months) compared with the D (16.82 months) and S arms (18.43 months) (Table 20). Median TTR from randomization for patients with confirmed objective response based on Investigator assessment according to RECIST 1.1 was

approximately 1 month shorter for patients in the T300+D and D arms (2.09 and 2.17 months, respectively) compared with the S arm (3.78 months).

**Table 20 Duration of Response and Time to Onset of Objective Response in HIMALAYA (Final Analysis) According to Investigator Assessment per RECIST 1.1 (FAS)**

| | Investigator per RECIST 1.1 [a] | | |
|---|---|---|---|
| | D (N = 66) | T300+D (N = 79) | S (N = 20) |
| Patients with objective response, n (%) | 38 | 44 | 13 |
| Median DoR from onset of response (months) [b, c] | 16.82 | 22.34 | 18.43 |
| Median TTR from randomization (months) | 2.09 | 2.17 | 3.78 |

[a] Confirmed responses only.
[b] DoR is the time from the first documentation of CR/PR until the date of progression, death, or the last evaluable RECIST assessment for patients who do not progress.
[c] Calculated using the Kaplan-Meier method.
Source: Table 14.2.7.1.1.3, HIMALAYA CSR, Module 5.3.5.1

The Applicant's Position:
The benefit of T300+D was also observed for DoR in HIMALAYA.

The FDA's Assessment:
FDA agrees with the Applicant's analysis results presented above. Based on the Kaplan-Meier method, median DoR was 22.3 months (95% CI: 13.7, NR [not reached]) for T300+D arm, 16.8 months (95% CI: 10.0, 32.2) for the durvalumab arm, and 18.4 months (95% CI: 6.5, 26.0) for the sorafenib arm.

**Persistence of Effect**

Data:
The endpoints of OS and PFS are based on time-to-event analysis; thus, persistence of efficacy is inherent in the chosen efficacy measures. See secondary efficacy endpoints: ORR and DoR.

The Applicant's Position:
In HIMALAYA, T300+D provided sustained survival benefits compared to S (see Section 8.1.2). The OS benefit in the T300+D arm vs S was sustained over time with a trend in benefit observed throughout all prespecified OS landmarks, as supported by the greater proportion of patients treated with T300+D that were alive at 18, 24, and 36 months (48.7%, 40.5%, and 30.7%, respectively) compared to patients treated with S (41.5%, 32.6%, and 20.2%, respectively). Importantly, 50% more patients on the T300+D arm were alive at 36 months compared to S, demonstrating a clinically meaningful, prolonged survival benefit in this long-term efficacy measure.

The FDA's Assessment:
HIMALAYA demonstrated a statistically significant improvement in OS of T300+D over sorafenib in patients with 1L uHCC. As stated above, the landmark OS analyses comparing the T300+D arm vs. the sorafenib arm are considered exploratory. Given the non-proportionality observed in the Kaplan-Meier curve comparing OS of T300+D arm versus sorafenib arm, FDA acknowledges that the landmark OS analyses at 18, 24, and 36 months may provide supportive evidence of the improved treatment effect for T300+D over sorafenib.

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

The Applicant's Position:

T300+D demonstrated a clinically meaningful delay in time to deterioration in a broad range of patient-reported symptoms, function, and global health status/QoL compared with S and lower patient-reported symptom, functional, and HRQoL burden over time as evidenced by the change from baseline scores compared with S in patient-reported symptoms, function, and global health status/QoL.

The FDA's Assessment:

There was no pre-specified statistical testing procedure or alpha allocation for any PRO endpoints. All PRO analyses are considered exploratory, and no conclusions can be drawn from these results. FDA does not agree with the Applicant's position that T300+D demonstrated a clinically meaningful delay in time to deterioration in patient-reported symptoms as no threshold to define clinically meaningful worsening has been agreed to. All comparative claims are unsupported.

For completeness, FDA reviewed the data presented in the CSR assessing patient-reported outcomes using the European Organization for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire (QLQ-C30), EORTC 18-item hepatocellular cancer health-related quality of life questionnaire (QLQ-HCC18), EQ-5D-5L index and visual analog scale (VAS), patients global impression of change (PGIC) scale, and Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). However, given the exploratory nature of the PRO analyses, FDA did not conduct independent analyses to replicate all the results.

To help evaluate the quality of the PRO data, FDA calculated the completion rate for each PRO as the number of patients who completed the PRO assessment form divided by the number of patients in the FAS for each PRO assessment at each visit by treatment arm.

The completion rates for each PRO instrument are summarized below:

- For EORTC QLQ-C30, the completion rates at baseline were 77% for T300+D arm, 82% for the durvalumab arm, and 83% for the sorafenib arm. The completion rates remained > 50% for all three arms (54% for T300+D arm, 62% for durvalumab arm, and 50% for sorafenib arm) through week 16.
- For EORTC QLQ-HCC18, the completion rates at baseline were 75% for T300+D arm, 81% for the durvalumab arm, and 83% for the sorafenib arm. The completion rates remained > 50% for all three arms (54% for T300+D arm, 62% for durvalumab arm, and 50% for sorafenib arm) through week 16.
- For EQ-5D-5L, the completion rates at baseline were 75% for T300+D arm, 81% for the durvalumab arm, and 83% for the sorafenib arm. The completion rates remained > 50% for all three arms (54% for T300+D arm, 62% for durvalumab arm, and 50% for sorafenib arm) through week 16.
- For PGIC, there were no measurements at the baseline. The completion rates remained > 50% for the T300+D arm (53%) and durvalumab arm (62%) and was 49% for the sorafenib arm through week 16.
- For PRO-CTCAE, the completion rates at baseline were 41% for T300+D arm, and 47% for both the durvalumab and sorafenib arms. The completion rates remained ≥ 30% for all three arms (32% for T300+D arm, 35% for durvalumab arm, and 31% for sorafenib

arm) through Week 16.

FDA notes that completion rates decreased over time which further increases uncertainty in interpretation of the exploratory PRO endpoints, especially time to deterioration.

Lastly, FDA notes that the EQ-5D-5L is a composite that incorporates self-reported ability to function, pain, and general health status as filled out by the patient. This instrument is a generic preference-based measure intended to provide a health utility index value for use in economic analyses and lacks content validity for use in estimating clinical benefit for the purposes of labeling claims, though we acknowledge that this instrument is often used by other regulatory authorities and/or payers.

**Additional Analyses Conducted on the Individual Trial**

Data: See the Applicant's Position below

The Applicant's Position:
A post-hoc analysis calculating piecewise constant treatment effects for the D vs S demonstrated an HR of 0.98 between 0 to 9 months and an HR of 0.77 for 9 months onwards (Table 16). The delay in separation observed is consistent with the known profile of IO-only regimens.

The FDA's Assessment:
FDA considers the post-hoc analysis presented by the Applicant exploratory.

### 8.1.3. Study 22 (D4190C00022)

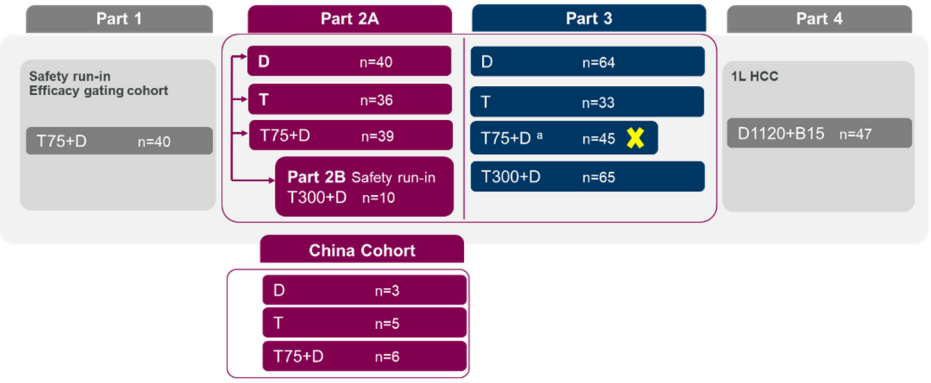
**Trial Design**

The Applicant's Description:
Supportive efficacy data have been drawn from the Phase I/II Study D4190C00022 (Study 22) that was an open-label, multicenter study to evaluate the safety, tolerability, and clinical activity of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab, in adult patients with advanced HCC, who were immunotherapy-naïve and had either progressed on, were intolerant to, or refused treatment with sorafenib or another VEGFR TKI. This was a multi-part study, as shown in Figure 14: Parts 1A (safety run-in cohort observing dose limiting toxicities), 1B (efficacy-gating cohort), 2A and 2B (safety run-in cohort for T300+D treatment arm), 3 (dose expansion cohort), and 4 plus a separate China cohort (which followed the study design for Part 2A). Patients were allocated to treatment without randomization in Parts 1, 2B, and 4 and randomized to treatment in Parts 2A, 3, and the China cohort.

Enrollment into the T75+D arm in Part 3 was closed following the results of an IA (DCO: 31 August 2018), which suggested that while all regimens were tolerable, T75+D did not provide added efficacy compared with D.

For this submission, Parts 2 and 3 of the study were used as supportive data; therefore, only results from Parts 2 and 3 will be presented in this document.

**Figure 14 Study 22: Study Design and Flow Diagram**




**D:** durvalumab monotherapy 1500 mg (20 mg/kg) Q4W
**T300+D:** tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W
**T:** tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W
**T75+D:** tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W
**D1120+B15:** durvalumab 1120 mg (15 mg/kg) + bevacizumab 15 mg/kg Q3W

The FDA's Assessment:
FDA agrees with the Applicant's description of the design of Study 22 and adds the following:

- For Part 2A, patients were randomized 1:1:1 to durvalumab, tremelimumab and T75+D arms stratified by viral status (uninfected, HCV infected, or HBV infected) and PD-L1 expression (positive, negative, or non-evaluable).
- For Part 3, patients were randomized 2:1:2 to durvalumab, tremelimumab and T300+D arms stratified by viral status (uninfected, HCV infected, or HBV infected) and sorafenib-based therapy (refusers, or all others).

**Study Endpoints**

The Applicant's Description:
The primary objective was to assess safety and tolerability across the different monotherapy and combination treatment regimens, based on Aes, SAEs, study treatment discontinuation due to toxicity, and changes from baseline in laboratory parameters, ECG, and vital signs. Evaluation of the efficacy of the different monotherapy and combination treatment regimens was a secondary objective, based on the following endpoints: OS, ORR, DCR, TTR, DoR, TTP, and PFS.

The FDA's Assessment:
FDA agrees with the Applicant's description of the study endpoints.

**Statistical Analysis Plan and Amendments**

The Applicant's Description:

All efficacy endpoints were analyzed in the FAS on the basis of randomized/allocated study IP(s), regardless of the study IP(s) actually received (iTT basis). In addition to the FAS, ORR was also analyzed on the Response Evaluable Population. No prespecified hypotheses and no formal statistical testing of efficacy endpoints were performed in this study.

The FDA's Assessment:

FDA agrees with the Applicant's description of the statistical analysis plan.

**Protocol Amendments**

The Applicant's Description:

The original CSP, dated 09 April 2015, was subject to 6 global amendments.

The FDA's Assessment:
FDA agrees with the Applicant's description of the protocol amendments.

### 8.1.4. Study Results: Study 22

**Compliance with Good Clinical Practices**

Data: Not applicable

The Applicant's Position:
The Sponsor's procedures, internal quality control measures, and audit program provide reassurance that the durvalumab and tremelimumab clinical development program is being conducted in accordance with GCP, as documented by the ICH.

The FDA's Assessment:
FDA agrees with the Applicant's position. There is no evidence that compliance with good clinical practices was violated during conduct of Study 22.

**Financial Disclosure**

Data:
Financial disclosures for Study 22 are addressed in Section 19.2 of this assessment aid.

The Applicant's Position:
The integrity of Study 22 data was not affected by the financial interest of the investigators.

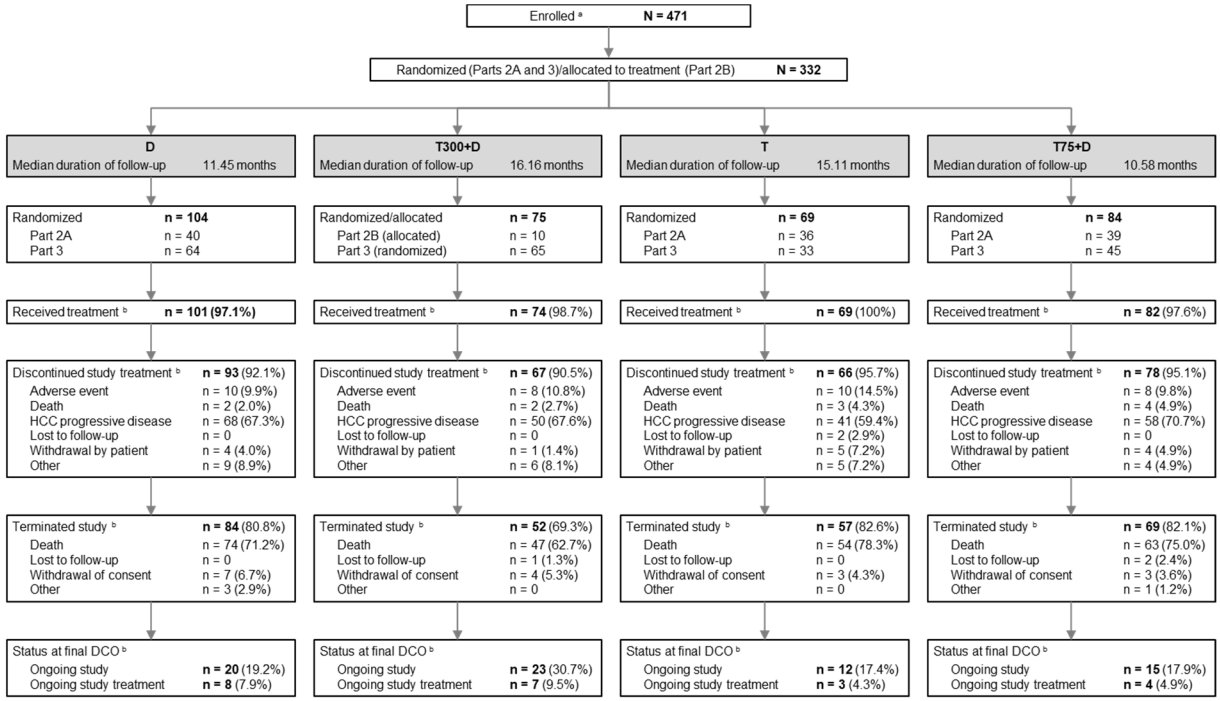
The FDA's Assessment:
Financial disclosure information for Study 22 is discussed above. See Section 19 for additional information.

**Patient Disposition**

Data: See the Applicant's Position below

The Applicant's Position:
For Parts 2 and 3, a total of 326 (98.2%) patients in the FAS received study treatment (Figure 15). At the final DCO, 93.3% of patients across all treatment arms discontinued study treatment. The most frequently reported reason for discontinuing study treatment was HCC disease progression in 66.6% of patients; 11% of patients discontinued due to Aes. The rate of study treatment discontinuation due to PD or Aes was similar across the T300+D and D treatment arms (Figure 15). Overall, the number and reasons for treatment discontinuation in Parts 2 and 3 did not raise any concerns about the conduct of the study.

**Figure 15 Patient Disposition in Study 22 (Parts 2A, 2B, and 3)**




[a] Patients who provided informed consent.
[b] Percentages calculated from the number of patients randomized (Parts 2A and 3)/allocated to treatment (Part 2B).
[c] Percentages calculated from the number of patients who received study treatment. For combination therapy arms (T300+D and T75+D), the reason for discontinuing durvalumab is reported.

Source: Tables 14.1.1, 14.1.1.2, 14.1.1.3, and 14.2.1, Study 22 CSR, Module 5.3.5.2

The FDA's Assessment:
FDA agrees with the Applicant's description of patient disposition. FDA notes that the number of patients allocated to treatment (N=332) did not include patients from the China-only cohort.

**Protocol Violations/Deviations**

Data: See the Applicant's Position below.

The Applicant's Position:
Thirteen patients (3.9%) in Parts 2 and 3 had important protocol deviations. The protocol deviations observed do not raise any concerns regarding the overall conduct or quality of the study, or with respect to the safety profile observed within the patient population enrolled. There were no protocol deviations resulting from the impact of COVID-19 pandemic restrictions.

The FDA's Assessment:
FDA agrees with the Applicant's description of important protocol deviations. Important protocol deviations were described by the following categories:

1. Patients randomized (Parts 2A and 3)/allocated to treatment (Parts 1, 2B and 4) but who did not receive study treatment.

2. Patients who deviate from key entry criteria per the Clinical Study Protocol (CSP) Amendment 6 (4-Jan-2019).

a) Inclusion criteria:

#5. Child-Pugh Score class A.

#6. ECOG performance status of 0 or 1.

b) Exclusion criteria: 1, 2, 4, 8, 11, 23.

#1. History of hepatic encephalopathy within past 12 months or requirement for medications to prevent or control encephalopathy (eg, no lactulose, rifaximin, etc if used for purposes of hepatic encephalopathy).

#2. GI Bleeding (eg, esophageal varices or ulcer bleeding) within 12 months. (Note: For patients with a history of GI bleeding for more than 12 months or assessed as high risk for esophageal variceal by the Investigator, adequate endoscopic therapy according to institutional standards is required).

#4. Main portal vein thrombosis (Vp4) as documented on imaging. (VP4 is defined as portal vein thrombosis in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe (or both)).

#8. Active or prior documented autoimmune or inflammatory disorders including inflammatory bowel disease (eg, colitis, Crohn's disease), diverticulitis, celiac disease, systemic lupus erythematosus; Wegener syndrome (granulomatosis with polyangitis); myasthenia gravis; Graves' disease; rheumatoid arthritis, hypophysitis, uveitis, etc. The following are exceptions to this criterion:

a) Subjects with vitiligo or alopecia.
b) Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement.
c) Subjects with psoriasis or eczema not requiring systemic treatment.

#11. Patients co-infected with HBV and HCV, or co-infected with HBV and hepatitis D virus (HDV). HBV positive [presence of hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibodies (anti-HBcAb) with detectable HBV DNA (≥10IU/ml)]; HCV positive (presence of anti-HCV antibodies); HDV positive (presence of anti-HDV antibodies).

#23. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension (defined as systolic blood pressure ≥ 150 mmHg and/or diastolic blood pressure ≥ 90 mmHg, with or without antihypertensive medication), unstable angina pectoris, cardiac arrhythmia, vena cava thrombosis, active peptic ulcer disease or gastritis, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from IP, or compromise the ability of the subject to give written informed consent.

3. Baseline RECIST scan > 42 days before randomization (Parts 2A and 3) or first dose of study drug (Parts 1, 2B and 4).

4. No baseline RECIST 1.1 assessment on or before date of randomization (Parts 2A and 3) or first dose of study drug (Parts 1, 2B and 4).
5. Received prohibited concomitant systemic anticancer therapy. Please refer to the Protocol Section 4.7.2 for the systemic anticancer agents that are detailed as being 'excluded' from permitted use during the study. This will be used as a guiding principle for the physician review of all medications prior to database lock.

Of the 13 patients with important protocol deviations, 2 were in the T300+D arm (2.7%), 6 were in the durvalumab arm (5.8%), 1 was in the tremelimumab arm (1.4%), and 4 were in the T75+D arm (4.8%).

**Table of Demographic Characteristics**

Data:

**Table 21 Demographic and Baseline Patient Characteristics in Parts 2 and 3 (FAS)**

| | Number (% of patients) | | | | |
|---|---|---|---|---|---|
| | **D (N = 104)** | **T300+D (N = 75)** | **T (N = 69)** | **T75+D (N = 84)** | **Total (N = 332)** |
| **Age (years)** | | | | | |
| Mean (standard deviation) | 64.0 (10.81) | 64.4 (11.24) | 61.5 (10.78) | 61.7 (11.10) | 63.0 (11.00) |
| Median | 64.5 | 66.0 | 62.0 | 61.5 | 64.0 |
| Minimum, maximum | 32, 89 | 26, 86 | 37, 81 | 28, 82 | 26, 89 |
| **Age group (years), n (%)** | | | | | |
| < 65 | 52 (50.0) | 34 (45.3) | 41 (59.4) | 48 (57.1) | 175 (52.7) |
| ≥ 65 – < 75 | 33 (31.7) | 31 (41.3) | 18 (26.1) | 26 (31.0) | 108 (32.5) |
| ≥ 75 | 19 (18.3) | 10 (13.3) | 10 (14.5) | 10 (11.9) | 49 (14.8) |
| **Sex, n (%)** | | | | | |
| Male | 92 (88.5) | 65 (86.7) | 57 (82.6) | 70 (83.3) | 284 (85.5) |
| Female | 12 (11.5) | 10 (13.3) | 12 (17.4) | 14 (16.7) | 48 (14.5) |
| **Region group, n (%)** | | | | | |
| Asia (except Japan) | 47 (45.2) | 31 (41.3) | 29 (42.0) | 38 (45.2) | 145 (43.7) |
| Rest of World (including Japan) | 57 (54.8) | 44 (58.7) | 40 (58.0) | 46 (54.8) | 187 (56.3) |
| **Race, n (%)** | | | | | |
| White | 35 (33.7) | 27 (36.0) | 26 (37.7) | 30 (35.7) | 118 (35.5) |
| Black or African American | 10 (9.6) | 4 (5.3) | 2 (2.9) | 5 (6.0) | 21 (6.3) |
| Asian | 55 (52.9) | 44 (58.7) | 39 (56.5) | 47 (56.0) | 185 (55.7) |
| Native Hawaiian or other Pacific Islander | 2 (1.9) | 0 | 1 (1.4) | 0 | 3 (0.9) |
| American Indian or Alaska Native | 1 (1.0) | 0 | 0 | 1 (1.2) | 2 (0.6) |
| Other | 1 (1.0) | 0 | 1 (1.4) | 1 (1.2) | 3 (0.9) |
| **Ethnic group, n (%)** | | | | | |
| Hispanic or Latino | 5 (4.8) | 4 (5.3) | 4 (5.8) | 5 (6.0) | 18 (5.4) |
| Not Hispanic or Latino | 99 (95.2) | 71 (94.7) | 65 (94.2) | 79 (94.0) | 314 (94.6) |
| **Weight group (kg), n (%)** | | | | | |
| < 70 | 47 (45.2) | 49 (65.3) | 37 (53.6) | 44 (52.4) | 177 (53.3) |

**Table 21 Demographic and Baseline Patient Characteristics in Parts 2 and 3 (FAS)**

| | Number (% of patients) | | | | |
|---|---|---|---|---|---|
| | D (N = 104) | T300+D (N = 75) | T (N = 69) | T75+D (N = 84) | Total (N = 332) |
| ≥ 70 – < 90 | 41 (39.4) | 20 (26.7) | 23 (33.3) | 26 (31.0) | 110 (33.1) |
| ≥ 90 | 15 (14.4) | 5 (6.7) | 9 (13.0) | 12 (14.3) | 41 (12.3) |
| Missing | 1 (1.0) | 1 (1.3) | 0 | 2 (2.4) | 4 (1.2) |
| **BMI group (kg/m$^2$), n (%)** | | | | | |
| Underweight (< 18.5) | 7 (6.7) | 4 (5.3) | 3 (4.3) | 3 (3.6) | 17 (5.1) |
| Normal (≥ 18.5 – < 25.0) | 47 (45.2) | 47 (62.7) | 32 (46.4) | 45 (53.6) | 171 (51.5) |
| Overweight (≥ 25.0 – < 30.0) | 32 (30.8) | 17 (22.7) | 21 (30.4) | 22 (26.2) | 92 (27.7) |
| Obese (≥ 30.0) | 17 (16.3) | 6 (8.0) | 13 (18.8) | 12 (14.3) | 48 (14.5) |
| Missing | 1 (1.0) | 1 (1.3) | 0 | 2 (2.4) | 4 (1.2) |
| **PD-L1 expression level [a]** | | | | | |
| TIP ≥ 1% | 55 (52.9) | 27 (36.0) | 40 (58.0) | 41 (48.8) | 163 (49.1) |
| TIP < 1% | 35 (33.7) | 38 (50.7) | 24 (34.8) | 31 (36.9) | 128 (38.6) |
| Missing | 14 (13.5) | 10 (13.3) | 5 (7.2) | 12 (14.3) | 41 (12.3) |

[a] PD-L1 status was defined as TIP ≥ 1% if PD-L1 staining of any intensity in tumor cell membranes and/or tumor-associated immune cells covered ≥ 1% of tumor area, and TIP < 1% if PD-L1 staining of any intensity in tumor cell membranes and/or tumor-associated immune cells covered < 1% of tumor area.

Baseline was the last assessment prior to the intake of the first dose of any study drug; for patients not treated, the last assessment on or prior to allocation/randomization was used.
Source: Tables 14.1.4 and 14.1.5 Study 22 CSR, Module 5.3.5.2

The Applicant's Position:
The demographic characteristics of patients in the FAS were representative of the intended patient population and were generally balanced across the 4 treatment arms, with the exception of weight, BMI, and PD-L1 expression level (Table 21).

The FDA's Assessment:
FDA agrees with the Applicant's summary of patients' demographic characteristics.

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Data: See the Applicant's Position below.

The Applicant's Position:
Baseline patient characteristics were generally similar between the 1L (ie, no prior sorafenib/VEGFR TKI therapy) and second-line subgroups (ie, patients who received prior sorafenib/VEGFR TKI therapy), and were balanced across treatment arms in both subgroups, with the exception of imbalances in BMI and weight as observed in the overall population (Table 21).

All patients in the FAS were required to have confirmed HCC based on histopathological findings from tumor tissues. Diagnosis of advanced HCC was confirmed pathologically or with non invasive methods.

At baseline, the majority of patients had Child-Pugh class A/5 (68.7%) or A/6 (28.9%) liver disease, reflecting well-preserved liver function. The remaining 2.4% of patients were Child-Pugh class B/7 and had been enrolled prior to protocol amendment 2 (30 March 2016), after which only patients with Child-Pugh class A were eligible for the study. Serum AFP levels were balanced across treatment arms.

The majority of patients (66.3% overall) received prior systemic therapy with sorafenib/VEGFR TKI, and the proportion of such patients was highest in the T300+D arm (73.3%) compared to the other 3 arms. Approximately half of patients (51.8%) entering Parts 2 and 3 experienced disease progression on prior sorafenib therapy, while 15.4% were classed as intolerant (47 patients who previously received sorafenib did not tolerate it; sorafenib was contraindicated in 4 patients). Sorafenib was refused by 32.8% of patients (1L HCC).

The FDA's Assessment:
FDA agrees with the Applicant's summary of patients' disease characteristics and description of prior therapy. Study 22 included both randomized and non-randomized adult patients with advanced HCC, who were immunotherapy-naïve and had either progressed on, were intolerant to, or refused treatment with sorafenib or another VEGFR TKI which differed from the population in the HIMALAYA trial and should be considered when interpreting study results.

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

Data:
The administration of all study drugs (including study treatment) was recorded in the appropriate sections of the eCRF. The most commonly received allowed concomitant medications by ≥ 20% of patients across all treatment arms were protein kinase inhibitors (77.1%), proton pump inhibitors (49.1%), nucleoside and nucleotide reverse transcriptase inhibitors (45.5%), glucocorticoids (35.2%), anilides (33.7%), natural opium alkaloids (33.1%), dihydropyridine derivatives (28.3%), sulfonamides plain (25.6%), osmotically acting laxatives (23.2%), and propulsives (21.1%).

The Applicant's Position:
Durvalumab and tremelimumab were administered via IV infusion at study sites. The level of study compliance (ie, attendance of planned visits and planned monitoring and laboratory tests) did not raise any concerns about the conduct of the study.

In Study 22 Parts 2 and 3, excluding corticosteroids and other medications used in the management of Aes of special interest including imAEs, the concomitant treatments administered during the study were generally balanced across treatment arms and were considered representative of those commonly prescribed to patients in the target population.

The FDA's Assessment:
FDA agrees with the Applicant's position.

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

Data: See the Applicant's Position below.

The Applicant's Position:
The primary objective of Study 22 was to assess safety and tolerability. Evaluation of the efficacy of the different monotherapy and combination treatment regimens was a secondary objective, based on the following endpoints: OS, ORR, DCR, TTR, DoR, TTP, and PFS, which are detailed below in Efficacy Results – Secondary and other relevant endpoints.

The FDA's Assessment:
FDA agrees with the Applicant's position. FDA is limited in the conclusions that can be made regarding

the safety and tolerability of the various tremelimumab regimens due to the absence of an appropriate comparator arm in the study.

**Data Quality and Integrity**

Data: Not applicable

The Applicant's Position:
No quality or integrity issues were identified for Study 22.

The FDA's Assessment:
FDA agrees with the Applicant's position.

**Efficacy Results – Secondary and Other Relevant Endpoints**

Data: See Table 22 for data from Study 22.

The Applicant's Position:
In Study 22, T300+D demonstrated the most clinically meaningful and durable benefit in terms of OS, ORR, and DoR when compared to D, T, or T75+D. Data from Study 22 act as an independent measure of contribution of components and demonstrated similar results to HIMALAYA in a predominately second-line uHCC population.

The FDA's Assessment:
FDA agrees with the Applicant's analysis results. Given that Study 22 was a multi-part phase I/II trial with efficacy endpoints as secondary endpoints and a study population that differed from the proposed indication in this application (i.e., 1L uHCC), FDA considers Study 22 to be a supportive trial.

**Dose/Dose Response**

Data: Not applicable for Study 22.

The Applicant's Position: Not applicable for Study 22.

The FDA's Assessment:
Not applicable.

**Durability of Response**

Data: See Table 22 for data from Study 22.

The Applicant's Position:
In Study 22, T300+D demonstrated the most clinically meaningful and durable benefit in terms of OS, ORR, and DoR when compared to D, T, or T75+D. Data from Study 22 act as an independent measure of contribution of components and demonstrated similar results to HIMALAYA in a predominately second-line uHCC population.

The FDA's Assessment:
FDA agrees with the Applicant's analysis results. Given that Study 22 was a multi-part phase I/II trial with efficacy endpoints as secondary endpoints and a study population that differed from the proposed indication in this application (i.e., 1L uHCC), FDA considers Study 22 to be a supportive trial.

**Persistence of Effect**

Data: Not applicable for Study 22.

The Applicant's Position: Not applicable for Study 22.

The FDA's Assessment:
Not applicable.

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

Data: Not applicable for Study 22.

The Applicant's Position: Not applicable for Study 22.

The FDA's Assessment:
Not applicable.

**Additional Analyses Conducted on the Individual Trial**

Data: Not applicable for Study 22.

The Applicant's Position: Not applicable for Study 22.

The FDA's Assessment:
Not applicable.

### 8.1.5. Integrated Review of Effectiveness

The FDA's Assessment:
Based on the results of the HIMALAYA trial, T300+D demonstrated a statistically significant and clinically meaningful effect on OS compared to sorafenib in patients with previously untreated uHCC, with a stratified HR of 0.78 (95% CI: 0.66, 0.92; p=0.0035). This effect corresponds to a 2.6-month improvement in median OS. FDA notes that durvalumab monotherapy did not demonstrate a statistically significant effect on OS when compared to sorafenib. FDA considered the results of the durvalumab v. sorafenib in the assessment of contribution of components for the T300+D regimen.

Study 22 provided supportive data to demonstrate the treatment effect of the proposed T300+D regimen, in addition to the treatment effect of tremelimumab and durvalumab monotherapy, in the second line uHCC setting. Descriptive survival and response data directionally favored T300+D and supported the primary efficacy results from the HIMALAYA trial. However, as Study 22 contained both randomized and non-randomized patients with only descriptive efficacy analyses, and the study population differed from the proposed indication in this application (i.e., 1L uHCC), no definite conclusion can be made.

### 8.1.6. Assessment of Efficacy Across Trials

**Primary Endpoints**

Data:

**Table 22 Data From HIMALAYA and Study 22 Relevant to the Recommended T300+D Regimen in Patients with uHCC**

| **Study**<br>**Analysis set** | **HIMALAYA**<br>**FAS (Final Analysis)** | | **Study 22 (Parts 2 and 3)**<br>**FAS (Final Analysis)** | | |
|---|---|---|---|---|---|
| | **D**<br>**(N = 389)** | **T300+D**<br>**(N = 393)** | **D**<br>**(N = 104)** | **T300+D**<br>**(N = 75)** | **T**<br>**(N = 69)** |
| **Median OS (months)** [a] | 16.56 | 16.43 | 12.91 | 17.05 | 17.05 |
| 95% CI for median OS | 14.06, 19.12 | 14.16, 19.58 | 8.74, 16.79 | 10.55, 22.83 | 11.33, 20.24 |
| HR (95% CI): T300+D vs D | 0.90 (0.76, 1.07) | | – | – | – |
| OS rate at 12 months, % [a] | 59.3 | 60.2 | 50.4 | 57.6 | 59.8 |
| OS rate at 18 months, % [a] | 47.4 | 48.7 | 34.0 | 47.8 | 43.3 |
| OS rate at 24 months, % [a] | 39.6 | 40.5 | 26.2 | 38.3 | 30.9 |
| OS rate at 36 months, % [a] | 24.7 | 30.7 | – | – | – |
| **Tumor response assessment** | **Investigator Assessment per RECIST 1.1** | | **BICR per RECIST 1.1** | | |
| **Median PFS (months)** [a] | 3.65 | 3.78 | 2.07 | 2.17 | 2.69 |
| 95% CI for median PFS | 3.19, 3.75 | 3.68, 5.32 | 1.84, 2.86 | 1.91, 5.42 | 1.87, 5.29 |
| Progression-free at DCO n (%) | 32 (8.2) | 49 (12.5) | 8 (7.7) | 11 (14.7) | 4 (5.8) |
| **ORR (%)** [b] | 17.0 | 20.1 | 11.5 | 24.0 | 7.2 |
| Complete response | 6 (1.5) | 12 (3.1) | 0 | 1 (1.3) | 0 |
| Partial response | 60 (15.4) | 67 (17.0) | 12 (11.5) | 17 (22.7) | 5 (7.2) |
| **DCR (%)** | 54.8 [c] | 60.1 [c] | 37.5 [b] | 45.3 [b] | 49.3 [b] |
| **Median DoR (months)** [c, d] | 16.82 | 22.34 | 14.95 | 18.43 | 23.95 |
| **Median TTR (months)** [c, e] | 2.09 | 2.17 | 3.65 | 2.28 | 1.81 |

[a] Calculated using the Kaplan-Meier method.

[b] Confirmed responses only.

[c] Response did not require confirmation.

[d] DoR is the time from the first documentation of CR/PR until the date of progression, death, or the last evaluable RECIST assessment for patients who do not progress.

[e] TTR is the time to onset of confirmed response from randomization (HIMALAYA; Study 22 Parts 2A and 3) or from treatment allocation (Study 22 Part 2B).

Source: Table 14.2.1.1, Table 14.2.1.2, Table 14.2.2.1, 14.2.4.1.1.2, Table 14.2.5.1.9, Table 14.2.6.1, and Table 14.2.7.1.1.3, HIMALAYA CSR, Module 5.3.5.1, and Table 14.2.1, Table 14.2.2.1, Table 14.2.3.1, Table 14.2.4.1, Table 14.2.5.1, and Table 14.2.6.1, Study 22 CSR, Module 5.3.5.2

The Applicant's Position:

***Contributions of Durvalumab and Tremelimumab to the Treatment Effect of T300+D***

Two independent well-conducted studies (HIMALAYA and Study 22) support a robust evaluation of the contribution of each component of the proposed T300+D regimen in 1L and second-line uHCC. Overall, the results support that a single priming dose of tremelimumab combined with durvalumab improves efficacy and has a clinically meaningful improvement over durvalumab monotherapy, with benefit of the tremelimumab priming dose observed across both studies (Table 22). Section 8.2.4 summarizes contributions of durvalumab and tremelimumab to the safety and tolerability profile of T300+D.

The mechanisms of action of CTLA-4 and PD-1 are non-redundant, meaning that targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity (Pardoll, 2012). In the proposed treatment regimen, a single priming dose of tremelimumab is added to durvalumab to derive benefit from dual

checkpoint blockade while minimizing exposure to CTLA-4 inhibition. As demonstrated in this study, the T300+D regimen increases both CD4+ and CD8+ T cells over that observed with durvalumab alone, supporting the proposed mechanism of action and additive nature of dual-checkpoint blockade. These pharmacodynamic data indicate that T300+D is capable of expanding a functionally and structurally distinct immune cell subset compared to D alone providing the biologic rationale supporting the differentiated clinical activity.

*Overall Survival: Contribution of Durvalumab*

Overall, the results from Study 22 and HIMALAYA support that durvalumab is an active therapy for the treatment of patients with uHCC based on the following conclusion:

- Durvalumab demonstrated NI to S, an active agent approved and recommended in the NCCN guidelines for 1L treatment of patients with uHCC, but did not cross the statistical boundary for superiority to S. Moreover, the data from Study 22 suggest similar survival estimates for D monotherapy when compared to OS results for D monotherapy from HIMALAYA.

*Overall Survival: Contribution of Tremelimumab to the T300+D regimen*

An external (non-sponsored) Phase II, uncontrolled study of high-dose tremelimumab monotherapy in patients with HCV-positive uHCC provided early evidence of promising antitumor activity with tremelimumab monotherapy in uHCC (Sangro et al 2013). Tremelimumab as a monotherapy was further investigated in Study 22 where clinical activity with durable responses coupled with prolonged OS in patients with uHCC was also demonstrated.

Overall, a single dose of tremelimumab resulted in a clinically meaningful prolonged survival benefit over D monotherapy with data from HIMALAYA supporting the overall benefit-risk conclusions:

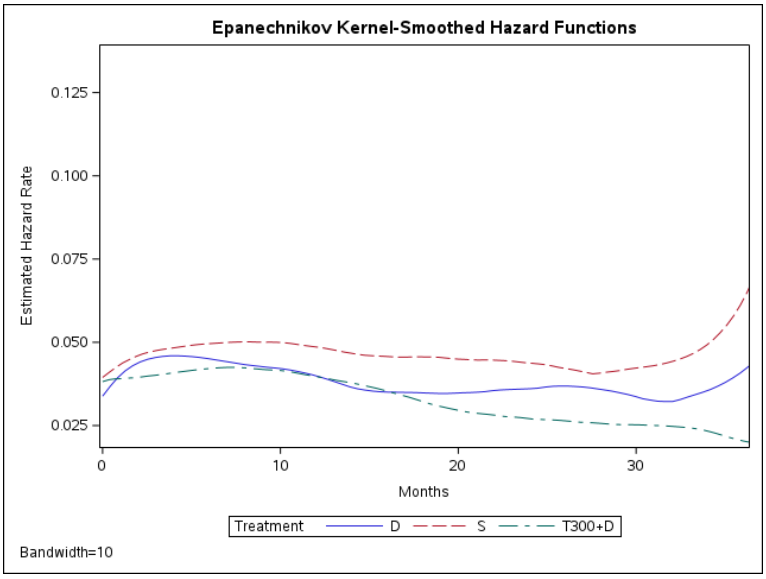
- The HIMALAYA study was designed to demonstrate superiority of T300+D vs S and was amended to demonstrate NI of D vs S based on findings from previous IO monotherapy Phase III trials like CheckMate 459 (Yau et al 2019) and KEYNOTE-240 (Finn et al 2020a). As hypothesized, while NI was demonstrated for D vs S, D failed to show superiority over S.
- An approximately 10% reduction in the average risk of death was observed with T300+D vs D (Table 22).
- A clear and sustained separation of the T300+D and D OS curves occurs at 24 months with a large proportion of patients (approximately 40% for T300+D and D) still at risk for an event at this time. The median duration of follow-up in patients for T300+D and D curves are 33 and 32 months, respectively, indicating a degree of stability of the OS curves at this time and where the T300+D curve begins to show a plateau.
- Prespecified OS rates of 18, 24, and 36 months in HIMALAYA numerically favored T300+D over D, with OS rate at 36 months of 30.7% with T300+D vs 24.7% for D, consistent with the tail effect expected with a CTLA-4 inhibitor as monotherapy and in combination (Table 22).
- Importantly, the T300+D curve separated from S at 4 months compared to a separation at 9 months for D vs S. A post-hoc analysis calculating piecewise constant treatment effects for the D vs S demonstrated an HR of 0.98 between 0 to 9 months and an HR of 0.77 for 9 months onwards (Table 16). The delay in separation observed is consistent with the known profile of IO-only regimens.

- Finally, the prespecified OS rates of 18, 24, and 36 months numerically favored T300+D over D. While not formally tested due to its position in the MTP, the 36-month OS rate demonstrated a nominally statistically significant improvement in T300+D compared to S ($p < 0.0029$).

Consistent results were reported from Study 22. Survival data demonstrate an increased benefit of the T300+D as compared to D monotherapy.

Finally, a Kernel-smoothed estimate of the hazard functions were used on the HIMALAYA data to contextualize the change in estimated hazard rates over time. This analysis illustrated that the T300+D hazard rate markedly decreased over time compared to S (Figure 16). The T300+D and D curves were similar until approximately 18 months from randomization, after which the hazard rates for T300+D decreased beyond that observed for D. This is consistent with the known mechanism of action of CTLA-4 inhibitors and combinations thereof, which drive a difference in the tails in the survival curve.

**Figure 16 HIMALAYA Kernel-smoothed Estimate of OS Hazard Rates**




Source: Figure 14.2.1.10, HIMALAYA CSR, Module 5.3.5.1

Collectively, these data support the clinical benefit of a single priming dose of tremelimumab in combination with durvalumab to improve OS.

The FDA's Assessment:
FDA acknowledges the Applicant's position. FDA agrees that HIMALAYA demonstrated a statistically significant and clinically meaningful improvement in OS for the T300+D vs. sorafenib comparison. With respect to the Applicant's statement that "… the results support that a single priming dose of tremelimumab combined with durvalumab improves efficacy and has a clinically meaningful improvement over durvalumab monotherapy," FDA notes that the HIMALAYA trial was not designed to evaluate overall survival of T300+D vs durvalumab. As such, comparisons of these two arms are descriptive and cannot be used to serve as basis to conclude whether T300+D is more efficacious than durvalumab alone. However, given the durvalumab treatment failed to demonstrate a statistically significant improvement in OS compared to sorafenib, the results of this analysis provide support that

both components of the T300+D combination regimen are necessary to achieve a statistically significant OS effect over sorafenib.

FDA also acknowledges that Study 22 provides support for the contribution of each component of the proposed T300+D regimen in patients with 2L uHCC. Median OS in T300+D arm (17.1 months [95% CI: 10.5, 23.0]) was numerically higher than median OS in D arm (12.9 months [95% CI: 8.7, 16.8]). However, given that Study 22 pooled efficacy results from multi-part of the study, which contains both randomized and non-randomized patients, with efficacy endpoints as secondary endpoints without formal testing and a study population that differed from the proposed indication in this application (i.e., 1L uHCC), FDA considers Study 22 to be supportive only.

**Secondary and Other Endpoints**

Data:
See Table 22.

The Applicant's Position:

***Tumor Response Endpoints***
The addition of a single priming dose of tremelimumab to durvalumab increases response while maintaining durability.

- Objective response rates in HIMALAYA were 20.1% with T300+D and 17.0% with D, and were also higher with T300+D than D in Study 22 (24.0% vs 11.5%) (Table 22).
- Twice as many BORs of CR were observed in HIMALAYA with T300+D (12 [3.1%]) compared to D (6 [1.5%]) (Table 22), and DCRs were higher in the T300+D arm (60.1%) compared to D (54.8%).
- Treatment with T300+D resulted in a longer median DoR (22.34 months) compared to D (16.82 months) in HIMALAYA and in Study 22 (18.43 months compared to 14.95 months) (Table 22).
- Tremelimumab demonstrated clinical activity and durable response in patients with uHCC (Table 22). While the response rate for tremelimumab monotherapy was 7.2%, responses were durable (23.95 months). The median OS of 17.05 months for T was similar to that observed with T300+D (Table 22). Thus, the limited ORR in patients receiving tremelimumab does not preclude an OS benefit.

*Progression-free Survival*
PFS may not be an appropriate endpoint to capture clinical benefit in the metastatic setting for HCC, as emergent data suggest that the pattern of progression may be more relevant for predicting survival outcomes (Bruix et al 2017, Bruix et al 2019, Reig et al 2013, Terashima et al 2016). The median PFS for T300+D was 3.78 months and 4.07 months for Sorafenib (HR = 0.90 [95% CI: 0.77, 1.05]) and was similar between the T300+D and D (HR = 1.02). However, more patients receiving T300+D remained progression-free at the final DCO (13% in T300+D compared to 5% in Sorafenib, which is consistent with the overall tail effect in the OS KM curve. In addition, almost 50% of patients in the HIMALAYA IO arms continued to receive treatment after RECIST 1.1 progression, indicating that patients were receiving clinical benefit per Investigator assessment and suggesting that progression did not imply treatment resistance. Most patients received at least 3 cycles of treatment after disease progression, with the highest proportion in the T300+D arm: 52% in T300+D arm compared to 34% in the S arm. In addition, patients with a BOR of PD in the T300+D arm experienced a better OS outcome when compared with

the same group of patients in the S arm further supporting that PFS is not a direct measure of clinical benefit.

*Patient-reported Outcomes*
A single priming dose of tremelimumab combined with durvalumab also results in clinically meaningful improvement in patient-reported symptoms, functioning, and HRQoL. Longer median time to deterioration of EORTC QLQ-C30 nausea and EORTC QLQ-HCC18 abdominal swelling were only observed with T300+D vs S and not with D.

***Conclusions for Contribution of Components***
The data contained in this application provide for a robust analysis of the contribution of components. Taken together, data from HIMALAYA and Study 22 indicate that a single priming dose of tremelimumab combined with durvalumab improves efficacy and has a clinically meaningful improvement over durvalumab monotherapy. Consistency of improved benefit of the T300+D over D was observed across all prespecified endpoints from 2 independent studies.

The FDA's Assessment:
FDA acknowledges the Applicant's position. Given ORR, DoR, PFS and PRO endpoints were not adjusted for multiplicity in HIMALAYA, the analyses of these endpoints are considered exploratory. Similarly, as stated above, efficacy analysis results from Study 22 are also considered exploratory and supportive. Conclusions regarding the necessity of tremelimumab to durvalumab are primarily based on the statistically significant improvement in OS that was observed with the T300+D regimen compared to S but was not demonstrated in the comparison of durvalumab to sorafenib in the HIMALAYA trial.

### Subpopulations

Data: Not applicable.

The Applicant's Position: Not applicable.

The FDA's Assessment:
Not applicable.

### Additional Efficacy Considerations

The FDA's Assessment:
Not applicable.

## 8.1.7. Integrated Assessment of Effectiveness

Data:
See efficacy results for HIMALAYA and Study 22 in Sections 8.1.2 and 8.1.4.

The Applicant's Position:
Overall, the study results were as expected based on the mechanism of immune checkpoint blockade in this indication and reflected in the design of the MTP.

The T300+D regimen met the primary objective of superiority over S demonstrating a statistically significant, clinically meaningful, sustained OS benefit in patients with uHCC (HR = 0.78; 96.02% CI: 0.65, 0.93; p = 0.0035).

Contribution of components data from both HIMALAYA (a 3-arm design) and Study 22 support that a single priming dose of tremelimumab combined with durvalumab improves efficacy and has a clinically meaningful prolonged survival benefit over durvalumab monotherapy. Moreover, the data are consistent with the biological rationale that dual immune checkpoint blockade mobilizes distinct immune cell repertoire that ultimately manifests in additive clinical benefit over durvalumab monotherapy. This rationale was supported by pharmacodynamic data from Study 22.

Furthermore, data demonstrate that the benefit observed for T300+D was consistent across HIMALAYA and Study 22, suggesting that the T300+D regimen provided a clinically meaningful improvement in tumor response and survival in patients with uHCC.

The FDA's Assessment:
HIMALAYA was a randomized, open-label, active-controlled, multicenter clinical trial in patients with uHCC who are not eligible for locoregional therapy and have not received prior systemic therapy. Patients were randomized (1:1:1) to received tremelimumab (1500 mg) as a one-time single dose administered intravenously (IV) in combination with durvalumab 1500 mg on the same day, followed by durvalumab 1500 mg Q4W (T300+D); durvalumab 1500 mg Q4W (D); or sorafenib 400 mg given orally twice daily (S). The trial demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of OS comparing T300+D with sorafenib (stratified HR=0.78 [95% CI: 0.66, 0.92]; stratified log-rank 2-sided p-value=0.0035), corresponding to a 2.6-month improvement in median OS. However, the trial failed to demonstrate a statistically significant improvement in the key secondary endpoint of OS comparing durvalumab to sorafenib (stratified HR=0.86 [95% CI: 0.73, 1.01]; stratified log-rank 2-sided p-value=0.0674). This demonstrated that both components of the T300+D combination regimen are necessary to achieve a statistically significant OS effect over sorafenib. Additional information regarding the anti-tumor activity of the T300+D regimen durvalumab monotherapy was provided by Study 22, a Phase I/II study in patients with advanced HCC, who were immunotherapy-naïve and had either progressed on, were intolerant to, or refused treatment with sorafenib or another VEGFR TKI.

## 8.2. Review of Safety

Data:
The evidence supporting the evaluation of safety and tolerability in the proposed indication is based on the results of HIMALAYA and Study 22.

In addition, this application package includes supportive safety data that comprises 5 safety pools: HCC T300+D pool (N = 462), HCC D pool (N = 492), Pan-tumor D pool (N = 4045), Pan-tumor T75+D pool (N = 3319), and Pan-tumor T750 pool (N = 643). Data supporting safety and tolerability claims are presented in the below sections.

The Applicant's Position:
Overall, the safety and tolerability of tremelimumab administered in combination with durvalumab was consistent with the known safety profile for each agent, and AEs were well tolerated and manageable according to toxicity management guidelines (Section 8.2.11).

The FDA's Assessment:
The data supporting FDA's assessment of the safety of tremelimumab in combination with durvalumab is based primarily on the HIMALAYA trial, a global, randomized, controlled study of T300+D (n=388) versus sorafenib (n=374) for the treatment of unresectable HCC in patients with no prior systemic therapy. The safety analysis population consists of patients who received tremelimumab at a dose of 300 mg IV x1 in combination with durvalumab 1500 mg IV or sorafenib 400 mg taken orally (PO) twice daily (BID). Study treatment continued until unacceptable toxicity, disease progression, withdrawal of consent or end of study.

The safety profile, including adverse events of special interest (AEOSI) and immune-mediated AEs, in patients who received tremelimumab in combination with durvalumab is generally consistent (with regard to the types of adverse events observed) with the established and well characterized safety profile of durvalumab and the safety profile that has been observed in studies of tremelimumab, as well as the combination of dual immune checkpoint inhibition. Overall, the safety profile based on the HIMALAYA safety dataset did not reveal new or unexpected safety events in patients with unresectable HCC. Treatment with tremelimumab plus durvalumab did not result in excess deaths compared to the control arm.

### 8.2.1. Safety Review Approach

Data: Not applicable

The Applicant's Position:
The safety dataset used to characterize the safety profile of durvalumab in combination with tremelimumab in the proposed indication was derived from the HCC tumor pools. Supportive assessments of the safety and tolerability of tremelimumab and durvalumab were provided through evaluation of pooled data from multiple tumor types, predominately included data from lung and head and neck cancers.

The evidence supporting the safety and tolerability in the proposed indication is based on data from patients who received the T300+D regimen in HIMALAYA pooled with Study 22 (N = 462) as well as data from the T300+D arm (N = 388) of the HIMALAYA study. Patients from HIMALAYA and Study 22 contributed to the evaluation of safety if they received at least 1 dose of durvalumab given at a dose of 1500 mg IV Q4W (or equivalent) in combination with tremelimumab 300 mg IV × 1 dose (or equivalent).

The frequency of ADRs with T300+D in patients with uHCC has been primarily derived from the HCC T300+D pool. This population is considered the most appropriate to define ADRs as it directly reflects the safety profile observed in the target population. Supportive safety data are provided from a HCC D pool and 3 Pan tumor pools from other studies in the Sponsor's development program from studies in Table 12 defined as follows:

> HCC D pool (N = 492): all patients from HIMALAYA and Study 22 who have received at least 1 dose of durvalumab given at a dose of 20 mg/kg Q4W IV (or equivalent) for HCC for any line of therapy.

Pan-tumor D pool (N = 4045): all patients from included studies who have received at least 1 dose of durvalumab monotherapy given at a dose of either 10 mg/kg Q2W IV (or equivalent) or 20 mg/kg Q4W IV (or equivalent) for any line of therapy (across tumor types, including HCC).
Pan-tumor T75+D pool (N = 3319): all patients from included studies who have received at least 1 dose of durvalumab monotherapy given at a dose of 20 mg/kg Q4W IV (or equivalent) in combination with tremelimumab 1 mg/kg Q4W IV (or equivalent) for any line of therapy (across tumor types, including HCC).
Pan-tumor T750 pool (N = 643): all patients from included studies who have received at least 1 dose of tremelimumab monotherapy 10 mg/kg Q4W (or equivalent), for any line of therapy (across tumor types, including HCC).

The FDA's Assessment:

The FDA safety review focused on analyses of the incidence of key adverse event (AE) categories including fatal and nonfatal SAEs, AEs resulting in permanent discontinuation of treatment, common AEs, Grade >3 AEs, and AEOSI in patients receiving tremelimumab in combination with durvalumab on the HIMALAYA study. There were no clinical holds for safety during the development program for tremelimumab in combination with durvalumab. Furthermore, as stated in a Written Response Letter on March 2, 2020, the FDA agrees to the presentation of individual (HIMALAYA trial) and pooled datasets (as listed above) to support the application review of safety.

FDA agrees with each select AE category including AEs regardless of causality, and events occurring within 90 days of the last dose of study drug(s). FDA is also in agreement with the definition of an adverse event of special interest (AEOSI) which includes, but was not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as treatment with steroids, immunosuppressants, and/or hormone replacement therapy. The Applicant defined an immune-mediated adverse event (imAE) as an AEOSI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. AEOSI reported to the associated with durvalumab and/or tremelimumab include the following:

- Diarrhea/colitis
- Pneumonitis/ILD
- ALT/AST increases/hepatitis/hepatotoxicity
- Neuropathy/neuromuscular toxicity (e.g., Guillain-Barré and myasthenia gravis)
- Endocrinopathies (i.e., events of hypophysitis, hypopituitarism adrenal insufficiency, diabetes insipidus, hyper- and hypothyroidism, and type I diabetes mellitus)
- Rash/dermatitis
- Nephritis/blood creatinine increases
- Pancreatitis (or laboratory results suggestive of pancreatitis - increased serum, lipase, increased serum amylase)
- Other inflammatory responses that are rare with a potential immune-mediated etiology include, but are not limited to, myocarditis, pericarditis, and uveitis

### 8.2.2. Review of the Safety Database

**Overall Exposure**

Data:
The HCC T300+D pool, which included 462 patients with uHCC from HIMALAYA and Study 22 who received T300+D. These patients had a median total duration of exposure to durvalumab of 20.0 weeks (range: 2 to 185), and approximately 50% received at least 20 weeks of durvalumab treatment. Supportive data are provided by the Pan-tumor T75+D pool, which included 3319 patients across tumor types who had a median total duration of exposure to durvalumab of 16.0 weeks (range: 1 to 222), and approximately 40% received at least 20 weeks of durvalumab treatment. HIMALAYA and Study 22 were conducted in 16 and 9 countries, respectively, worldwide.

The mean number of tremelimumab infusions was 1.1 in the HIMALAYA T300+D arm and in the HCC T300+D pool, both of which included 1 scheduled dose of tremelimumab. The mean number of tremelimumab infusions was 3.1 in the Pan tumor T75+D pool, which included 3 scheduled doses of tremelimumab. Of note, patients in the T300+D or T75+D arms of HIMALAYA who completed the first 5 cycles of the initial treatment phases with clinical benefit (per investigator judgement) but who subsequently had evidence of PD during the scheduled durvalumab monotherapy phase could be rechallenged with tremelimumab if they met the eligibility criteria for rechallenge.

The median total duration of exposure to S in HIMALAYA was 17.8 weeks (range: 0 to 168).

The Applicant's Position:
The duration of exposure in the HIMALAYA T300+D arm and tumor pools is sufficient to evaluate the safety and tolerability of durvalumab and tremelimumab in combination in the proposed indication.

The FDA's Assessment:
FDA agrees with the Applicant's presentation of exposure as it pertains to the HIMALAYA trial. The overall exposure was lower in the sorafenib arm compared to the T300+D arm. The median total (which includes initial treatment and when rechallenge with tremelimumab occurred) treatment duration was longer in the T300+D arm compared to the sorafenib arm (5.5 months versus 4.1 months) and there were no tremelimumab or durvalumab dose reductions for weight-based dosing. In the T300+D arm all patients in the safety analysis set received the single dose of tremelimumab 300 mg in Cycle 1, with just 30 patients rechallenged with 1 additional dose of tremelimumab 300 mg administered in combination with durvalumab. The median number of durvalumab treatment cycles received in the T300+D arm was 6.0 (Q1 to Q3 2.0 to 16.0) and the mean number of doses in the sorafenib arm was 219.6. The mean relative dose intensity (RDI) was higher in the T300+D arm (100% for tremelimumab and 97.7% for durvalumab) versus the sorafenib arm (78.3%). The median number of treatment cycles (1 cycle equals 28 days) received in the T300+D arm 3.0 and 2.0 in the sorafenib arm.

Despite the lower overall exposure of sorafenib compared to T300+D, the overall exposure rate is still adequate to support characterization of the safety profile in both arms. The incidence of safety events in the T300+D arm are evaluated in the context of a slightly longer median duration of treatment compared to the sorafenib arm.

**Relevant Characteristics of the Safety Population:**

Data:
For details on demographic and baseline characteristics, see Table 14 for HIMALAYA; Table 21 for Study 22.

The Applicant's Position:
Overall, the demographic and disease characteristics of patients were generally well balanced and consistent between the HIMALAYA T300+D arm and HCC T300+D pool and were representative of patients who will receive T300+D in line with the proposed label and in line with clinical practice. In HIMALAYA, the T300+D and S arms were balanced in terms of demographic and baseline characteristics.

The FDA's Assessment:
FDA agrees with the Applicant's description of the demographic and baseline characteristics of the study population. There were 4 of 393 (1%) patients randomized to the T300+D arm and 15 of 389 (3.9%) patients randomized to the sorafenib arm in the HIMALAYA trial who did not initiate study treatment. There were no important differences identified in the demographic and disease characteristics between the ITT and the safety population.

FDA notes that HCC is 2 to 4 times more common in males than in females and this ratio is reflected in the study population. The HIMALAYA trial was conducted in sites within the United States (U.S.), Canada, Brazil, Europe, Russia, and Asia; there were no clinical trial sites in sub-Saharan Africa where the incidence of HCC is one the highest in the world.

Seventy-one participants (9%) from the U.S. were randomized to either T300+D (n=31) or the sorafenib arm (n=40). FDA notes that the incidence of HCC in the U.S. is highest amongst patients who identify as American Indian/Alaskan Native, followed by Hispanic (any race), Asian/Pacific Islander, Black, and White (SEER 2019). The HIMALAYA study population included only 22 patients of Hispanic ethnicity, 17 Black patients, 1 Native Hawaiian/Pacific Islander patient, and no American Indian/Alaskan Native patients randomized to the T300+D or sorafenib arms, so it is not possible to draw any definitive safety conclusions based on a diverse study population. There is a balanced representation of older patients across the treatment arms (≥75 consisted of 13.5% of participants in the T300+D arm and 14.7% in the S arm).

**Adequacy of the Safety Database:**

Data:
The safety dataset used to characterize the safety profile of durvalumab in combination with tremelimumab in the proposed indication was derived from pooled data from HIMALAYA and Study 22 (HCC T300+D pool [N = 462]) as well as data from the T300+D arm (N = 388) of the HIMALAYA study. Supportive safety data are also provided from a HCC D pool and based on HIMALAYA and Study 22 and 3 Pan tumor pools, which maximize the utility of data within the Sponsor's development program and allow for the identification of additional rare AEs and the characterization of the safety profile of tremelimumab in combination with durvalumab in a larger patient population that includes patients across various tumor types and stages of disease.

The Applicant's Position:
The size and duration of exposure in the HIMALAYA T300+D arm and tumor pools is sufficient to

evaluate the safety and tolerability of durvalumab and tremelimumab in combination in the proposed indication.

The FDA's Assessment:
FDA agrees that the safety database supporting the application is adequate in size with sufficient duration of treatment with the investigational regimen at the proposed dose for a thorough assessment of adverse events. Overall, the disease characteristics of the study population are relevant to the target US population.

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

**Issues Regarding Data Integrity and Submission Quality**

Data:
No issues relating to data integrity or quality were identified for the HIMALAYA study.

The Applicant's Position:
The submission contains all required components of the eCTD. The overall quality and integrity of the application is adequate for substantive review to be completed. No meaningful concerns affecting a complete review of safety have been reported.

The FDA's Assessment:
FDA acknowledges the Applicant's position; the review did not uncover any data integrity issues related to safety. FDA agrees that the BLA submission was complete.

On August 24, 2022 the Applicant notified FDA regarding data anomalies at clinical site 6208 in Russia. This site randomized 14 patients into the HIMALAYA study between December 2017 and July 2019 (4 patients randomized to D monotherapy, 2 patients randomized to T300+D, 2 patients randomized to T75+D and 6 patients randomized to Sorafenib).

During a routine monitoring visit the site notified the Applicant CRA about discrepancies in survival data identified when site staff compared study data to that reported in the local oncology registry. In July 2022, the Applicant conducted an onsite investigation to review the survival data of all randomized patients at site 6208, As part of this investigation the Applicant requested the site compare death dates reported in the CRF to those recorded in the local oncology registry. Medical records, source documents and data from the local oncology registry were reviewed for all 14 patients randomized at site 6208, including review of documentation supporting informed consent collection, randomization, dosing, treatment discontinuation and safety data. Death dates from source data and have been compared to a local registry data and death certificates for the 13 deceased patients. Data anomalies were identified for 4 of the 14 patients randomized at this site. The survival data in the CRF and source documents for the remaining 10 patients were consistent with the local oncology registry and death certificates.

- (b) (6) – Randomized to T300+D and per the source documents and CRF, the recorded death date was (b) (6) however, the date of death in the local oncology registry is (b) (6) (b) (6) Review of the patient's death certificate confirms the date of death as (b) (6)
- (b) (6) – Randomized to durvalumab monotherapy and the recorded death date was (b) (6) (b) (6) but a withdrawal from further treatment form appears to have been signed by the



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

patient on (b) (6) which is after the recorded date of the patient's death in the local oncology registry (b) (6) Review of the patient's death certificate confirms that date of death as (b) (6)

- (b) (6) – Randomized to S, the recorded death date was (b) (6) however, the date of death in the local oncology registry is (b) (6) (a day earlier).
- (b) (6) – Randomized to Sorafenib, the patient was reported alive on the survival CRF at the time of the primary analysis database lock (b) (6) but local oncology registry noted the patient died on (b) (6) and death certificate confirmed this. In addition, the source document recording telephone contact between the sub-investigator and the patient on (b) (6) could not be found and was determined to be lost by the site.

For patient (b) (6) the death discrepancy of 1 day was attributed to human error. For the other 3 patients the discrepancies above involve the same sub-investigator who is no longer affiliated with the site. The date of death on the death certificate was earlier than the date reported by the sub-investigator with variability ranging from 11 to 275 days. There was no clear pattern identified in the death date anomalies to suggest a specific motive for the data discrepancies. The PI at this site became aware of the death date discrepancies during preparation for a data monitoring visit by the Applicant. This PI also acknowledged that the sub-investigator associated with three of these cases had limited experience with clinical trials and inadequate oversight was provided. Considering the significant data anomalies at this site were limited to 3 patients treated by the same sub-investigator, FDA agrees with the Applicant's conclusion that this quality issue is most likely confined to one sub-investigator at this site.

Sensitivity analyses were conducted to determine the impact of these data anomalies on the primary OS endpoint. Overall survival results for these sensitivity analyses were consistent with the original FAS population with only decimal differences (Table 17). See Section 8.1.2 (Data Quality and Integrity) for additional information.

**Categorization of Adverse Event**

Data: See the Applicant's Position below.

The Applicant's Position:
The evaluation of safety and tolerability was based on the overall incidence and nature of AEs, CTCAE Version 4.03 Grade 3 or 4 AEs, SAEs, AEs leading to death, AEs leading to discontinuation of durvalumab or tremelimumab, AEs leading to dose delays or dose interruptions, AESIs, AEPIs, and imAEs, and on data pertaining to clinical laboratory results (clinical chemistry, hematology, and urinalysis), vital signs, ECGs, and physical examination findings.

The integrated analysis of AEs for the safety pools was based on all treatment-emergent AEs as defined in each individual study. There are some minor differences in data conventions. These differences are minor and they do not have a significant impact on the ability to pool data from these studies.

MedDRA v23.1 was used for coding of AE data. Data from studies originally reported in previous versions of MedDRA were upcoded to MedDRA v23.1 for the integrated safety database.

A programmatic process (via Applicant-defined "imAE algorithm") allows for imAE frequencies to be calculated from both AEOSI and AEPI based on an algorithm that considers interventions involving systemic steroid therapy, high-dose steroid, immunosuppressant use, and/or endocrine therapy (which, in the case of AEPI, occurs after first applying consideration of an Investigator's causality assessment of the AE to any study treatment and/or an Investigator's designation of an event as immune-mediated).

The FDA's Assessment:
FDA agrees with the Applicant's description of the methods used for coding, categorizing, and grading AEs and the procedures for interrogating the safety data for pre-specified IMAE. FDA described the assessment and agreement with definition and categorization of AEs, AEOSI and imAEs in Section 8.2.1.

**Routine Clinical Tests**

Data: See the Applicant's Position below.

The Applicant's Position:
The pooled laboratory analyses are based on the data collected during the treatment period, which is defined as up to 90 days after the last dose of study treatment or date of initiation of subsequent systemic anticancer therapy excluding palliative radiotherapy (whichever occurred first). All laboratory values are graded according to CTCAE version 4.03 and the reference ranges used in the individual studies.

The FDA's Assessment:
FDA reviewed the study protocol and agreed with the method of the routine clinical and laboratory assessments obtained during the HIMALAYA trial. Safety monitoring employed during the HIMALAYA trial is considered to be adequate and consistent with the safety monitoring of patients receiving standard of care immune checkpoint inhibitor therapy for first line uHCC. Routine laboratory assessments were required within 28 days of randomization followed by every 4 weeks during study treatment (within 3 days prior to dosing in each cycle) and at 30 and 90 days after the last dose of study treatment.

### 8.2.4. Safety Results

**Deaths**

Data:

**Table 23 Adverse Events with Outcome of Death, by Preferred Term (Safety Analysis Set)**

| | Number (%) of Patients [a] | | | | |
|---|---|---|---|---|---|
| | HCC-tumor Pool | | Pan-tumor Pool | | |
| | T300+D | D | D | T75+D | T750 |
| MedDRA Preferred Term | (N = 462) | (N = 492) | (N = 4045) | (N = 3319) | (N = 643) |
| Patients with any AE with outcome of death | 34 (7.4) | 30 (6.1) | 231 (5.7) | 229 (6.9) | 44 (6.8) |
| Death | 5 (1.1) | 8 (1.6) | 21 (0.5) | 17 (0.5) | 0 |
| Cardiac arrest | 2 (0.4) | 1 (0.2) | 7 (0.2) | 6 (0.2) | 1 (0.2) |
| Haemorrhage intracranial | 2 (0.4) | 0 | 0 | 0 | 0 |

**Table 23 Adverse Events with Outcome of Death, by Preferred Term (Safety Analysis Set)**

| | Number (%) of Patients [a] | | | | |
|---|---|---|---|---|---|
| | HCC-tumor Pool | | Pan-tumor Pool | | |
| | T300+D | D | D | T75+D | T750 |
| MedDRA Preferred Term | (N = 462) | (N = 492) | (N = 4045) | (N = 3319) | (N = 643) |
| Hepatic failure | 2 (0.4) | 3 (0.6) | 5 (0.1) | 2 (< 0.1) | 0 |
| Immune-mediated hepatitis | 2 (0.4) | 0 | 0 | 0 | 0 |
| Pneumonia | 2 (0.4) | 0 | 15 (0.4) | 22 (0.7) | 3 (0.5) |
| Pneumonitis | 2 (0.4) | 1 (0.2) | 7 (0.2) | 10 (0.3) | 0 |
| Acute kidney injury | 1 (0.2) | 0 | 3 (<0.1) | 4 (0.1) | 0 |
| Acute respiratory distress syndrome | 1 (0.2) | 0 | 0 | 1 (< 0.1) | 0 |
| Cerebral haemorrhage | 1 (0.2) | 0 | 0 | 1 (< 0.1) | 0 |
| Gastric ulcer haemorrhage | 1 (0.2) | 0 | 0 | 0 | 0 |
| Gastrointestinal haemorrhage | 1 (0.2) | 3 (0.6) | 5 (0.1) | 1 (< 0.1) | 0 |
| Hepatitis | 1 (0.2) | 0 | 0 | 2 (< 0.1) | 0 |
| Internal haemorrhage | 1 (0.2) | 0 | 0 | 0 | 0 |
| Myasthenia gravis | 1 (0.2) | 0 | 0 | 0 | 0 |
| Myocardial infarction | 1 (0.2) | 1 (0.2) | 8 (0.2) | 1 (< 0.1) | 3 (0.5) |
| Myocarditis | 1 (0.2) | 0 | 0 | 0 | 0 |
| Nervous system disorder | 1 (0.2) | 0 | 0 | 0 | 0 |
| Oesophageal varices haemorrhage | 1 (0.2) | 1 (0.2) | 1 (< 0.1) | 1 (< 0.1) | 1 (0.2) |
| Pulmonary embolism | 1 (0.2) | 0 | 6 (0.1) | 13 (0.4) | 1 (0.2) |
| Sepsis | 1 (0.2) | 0 | 13 (0.3) | 14 (0.4) | 1 (0.2) |
| Septic shock | 1 (0.2) | 1 (0.2) | 6 (0.1) | 9 (0.3) | 0 |
| Thrombocytopenia | 1 (0.2) | 0 | 0 | 0 | 0 |
| Upper gastrointestinal haemorrhage | 1 (0.2) | 0 | 0 | 0 | 0 |
| Asthenia | 0 | 1 (0.2) | 1 (< 0.1) | 0 | 1 (0.2) |
| Bleeding varicose vein | 0 | 2 (0.4) | 2 (< 0.1) | 0 | 0 |
| Cardio-respiratory arrest | 0 | 1 (0.2) | 6 (0.1) | 1 (< 0.1) | 1 (0.2) |
| Cerebrovascular accident | 0 | 1 (0.2) | 4 (< 0.1) | 5 (0.2) | 0 |
| Completed suicide | 0 | 1 (0.2) | 3 (< 0.1) | 0 | 0 |
| Hepatic cirrhosis | 0 | 1 (0.2) | 1 (< 0.1) | 0 | 0 |
| Hepatic function abnormal | 0 | 1 (0.2) | 2 (< 0.1) | 0 | 0 |
| Hepatorenal syndrome | 0 | 1 (0.2) | 1 (< 0.1) | 0 | 0 |
| Peripheral ischaemia | 0 | 1 (0.2) | 1 (< 0.1) | 0 | 0 |
| Restlessness | 0 | 1 (0.2) | 1 (< 0.1) | 0 | 0 |

[a] Number (%) of patients with AEs, sorted by decreasing frequency of preferred term (HCC-tumor pool T300+D column) and alphabetically for preferred term.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication, or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.

Percentages are based on the total numbers of patients in the treatment group (N).

MedDRA version 23.1.

Source: Table 2.7.4.3.1, Pooled Safety Outputs, Module 5.3.5.3

The Applicant's Position:

The majority of deaths in the HCC T300+D pool were due to the disease under investigation, and the incidence of AEs with an outcome of death was consistent in the HCC T300+D pool and HIMALAYA S arm

(7.4% vs 7.2%, respectively). In the HCC T300+D pool, the only AE with an outcome of death reported in > 1% of patients was the PT of death. In the HIMALAYA T300+D arm, 9 patients (2.3%) experienced fatal, treatment-related AEs, 7 of which were attributed to disease progression, metastases, or viral etiology, but the role of study treatment could not be definitively ruled out.

The type and incidence of AEs with an outcome of death in the HCC T300+D pool (7.4%) were generally consistent with those in the Pan-tumor T75+D pool (6.9%).

In the HIMALAYA S arm, the most frequently reported AEs with an outcome of death (reported by > 1% patients) were AEs of death (1.3%) and hepatic failure (1.1%).

The FDA's Assessment:

FDA notes that the incidence of Grade 5 TEAEs from the Table 23 is based on a pooled dataset comprising patients from the HIMALAYA trial and Study 22. FDA performed an analysis of Grade 5 TEAEs on the HIMALAYA trial which is presented in Table 24.

There were 30 (8%) and 27 (7%) patients in the T300+D and S arms, respectively, who had fatal adverse events within the safety reporting period. Although there were nominal differences in the incidence of some adverse events (nervous system and gastrointestinal system events were more common on the T300+D arm and infections and infestations were more common on the sorafenib arm), there were no Grade 5 adverse events observed to occur disproportionately higher in either study arm.

As described in the death summary in Table 25, there was a higher incidence of death due to any cause (overall death), death within 30 days of last dose, and death due to progression in the sorafenib arm compared to the T300+D arm. Most deaths in both treatment arms were due to disease progression. The incidence of AEs with an outcome of death was similar in the T300+D and sorafenib arms.

FDA reviewed all narratives describing adverse events that resulted in death in patients treated with T300+D. In the FDA review of death narratives, there were 9 patients whose cause of death was reported to be unknown. These 9 patient narratives are presented below in Table 26. For 6 of the 9 patients with an unknown cause of death, FDA has concluded that the cause of death was possibly related to disease progression. In another patient the cause of death is possibly due to an immune-mediated complication from T300+D.

Of note, there were a total of four death narratives that were missing (b) (6) (b) (6) An Information Request was sent for the narratives and the Applicant provided the patient narratives and stated that the death events for the four cases occurred outside of the protocol-defined 90-day safety follow-up window and/or after start of subsequent anticancer therapy, therefore the deaths were not assessed to be treatment related. The four narratives were provided and are summarized below.

**Table 24 - Summary of Grade 5 TEAEs**

| System Organ Class - Preferred Term | T300 + D (N=388) | Durva Mono (N=388) | Sorafenib (N=374) |
|---|---|---|---|
| | Grade 5 n (%) | Grade 5 n (%) | Grade 5 n (%) |
| **Hepatobiliary disorders** | **5 (1.3)** | **3 (0.8)** | **5 (1.3)** |
| Hepatic failure | 2 (0.5) | 2 (0.5) | 4 (1.1) |
| Immune-mediated hepatitis | 2 (0.5) | 0 (0.0) | 0 (0.0) |
| Hepatitis | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Hepatic cirrhosis | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| Hepatorenal syndrome | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| **Nervous system disorders** | **5 (1.3)** | **1 (0.3)** | **2 (0.5)** |
| Haemorrhage intracranial | 2 (0.5) | 0 (0.0) | 0 (0.0) |
| Cerebral haemorrhage | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Myasthenia gravis | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Nervous system disorder | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Cerebral haematoma | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| Cerebrovascular accident | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| Hepatic encephalopathy | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| **Cardiac disorders** | **4 (1.0)** | **3 (0.8)** | **4 (1.1)** |
| Cardiac arrest | 2 (0.5) | 1 (0.3) | 2 (0.5) |
| Myocardial infarction | 1 (0.3) | 1 (0.3) | 2 (0.5) |
| Myocarditis | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Cardio-respiratory arrest | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| **Gastrointestinal disorders** | **4 (1.0)** | **4 (1.0)** | **2 (0.5)** |
| Gastric ulcer haemorrhage | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Gastrointestinal haemorrhage | 1 (0.3) | 3 (0.8) | 0 (0.0) |
| Oesophageal varices haemorrhage | 1 (0.3) | 1 (0.3) | 1 (0.3) |
| Upper gastrointestinal haemorrhage | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Duodenal ulcer haemorrhage | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| **General disorders and administration site conditions** | **4 (1.0)** | **9 (2.3)** | **5 (1.3)** |
| Death | 4 (1.0) | 8 (2.1) | 5 (1.3) |
| Asthenia | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| **Respiratory, thoracic and mediastinal disorders** | **4 (1.0)** | **0 (0.0)** | **4 (1.1)** |
| Pneumonitis | 2 (0.5) | 0 (0.0) | 0 (0.0) |
| Acute respiratory distress syndrome | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Pulmonary embolism | 1 (0.3) | 0 (0.0) | 1 (0.3) |
| Dyspnoea | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| Epistaxis | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| Respiratory failure | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| **Infections and infestations** | **2 (0.5)** | **1 (0.3)** | **5 (1.3)** |
| Sepsis | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Septic shock | 1 (0.3) | 1 (0.3) | 1 (0.3) |
| Liver abscess | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| Peritonitis | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| Pneumonia | 0 (0.0) | 0 (0.0) | 2 (0.5) |

| System Organ Class - Preferred Term | T300 + D (N=388) | Durva Mono (N=388) | Sorafenib (N=374) |
|---|---|---|---|
| | Grade 5 | Grade 5 | Grade 5 |
| | n (%) | n (%) | n (%) |
| **Blood and lymphatic system disorders** | **1 (0.3)** | **0 (0.0)** | **0 (0.0)** |
| Thrombocytopenia | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| **Vascular disorders** | **1 (0.3)** | **3 (0.8)** | **0 (0.0)** |
| Internal haemorrhage | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Bleeding varicose vein | 0 (0.0) | 2 (0.5) | 0 (0.0) |
| Peripheral ischaemia | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| **Psychiatric disorders** | **0 (0.0)** | **2 (0.5)** | **0 (0.0)** |
| Completed suicide | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| Restlessness | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| **Renal and urinary disorders** | **0 (0.0)** | **0 (0.0)** | **1 (0.3)** |
| Hematuria | 0 (0.0) | 0 (0.0) | 1 (0.3) |

Source: OCS Analysis Studio, Safety Explorer. Adverse events missing severity/toxicity grades are not included in the above table.
Filters: TRT01A = "TREME 300 + DURVA" and SAFFL = "Y" (T300 + D); TRT01A = "DURVA MONO" and SAFFL = "Y" (Durva Mono); TRT01A = "SORA" and SAFFL = "Y" (Sorafenib ); TRTEMFL = "Y" and AETOXGRN = "Grade 5" (Adverse Events).

**Table 25 Death Summary – HIMALAYA Study**

| | T300 + D N=388 | D Mono N=388 | Sorafenib N=374 |
|---|---|---|---|
| **Total Deaths** | 258 | 279 | 283 |
| **Death due to Progression** | 221 | 245 | 256 |
| **Death within 30 days of last dose** | 20 | 22 | 56 |
| **Death 30 days after last dose** | 238 | 257 | 227 |
| **Death due to AE** | 30 | 26 | 27 |

Source: ADSL (Subject-Level Analysis Dataset) - 2022-02-23. Variables used: USUBJID, TRT01A, SAFFL, DTHCAUS, DTH30TFL, DTHA30FL, DTHDT, DTHFL, TRTEDT

**Table 26: Narratives for Cause of Death Listed as Unknown by Investigator**

| Subject ID | Age / Sex | Primary cause of death listed by investigator | Primary cause MedDRA preferred term | Reviewer Comment |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| (b) (6)<br><br>Death occurred outside of the protocol-defined 90-day safety follow-up window and/or after start of subsequent anticancer therapy | 71 / M | Unknown | Death | **Possibly due to progression of disease.**<br><br>The last dose of study medication was given on study day 169 due to objective disease progression. On study day 311 and 143 days after last dose, the patient died with the cause not established. Given the prior documented disease progression, the cause of death is possibly disease related. |
| (b) (6)<br><br>Death occurred outside of the protocol-defined 90-day safety follow-up window and/or after start of subsequent anticancer therapy | 22 / M | Unknown | Death | **Possibly due to progression of disease.**<br><br>Patient was given last dose of study medication on day 164 due to objective disease progression. 258 days after starting study medication and 95 days after receiving the last dose, the patient died. Primary cause at the time was not reported, no autopsy was performed. Given the prior documented disease progression, the cause of death is possibly disease related. |
| (b) (6) | 69 / M | Unknown | Death | **Likely due to progression of disease.**<br><br>On study day 56, a CT scan revealed disease progression in the lungs and pleural taps were stopped. On study day 65 and 36 days after last infusion, the patient died in sleep with the primary cause of death listed as unknown, but the reporting investigator considered the death related to underlying cancer. An autopsy was not performed. Given the prior documented disease progression, history of pleural effusions, the cause of death is likely disease related. |
| (b) (6)<br><br>Death occurred outside of the protocol-defined 90-day safety follow-up window and/or after start of subsequent anticancer therapy | 67 / M | Death of unknown cause | Death | **Possibly due to progression of disease.**<br><br>On study day 65, the patient discontinued study medication due to objective disease progression. The patient received 1 cycle of study treatment and 91 days after starting study medication the subject died, with primary cause listed as unknown though the reporting investigator considered the death related to their underlying cancer. Given the prior documented disease progression, the cause of death is possibly disease related. |
| (b) (6) | 33 / M | Death of unknown cause | Death | **Possibly due to progression of disease.**<br><br>On study day 123 the patient discontinued study medication due to subjective disease progression. On study day 208 and 85 days |

| | | | | |
|---|---|---|---|---|
| | | | | after the last infusion, the patient died with cause listed as unknown as he died at home. Given the prior documented disease progression, the cause of death is possibly disease related. |
| (b) (6)<br><br>Death occurred outside of the protocol-defined 90-day safety follow-up window and/or after start of subsequent anticancer therapy | 79 / F | Unknown | Death | **Cause of death unknown.**<br><br>The patient received only 1 cycle of therapy (T300+D) and 22 days after the infusion the patient experienced grade 2 diarrhea, which worsened to grade 3 on day 31. The patient was started on treatment with IV betamethasone and IV methylprednisolone and diarrhea resolved to Grade 1 on study day 32 and the event of diarrhea was determined to be an immune-mediated adverse event. On day 65 the patient discontinued study medication due to decline in clinical condition and 128 days after starting study medication the patient died, with the cause of death unknown. The event of diarrhea was considered as resolving at the time of the patient's death. Given the rapid response to high-dose steroids and improvement to Grade 1 diarrhea, and time elapsed from end of study treatment to the patient's death, FDA has concluded that this death is unlikely to be due to immune-mediated colitis. It is unclear whether this death is related to study medications. |
| (b) (6)<br><br>Death occurred outside of the protocol-defined 90-day safety follow-up window and/or after start of subsequent anticancer therapy | 54 / F | Unknown | Death | **Unknown**<br><br>150 days after starting study medication and 14 days after last infusion, the patient experienced an adverse event of ECOG performance status worsening, fatigue grade 3 and the study medication was discontinued on study day 151. Around the same time the patient experienced an adverse event of gamma-glutamyl transferase increase (grade 3). 272 days after starting study medication and 122 days after discontinuing study medication, the patient died, and no primary cause of death was noted. Upon FDA review, the cause of death is unknown and likely not related to study medications. |
| (b) (6)<br><br>Death occurred outside of the protocol-defined 90-day safety | 67 / M | Unknown cause of death | Death | This patient received three cycles of study medication. On study day 60 a CT scan revealed disease progression and the patient received the final dose of study medication on study day 61. On day 78 the |

| | | | | |
|---|---|---|---|---|
| follow-up window and/or after start of subsequent anticancer therapy | | | | patient withdrew from the trial, and it was reported the patient intended to participate in another trial. The patient died 431 days after starting study medication and 354 days after permanently discontinuing study treatment. Upon FDA review, the cause of death is unknown and likely not related to study medications. |
| (b) (6)<br><br>Death occurred outside of the protocol-defined 90-day safety follow-up window and/or after start of subsequent anticancer therapy | 74 / F | Unknown | Unknown | This patient received 18 cycles (day 478) of study treatment. On study day 506 a third event of disease progression was noted and subsequent treatment with Lenvatinib mesylate (study day 506 -700) was started. The patient experienced an event of Grade 3 UTI on study day 555 which was reported as resolved on study day 559. The patient died 873 days after starting and 368 days after permanently discontinuing study medication. Upon FDA review, the cause of death is unknown and likely not related to study medications. |

Source: Reviewer generated table from patient narratives submitted by Applicant.

**Table 27**: Narratives for Deaths other than Disease Progression Listed by Investigator **for T300+D Arm**

| Subject ID | Sex / Age | Primary cause of death by investigator | Applicant attribution to study treatment | FDA Reviewer Comment |
|---|---|---|---|---|
| (b) (6)<br><br>Death occurred outside of the protocol-defined 90-day safety follow-up window and/or after start of subsequent anticancer therapy | M / 69 | Pneumonia | No – attributed to disease progression. | Patient discontinued investigational therapy after receiving 1 cycle on study day 85 due to objective disease progression. 283 days after starting and receiving the last dose of study treatment, the patient died with the primary cause of death as pneumonia. The secondary cause of death was HCC. An autopsy was not performed. |
| (b) (6)<br><br>Death occurred outside of the protocol-defined 90-day safety follow-up window | F / 70 | Hepatorenal syndrome | No – attributed to disease progression. | On study day 219 the patient discontinued study treatment due to objective disease progression. 140 days after stopping study medication the patient died, with the primary cause of hepatorenal syndrome. Secondary cause was listed as HCC. |

| | | | | |
|---|---|---|---|---|
| and/or after start of subsequent anticancer therapy | | | | |
| (b) (6) | M / 84 | Intracranial hemorrhage | No | 43 days after starting study medication and 43 days after last dose the event of grade 5 intracranial hemorrhage occurred, and the patient died. The investigator considered the event of hemorrhage intracranial as not related to study medication and not related to other co-medication/study procedure.<br><br>*Reviewer comment – This was an 84-year-old patient with DM2, HTN and HLD. His age is a risk factor for intracranial hemorrhage.* |
| (b) (6)<br><br>Death occurred outside of the protocol-defined 90-day safety follow-up window and/or after start of subsequent anticancer therapy | F / 75 | Septic Shock | No | 233 days after starting study medication and 25 days after last infusion, the patient developed autoimmune nephritis, maximum grade 3. The patient was discharged from hospital on study day 287. 322 days after starting study treatment and 98 days after last dose of study medication, the patient died due to septic shock. |
| (b) (6) | F / 38 | Neurological alteration | Yes | On study day 17 and 16 days after starting study medication the event of grade 5 neurological disorder, with the investigator reporting the reason for death is due to neurological changes (metastasis) and considered the event as related to study medication. |
| (b) (6) | M / 74 | Cardiac arrest | No | 44 days after starting study medication and 16 days after last infusion, patient experienced cardiac arrest. An autopsy was not performed. It was reported that cardiac arrest was due to subject's cardiac history (atrial fibrillation, HTN, HLD, DM2 and prior myocardial infarctions). |
| (b) (6) | M / 72 | Hepatic failure | No | On study day 52 patient was admitted for decompensated cirrhosis with edema. 52 days after starting study medication and 24 days after last infusion, the patient died due to hepatic failure, with reporting investigator considering the death as not related to their underlying cancer. An autopsy was not performed. |
| (b) (6) | M / 74 | Respiratory distress syndrome | Yes | 45 days after starting study medication and 45 days after last infusion, the patient developed acute respiratory distress syndrome and died. An autopsy was not performed. The investigator considered the event as related to study treatment. |

| | | | | |
|---|---|---|---|---|
| (b) (6) | M / 76 | Hepatitis | Yes | 106 days after starting study medication and 50 days after last dose, the event of hepatitis grade 5 occurred, related to be an immune-mediated adverse event. |
| (b) (6) | M / 71 | Myocarditis | Yes | 21 days after starting and receiving the first and last infusion of study treatment, the patient died of myocarditis, related to study treatment. At baseline the subject's QTcF was normal and ECG at baseline was also normal. |
| (b) (6) | F / 66 | Esophageal variceal bleeding | No | 12 days after starting study medication and 12 days after last infusion of study medication, the patient died with the death due to esophageal variceal hemorrhage due to hepatic cirrhosis. |
| (b) (6) | M/ 66 | Brain hemorrhage | No | 30 days after starting study medication and 2 days after last infusion, the patient experienced a cerebral hemorrhage, leading to death. In (b) (6) the patient had a diagnosis of an intracranial aneurysm, and the cause was related to this and deemed not related to the study medication. |
| (b) (6) | M / 61 | Acute kidney injury 2/2 hepatorenal syndrome | No – attributed to disease progression. | Study day 194 the patient discontinued treatment due to objective disease progression and on day 236 the patient died with the cause being AKI related to hepatorenal syndrome due to underlying cancer. |
| (b) (6)<br><br>Death occurred outside of the protocol-defined 90-day safety follow-up window and/or after start of subsequent anticancer therapy | M / 47 | Cardiac arrest | No | On study day 48 the patient discontinued study treatment due to colitis, related to the study treatment (immune related). 135 days after last infusion, the patient died due to a cardiac arrest. No autopsy was done. |
| (b) (6) | M/ 63 | Thrombocytopenia | No | 132 days after starting study medication and 28 days after last infusion the patient developed SAE of thrombocytopenia, grade 3 and required hospitalization. Patient died 145 after starting study medication and 41 days after last dose. |
| (b) (6) | F / 56 | Pulmonary embolism | No | 35 days after starting study medication and 7 days after last infusion, the patient developed dyspnea and hypotensive shock and imaging revealed pulmonary embolism and the patient subsequently died. The investigator considered the patient's underlying conditions of IVC thrombosis, leg edema and history of thrombosis as risk factors for PE. |

| | | | | |
|---|---|---|---|---|
| (b) (6) | M / 70 | Pneumonitis | Yes | 462 after starting study medication and 58 days after the last infusion, the patient died due to pneumonitis. |
| (b) (6) | M / 66 | Gastrointestinal hemorrhage | No | 94 days after starting study medication and 38 days after last infusion, the patient developed cardiorespiratory failure due to GI hemorrhage. |
| (b) (6) | F / 77 | Upper GI hemorrhage | No | 107 days after starting study medication and 28 days after last infusion of study medication, the patient died due to upper GI bleed related to rupture of gastroesophageal varices. |
| (b) (6)<br><br>Death occurred outside of the protocol-defined 90-day safety follow-up window and/or after start of subsequent anticancer therapy | | Hemorrhagic shock | No | On day 114 of study, the patient discontinued study treatment due to objective disease progression. 142 days after starting study medication and 30 days after discontinuing medication the patient died due to hemorrhagic shock due to rupture of esophageal varices. |
| (b) (6) | F / 78 | Cardiac arrest | No | 62 days after starting study medication and 9 days after last infusion, the subject died due to cardiac arrest. No autopsy was performed. The investigator considered the subject's underlying medical history of stable angina as an alternative explanation for the event of death. |
| (b) (6) | M / 69 | Immune mediated hepatitis | Yes | On study day 13 and 12 days after last dose, the patient experienced immune mediated hepatitis that worsened to grade 3 on study day 91 and on study day 138 the patient died from liver failure. |
| (b) (6) | M / 80 | GI bleeding due to gastric ulcer | No | 130 days after starting study medication and 15 days after last dose the patient developed gastric ulcer hemorrhage and died due to this, with investigator reporting this was due to underlying cancer. |
| (b) (6) | M / 73 | Myocardial infraction | No | 44 days after starting study medication and 16 days after the last infusion, the patient experienced a serious adverse event of myocardial infarction and died 26 days after last infusion due to the adverse event. No autopsy was performed. |
| (b) (6) | M / 67 | Suspected internal hemorrhage | No | 50 days after starting study medication and 23 days after last infusion, the patient developed internal hemorrhage and died. No autopsy was not performed. |
| (b) (6) | M/ 66 | Death | No – attributed to disease progression | This patient received 1 cycle of study treatment and died 20 days later at home. No additional details were reported, and an autopsy was not performed. The primary |

| | | | | |
|---|---|---|---|---|
| | | | | cause of death was thought to be related to the underlying disease.<br><br>*Reviewer comment: Due to the proximity of the patient's death with the initiation of study treatment and the lack of additional details the possibility that this death may be treatment related cannot be excluded.* |
| (b) (6) | M / 77 | Pneumonitis | Yes | 4 days after starting study medication and the last infusion, the patient experienced serious adverse event of pneumonitis. Study day 7 the event worsened to grade 4, requiring intubation. 35 days after starting study medication the patient died due to respiratory failure, related to immune related pneumonitis. |
| (b) (6) | F/ 62 | Intracranial hemorrhage | No – attributed to HCC | This patient received 1 cycle of study treatment and experienced a serious adverse event of Stevens-Johnson syndrome on study day 24 and was hospitalized on study day 29. On study day 46 the patient experienced intracranial hemorrhage and died on study day 49.<br><br>*Reviewer comment: Spontaneous ICH in a patient with HCC may be due to underlying disease, however considering overall morbidity and ongoing immune-mediated adverse events, the possibility that this death may be treatment related cannot be excluded.* |
| (b) (6) | M / 63 | Sepsis | No | 384 days after starting study medication the same day as last dose the patient developed sepsis and died. |
| (b) (6)<br><br>Death occurred outside of the protocol-defined 90-day safety follow-up window and/or after start of subsequent anticancer therapy | F / 62 | Stroke | No | 908 days after starting study medication and 215 after the last dose, the patient died due to a cerebrovascular accident. No autopsy was performed. |
| (b) (6) | M / 65 | Cardiac arrest | No | 445 days after starting study medication and the same day as discontinuing the patient died due to a sudden cardiac arrest. No autopsy was performed. |
| (b) (6) | M / 69 | Immune mediated hepatitis | Yes | 28 days after starting study medication the patient developed grade 3 immune mediated hepatitis. 72 days after the first |

| | | | | |
|---|---|---|---|---|
| | | | | and last infusion, the patient died due to liver failure. |
| (b) (6) | M /45 | Liver failure | Yes | 28 days after starting study medication and after receiving the last dose, the patient developed hepatic failure, initially grade 3 and led to death. CT scan of abdomen showed a large hematoma adjuvant to the known liver lesion. |
| (b) (6) | M / 68 | Septic shock | No | 575 days after starting study medication and 31 days after last infusion, patient developed septic shock and died 2 days later. |
| (b) (6) | M / 72 | Myasthenia gravis | Yes | 46 days after starting study medication and 46 days after last infusion, the patient developed myasthenia gravis. 242 days after starting study medication and 242 days after last dose the patient died from myasthenia gravis. |

Source: Reviewer generated table from patient narratives submitted by Applicant in BLA.

**Serious Adverse Events**

Data:

**Table 28 Serious Adverse Events by System Organ Class and Preferred Term (≥ 2% Patients in Any Treatment Group) (Safety Analysis Set)**

| | Number (%) of Patients [a] | | | | |
|---|---|---|---|---|---|
| | HCC-tumor Pool | | Pan-tumor Pool | | |
| | T300+D | D | D | T75+D | T750 |
| MedDRA Preferred Term | (N = 462) | (N = 492) | (N = 4045) | (N = 3319) | (N = 643) |
| Patients with any SAE [b] | 189 (40.9) | 161 (32.7) | 1446 (35.7) | 1493 (45.0) | 338 (52.6) |
| Infections and infestations | 51 (11.0) | 28 (5.7) | 387 (9.6) | 410 (12.4) | 61 (9.5) |
| Pneumonia | 10 (2.2) | 4 (0.8) | 152 (3.8) | 186 (5.6) | 24 (3.7) |
| Respiratory, thoracic and mediastinal disorders | 15 (3.2) | 16 (3.3) | 330 (8.2) | 324 (9.8) | 69 (10.7) |
| Dyspnoea | 1 (0.2) | 3 (0.6) | 82 (2.0) | 60 (1.8) | 34 (5.3) |
| Gastrointestinal disorders | 64 (13.9) | 39 (7.9) | 244 (6.0) | 374 (11.3) | 163 (25.3) |
| Colitis | 10 (2.2) | 1 (0.2) | 11 (0.3) | 55 (1.7) | 36 (5.6) |
| Diarrhoea | 11 (2.4) | 5 (1.0) | 22 (0.5) | 91 (2.7) | 94 (14.6) |
| Hepatobiliary disorders | 16 (3.5) | 31 (6.3) | 80 (2.0) | 79 (2.4) | 10 (1.6) |
| Hepatic function abnormal | 1 (0.2) | 14 (2.8) | 21 (0.5) | 8 (0.2) | 3 (0.5) |
| General disorders and administration site conditions | 16 (3.5) | 22 (4.5) | 183 (4.5) | 188 (5.7) | 37 (5.8) |
| Pyrexia | 7 (1.5) | 8 (1.6) | 52 (1.3) | 67 (2.0) | 13 (2.0) |

[a] Number (%) of patients with SAEs, sorted by international order for system organ class and alphabetically for preferred term.

[b] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.

Patients with multiple SAEs are counted once for each system organ class/preferred term.
Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.
Percentages are based on the total numbers of patients in the treatment group (N).
MedDRA version 23.1.
Source: Table 2.7.4.4.1, Pooled Safety Outputs, Module 5.3.5.3

The Applicant's Position:

Serious AEs were most commonly reported (reported by ≥ 2% patients) in the System Organ Classes of Gastrointestinal disorders (13.9% patients), Infections and infestations (11.0% patients), and Metabolism and nutrition disorders (5.2% patients) for the HCC T300+D pool. In the HCC T300+D pool, the most frequently reported SAEs (reported by ≥ 2% patients) were diarrhea (2.4%), colitis (2.2%), and pneumonia (2.2%), and no treatment-related SAEs were reported by ≥ 2% of patients.

The type and incidence of SAEs in the HCC T300+D pool were generally consistent with those in the Pan-tumor T75+D pool.

In the HIMALAYA S arm, the most frequently reported SAE (reported by ≥ 2% patients) was pneumonia (2.1%), and no treatment-related SAEs were reported by ≥ 2% of patients.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of serious adverse events (SAE) including as noted in Table 23 based on an analysis of SAEs that occurred within 90 days from last dose of study treatment. It should be noted that the data presented in the USPI for SAEs are from safety analyses that include adverse events, excluding disease progression related adverse events, observed between the first dose of treatment until 90 days following the last dose of study drug. FDA also used a grouped term approach, evaluating similar adverse events together. Grouped terms used in the analysis of SAEs include the following:

Hemorrhage – gastrointestinal hemorrhage, upper gastrointestinal hemorrhage, esophageal varices hemorrhage, gastrointestinal ulcer hemorrhage, duodenal ulcer hemorrhage, hemorrhage intracranial, gastric varices hemorrhage, tumor hemorrhage, hematuria, internal hemorrhage, small intestinal hemorrhage, cerebral hemorrhage, hemoperitoneum, enterocolitis hemorrhagic, lower gastrointestinal hemorrhage, anal hemorrhage, hepatic hemorrhage, epistaxis, gastric ulcer hemorrhage, hemoptysis

Diarrhea – diarrhea, colitis, and enterocolitis

Pneumonia – pneumonia, pneumocystis jirovecii pneumonia, lower respiratory tract infection

Rash – rash, rash maculo-papular, erythema multiforme, palmar-plantar erythrodysaesthesia syndrome, dermatitis bullous, drug eruption, dermatitis, Stevens-Johnson syndrome

Vomiting – vomiting, hematemesis

AKI – acute kidney injury, renal failure

This approach is thought to provide a more comprehensive and clinically relevant description of drug safety.

SAEs occurred in 158 (41%) patients on the T300+D arm and 111 (30%) of patients on the S arm.

In the HIMALAYA trial, serious adverse events occurring in >1 % of patients included the following event terms: hemorrhage (6%), diarrhea (4%), sepsis (2.1%), pneumonia (2.1%), rash (1.5%), vomiting (1.3%), acute kidney injury (1.3%), and anemia (1.3%). The following SAEs had a higher incidence (difference ≥2%) on the T300+D arm: hemorrhage (6% vs 3.7%), diarrhea (4% vs 1.6%), and sepsis (2.1% vs 0). Given the risk of immune-mediated adverse events (IMAEs) with anti-PD-(L)1 antibodies, the increased frequency of diarrhea is possibly immune-mediated and not unexpected. There was a higher incidence of infections leading to SAEs in the T300+D arm compared to the S arm, led by sepsis and pneumonia.

The SAEs of retinal detachment (n=2), polymyalgia rheumatica (1), myasthenia gravis (1), myocarditis (1) that occurred in the T300+D arm are described in the durvalumab labeling and are considered expected adverse reactions for tremelimumab in combination with durvalumab. Due to the rare occurrence of these ARs specific information about each AR was not included separately in the Warnings and Precautions section of the tremelimumab-durvalumab label. These ARs are listed under the "Other Immune-Mediated Adverse Reactions" subsection in the drug labelling.

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

Data:

**Table 29 Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term (≥ 1% Patients in Any Treatment Group) (Safety Analysis Set)**

| | Number (%) of Patients [a] | | | | |
|---|---|---|---|---|---|
| | HCC-tumor Pool | | Pan-tumor Pool | | |
| | T300+D | D | D | T75+D | T750 |
| MedDRA Preferred Term | (N = 462) | (N = 492) | (N = 4045) | (N = 3319) | (N = 643) |
| Patients with any AE leading to discontinuation of any study treatment | 63 (13.6) | 47 (9.6) | 397 (9.8) | 550 (16.6) | 155 (24.1) |
| Respiratory, thoracic and mediastinal disorders | 4 (0.9) | 2 (0.4) | 84 (2.1) | 113 (3.4) | 9 (1.4) |
| Pneumonitis | 2 (0.4) | 1 (0.2) | 36 (0.9) | 49 (1.5) | 2 (0.3) |
| Gastrointestinal disorders | 14 (3.0) | 9 (1.8) | 41 (1.0) | 125 (3.8) | 98 (15.2) |
| Colitis | 2 (0.4) | 1 (0.2) | 6 (0.1) | 32 (1.0) | 26 (4.0) |
| Diarrhoea | 3 (0.6) | 2 (0.4) | 8 (0.2) | 37 (1.1) | 63 (9.8) |
| Investigations | 8 (1.7) | 6 (1.2) | 25 (0.6) | 42 (1.3) | 11 (1.7) |
| Aspartate aminotransferase increased | 5 (1.1) | 3 (0.6) | 6 (0.1) | 8 (0.2) | 1 (0.2) |

[a] Number (%) of patients with AEs leading to discontinuation, sorted by international order for system organ class and alphabetically for preferred term.

Patients with multiple AEs are counted once for each system organ class/preferred term.
Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication, or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.
Percentages are based on the total numbers of patients in the treatment group (N).
MedDRA version 23.1.
Source: Table 2.7.4.5.1.1, Pooled Safety Outputs, Module 5.3.5.3

The Applicant's Position:

Adverse events leading to discontinuation of any study treatment were most commonly reported (reported by ≥ 1% patients) in the System Organ Classes of Gastrointestinal disorders (3.0% patients), Hepatobiliary disorders (2.4% patients), Investigations (1.7% patients), Infections and infestations (1.1% patients), and Cardiac disorders (1.1% patients) for the HCC T300+D pool. In the HCC T300+D pool, the only AE leading to treatment discontinuation reported in > 1% of patients was AST increased (1.1%) (Table 29).

The type and incidence of AEs leading to treatment discontinuation in the HCC T300+D pool were generally consistent with those in the Pan-tumor T75+D pool.

The incidence of treatment-related AEs leading to treatment discontinuation was lower for T300+D (8.2%) vs S (11.0%).

In the HIMALAYA S arm, the most frequently reported AEs leading to treatment discontinuation (reported by > 1% patients) were palmar-plantar erythrodysesthesia syndrome (1.6%), diarrhea (1.3%), and abdominal pain (1.1%), and the most frequently reported treatment-related AEs leading to treatment discontinuation were palmar-plantar erythrodysesthesia syndrome (1.6%) and diarrhea (1.3%).

The FDA's Assessment:

FDA's analysis of the HIMALAYA safety dataset identified 53 patients (14%) in the T300+D arm and 63 patients (17%) in the sorafenib arm who experienced adverse events that resulted in discontinuation of study treatment. Most patients on the T300+D arm had Grade 3-4 AEs (35 patients) leading to treatment discontinuation (2 patients had grade 1 AEs of diarrhea and pneumonitis). Study treatment discontinuation was associated with fatal AEs for 19 patients on the T300+D arm. On the sorafenib arm, most patients had Grade 3-4 AEs (25 patients) leading to treatment discontinuation (2 patients had Grade 1 AEs of diarrhea and osteitis). Study treatment discontinuation was associated with fatal AEs for 17 patients on the sorafenib arm.

The most frequently reported AEs leading to treatment discontinuation in the T300+D arm (reported by ≥1% patients) were hemorrhage (1.8%), diarrhea (1.5%), aspartate aminotransferase increased (1.0%) and hepatitis (1.0%). The most frequently reported AEs leading to treatment discontinuation in the sorafenib arm (reported by ≥1% patients) were rash (3.5%), abdominal pain (1.3%), diarrhea (1.3%), fatigue (1.1%) and hemorrhage (1.1%).

While cross trial comparisons can be limited, and the agents included in the combination regimens differ in mechanism of action, the rates of AEs leading to discontinuation are slightly higher than what was

observed for atezolizumab in combination with bevacizumab (9%). The types of adverse events that most frequently resulted in discontinuation of T300+D appear consistent with what has been observed for other drug regimen for the treatment of unresectable HCC.

Source: ADSL (Subject-Level Analysis Dataset) - 2022-02-23, ADAE (Adverse Events Analysis Dataset) - 2022-02-23. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEACN1, AEACN2, AEBODSYS, AESER

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

Data: See the Applicant's Position below.

The Applicant's Position:
Adverse events leading to dose delays or interruptions of any study treatment were most commonly reported (reported by ≥ 4% patients) in the System Organ Classes of Investigations (10.2% patients), Gastrointestinal disorders (5.0% patients), Infections and infestations (4.8% patients), and Skin and subcutaneous tissue disorders (4.5% patients) for the HCC T300+D pool. In the HCC T300+D pool, the most frequently reported AEs leading to dose delays or interruptions (reported by ≥ 2% patients) were diarrhea (3.5%), AST increased (3.0%), ALT increased (2.8%), lipase increased (2.4%), and rash (2.2%).

In the HIMALAYA S arm, the most frequently reported AEs leading to dose delays or interruptions (reported by ≥ 2% patients) were palmar-plantar erythrodysesthesia syndrome (15.8%), diarrhea (5.6%), and hypertension (3.5%).

The incidence of treatment-related AEs leading to dose delay or interruption was lower for the HIMALAYA T300+D arm (21.4%) vs S (38.5%).

The FDA's Assessment:

No dose reductions of tremelimumab or durvalumab were allowed in the HIMALAYA trial. Dose reductions of sorafenib were allowed and 133 (36%) patients on the sorafenib arm had dose reductions. The adverse events that most frequently led to dose reduction in the sorafenib arm were rash (17%), diarrhea (6%), fatigue (3.2%), stomatitis (1.6%), abdominal pain (1.3%), AST increased (1.3%), hypertension (1.3%), and decreased appetite (1.1%). The rates of AEs leading to dose reduction of sorafenib were nominally lower in the HIMALAYA than what was observed in the trial that supported approval of lenvatinib (lenvatinib 62% vs sorafenib 56%). Other measures of the tolerability and safety profile of sorafenib in the HIMALAYA trial appeared similar to other contemporary trials evaluating sorafenib.

Adverse events leading to dose interruption were lower in the T300+ arm (35%) compared to the sorafenib (40%). The most frequently reported AEs leading to dose interruption in the T300+D arm (reported by ≥1% patients) were ALT increased (3.6%), diarrhea (3.6%), rash (3.6%), amylase increased (3.4%), AST increased (3.1%), lipase increased (2.8%), pneumonia (1.5%), hepatitis (1.5%), pyrexia (1.5%), anemia (1.3%), thrombocytopenia (1%), hyperthyroidism (1%), pneumonitis (1%), and blood creatinine increased (1%). The most frequently reported AEs leading to dose interruption in the sorafenib arm (reported by ≥1% patients) were rash (12%), diarrhea (5%), fatigue (3.5%), abdominal pain (2.7%), stomatitis (2.7%), hypertension (2.4%), nausea (2.1%), hemorrhage (1.9%), AST increased (1.6%), blood bilirubin increased (1.3%), vomiting (1.3%), decreased appetite (1.3%), hepatic function abnormal (1.3%), musculoskeletal pain (1.3%), ALT increased (1.1%), edema, (1.1%), pyrexia (1.1%), and transaminase increase (1.1%).

Overall, the toxicities leading to dose interruption in HIMALAYA are consistent with the established safety profiles of the study drugs and within the expected frequency for their individual safety profiles and condition of use.

Source: ADSL (Subject-Level Analysis Dataset) - 2022-02-23, ADAE (Adverse Events Analysis Dataset) - 2022-02-23. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEACN1, AEACN2, AEBODSYS, AESER

**Anti-drug Antibody Adverse Events**

Data: See the Applicant's Position below.

The Applicant's Position:
The incidence of treatment-emergent ADA positivity to durvalumab and tremelimumab was low and similar across the pools (durvalumab: 2.4% to 2.8%; tremelimumab: 8.0% to 12.1%). The overall safety and tolerability profile of patients with ADAs was similar to those without ADAs.

**Immune-Mediated Adverse Events**

Data:

**Table 30 Overview of imAEs in the HIMALAYA T300+D and S Arms and the HCC T300+D Pool (Safety Analysis Set)**

| | Number (%) of Patients [a] | | |
|---|---|---|---|
| AE Category | HCC T300+D Pool (N = 462) | HIMALAYA T300+D Arm (N = 388) | HIMALAYA S Arm (N = 374) |
| Any imAE | 165 (35.7) | 139 (35.8) | 30 (8.0) |
| Any imAE of CTCAE Grade 3 or 4 | 61 (13.2) | 49 (12.6) | 9 (2.4) |
| Any imSAE (including AEs with outcome of death) [b] | 49 (10.6) | 41 (10.6) | 4 (1.1) |
| Any imAE with outcome of death | 6 (1.3) | 6 (1.5) | 0 |
| Received systemic corticosteroids | 119 (25.8) | 96 (24.7) | 16 (4.3) |
| Received high dose corticosteroids | 93 (20.1) | 78 (20.1) | 7 (1.9) |
| Received endocrine therapy | 70 (15.2) | 66 (17.0) | 13 (3.5) |
| Received other immunosuppressants | 16 (3.5) | 14 (3.6) | 1 (0.3) |
| Any AE leading to discontinuation of study treatment | 26 (5.6) | 22 (5.7) | 6 (1.6) |

[a] Patients with multiple events in the same category are counted only once in that category; patients with events in more than 1 category are counted once in each of those categories.

[b] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.

Note: Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study treatment or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Source: Table 14.3.2.30, HIMALAYA CSR, Module 5.3.5.1, and Table 2.7.4.7.1, Pooled Safety Outputs, Module 5.3.5.3

The Applicant's Position:
Overall, the type and incidence of imAEs reported in the HCC T300+D pool was consistent with the established safety profile for each agent, and manageable according to toxicity management guidelines.

Immune-mediated AEs did not impact patient's ability to continue on T300+D treatment, as evidenced by the low rates of treatment discontinuations (Table 30).

The HCC T300+D pool, the most frequently reported imAEs (reported by ≥ 2% patients) were as follows:

- Hypothyroid events (10.0%), driven by hypothyroidism (9.3%)
- Hepatic events (7.4%), driven by ALT increased, AST increased, and hepatitis (2.2% each)
- Diarrhea/colitis events (6.7%), driven by diarrhea (4.8%) and colitis (2.2%)
- Dermatitis/rash events (5.6%), driven by rash (2.8%)
- Hyperthyroid events (4.5%), driven by hyperthyroidism (4.5%)

The majority of imAEs were CTCAE Grade 1 or 2. The median time to onset was 29 days (range: 13 to 313 days) for hepatic events, 23 days (range: 2 to 479 days) for diarrhea/colitis events, and 24.5 days (range: 2 to 933 days) for dermatitis/rash events. The median time to resolution was 60 days (range: 8 to 382 days) for hepatic events, 26 days (range: 6 to 135 days) for diarrhea/colitis events, and 32.5 days (range: 4 to 358 days) for dermatitis/rash events.

The type and incidence of imAEs in the HCC T300+D pool was generally consistent with the Pan-tumor T75+D pool.

The median time to onset was shorter for the HCC T300+D pool compared to the Pan-tumor T75+D pool. The median time to onset was 29 days (range: 13 to 313 days) vs 42.5 days (range: 1 to 826 days) for hepatic events, 23 days (range: 2 to 479 days) vs 58 days (range: 2 to 1296 days) for diarrhea/colitis events, and 24.5 days (range: 2 to 933 days) vs 37.5 days (range: 1 to 1169 days) for dermatitis/rash events. The median time to resolution was longer for the HCC T300+D pool compared to the Pan tumor T75+D pool for hepatic events (60 days [range: 8 to 382 days] vs 35.5 days [range: 3 to 1161 days], respectively) and diarrhea/colitis events (26 days [range: 6 to 135 days] vs 19 days [range: 1 to 192 days], respectively), and shorter for dermatitis/rash events (32.5 days [range: 4 to 358 days] vs 42 days [range: 1 to 691 days], respectively). These differences should be interpreted with caution, however, given the differing populations (HCC vs Pan-tumor) and population sizes (N = 388 vs N = 3319).

As expected, imAEs were more frequent with IO therapy than with S. In the HIMALAYA S arm, the most frequently reported imAEs (reported by ≥ 2% patients) were hypothyroid events (2.9%; driven by hypothyroidism [2.9%]) and dermatitis/rash (3.5%; driven by rash [1.6%]).

Six patients (1.5%) in the HIMALAYA T300+D arm died due to imAEs (pneumonitis, 3 hepatic events [1 hepatitis and 2 immune-mediated hepatitis], myocarditis, and myasthenia gravis); there were no fatal imAEs in the S arm.

The FDA's Assessment:
Of the patients who received T300+D and who were evaluable for the presence of anti-drug-antibodies (ADA) against tremelimumab, 11 % (20 of 182 evaluable patients) tested positive for ADAs and neutralizing antibodies against tremelimumab were detected in 40% (8 of 20 evaluable patients) of patients. In patients who received the T300+D regimen and who were evaluable for presence of ADA against durvalumab, 3.1 % (9/294) of patients tested positive for anti-durvalumab antibodies and 56% (5/9) of patients tested positive for neutralizing antibodies against durvalumab. The was no apparent effect on tremelimumab exposure due to the presence of ADAs against tremelimumab. There was also no relationship observed between the presence of ADAs against tremelimumab and safety. Refer to Section 6 for additional information.

The Applicant's definition of AEOSI and imAE are reviewed in Section 8.1.2. The Applicant defined imAEs in the CSR as "an AE that was associated with drug exposure and was consistent with an immune-mediated mechanism of action for which there was no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, were used to support an imAE diagnosis. Appropriate efforts were made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE." This method of identifying imAEs has been discussed in prior meetings with the FDA. FDA agrees with this approach for characterizing imAE.

The following immune-mediated adverse events were observed in the T300+D arm:

- Pneumonitis occurred in 1.3% (5/388) of patients
  - includes preferred terms interstitial lung disease and pneumonitis
- Hepatitis/immune-mediated hepatic events occurred in 8% (29/388) of patients
  - Includes preferred terms ALT increased, AST increased, autoimmune hepatitis, hepatic enzyme increased, hepatic function abnormal, hepatitis, hepatotoxicity, immune-mediated hepatitis, liver function test increased, transaminases increased
- Colitis occurred in 6% (23/388) of patients
  - Includes preferred terms autoimmune enteropathy, colitis, diarrhea, enterocolitis
- Adrenal insufficiency occurred in 1.5% (6/388) of patients
- Hypophysitis occurred in 1% (4/388) of patients
  - Includes preferred terms ACTH deficiency, hypophysitis, hypopituitarism
- Hyperthyroidism occurred in 4.6% (18/388) of patients
- Hypothyroidism occurred in 11% (42/388) of patients
  - Includes preferred terms blood thyroid stimulating hormone increased, hypothyroidism, immune-mediated hypothyroidism, secondary hypothyroidism
- Thyroiditis occurred in 1.5% (6/388) of patients
  - Includes preferred terms autoimmune thyroiditis, immune-mediated thyroiditis, thyroiditis, thyroiditis subacute.
- Nephritis/immune-mediated renal events occurred in 1% (4/388) of patients
  - Includes preferred terms autoimmune nephritis, blood creatinine increased, immune-mediated nephritis
- Dermatitis occurred in 4.9% (19/388) of patients
  - Included preferred terms erythema, erythema multiforme, immune-mediated dermatitis, pruritis, rash, rash maculo-papular, Stevens-Johnson syndrome
- Pancreatitis occurred in 2.3% (9/388) of patients
  - Included preferred terms amylase increased, lipase increased, pancreatitis

Six patients (1.5%) in the T300+D died due to an imAE (pneumonitis, 3 hepatic events, myocarditis, and myasthenia gravis); there were no fatal imAEs in the sorafenib arm.

As expected, there were fewer patients on the sorafenib arm who were reported to have experienced immune-mediated AEs.

**Table 31: FDA Summary of Immune-Mediated Adverse Events**

| System Organ Class - Preferred Term | T300 + D (N=388) n (%) | D Mono (N=388) n (%) | Sorafenib (N=374) n (%) |
|---|---|---|---|
| **Endocrine disorders** | **70 (18.0)** | **27 (7.0)** | **14 (3.7)** |
| Hypothyroidism | 39 (10.1) | 15 (3.9) | 11 (2.9) |
| Hyperthyroidism | 18 (4.6) | 4 (1.0) | 1 (0.3) |
| Adrenal insufficiency | 6 (1.5) | 6 (1.5) | 0 (0.0) |
| Thyroiditis | 3 (0.8) | 1 (0.3) | 2 (0.5) |
| Hypophysitis | 2 (0.5) | 0 (0.0) | 0 (0.0) |
| Secondary hypothyroidism | 2 (0.5) | 0 (0.0) | 0 (0.0) |
| Adrenocorticotropic hormone deficiency | 1 (0.3) | 1 (0.3) | 0 (0.0) |
| Autoimmune thyroiditis | 1 (0.3) | 1 (0.3) | 0 (0.0) |
| Hypopituitarism | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Immune-mediated hypothyroidism | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Immune-mediated thyroiditis | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Thyroiditis subacute | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Primary hypothyroidism | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| **Gastrointestinal disorders** | **31 (7.9)** | **4 (1.0)** | **1 (0.3)** |
| Diarrhoea | 17 (4.4) | 1 (0.3) | 1 (0.3) |
| Colitis | 6 (1.5) | 2 (0.5) | 0 (0.0) |
| Pancreatitis | 6 (1.5) | 2 (0.5) | 0 0.0 |
| Autoimmune enteropathy | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Enterocolitis | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| **Investigations** | **22 (5.7)** | **19 (4.9)** | **1 (0.3)** |
| Alanine aminotransferase increased | 8 (2.1) | 14 (3.6) | 1 (0.3) |
| Aspartate aminotransferase increased | 7 (1.8) | 14 (3.6) | 1 (0.3) |
| Lipase increased | 5 (1.3) | 1 (0.3) | 0 (0.0) |
| Amylase increased | 4 (1.0) | 0 (0.0) | 0 (0.0) |
| Transaminases increased | 2 (0.5) | 1 (0.3) | 0 (0.0) |
| Blood creatinine increased | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Blood thyroid stimulating hormone increased | 1 (0.3) | 3 (0.8) | 0 (0.0) |
| Hepatic enzyme increased | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Liver function test increased | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Thyroxine decreased | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| **Skin and subcutaneous tissue disorders** | **19 (4.9)** | **3 (0.8)** | **13 (3.5)** |
| Rash | 9 (2.3) | 2 (0.5) | 6 (1.6) |
| Rash maculo-papular | 5 (1.3) | 0 (0.0) | 2 (0.5) |
| Pruritus | 2 (0.5) | 0 (0.0) | 1 (0.3) |
| Erythema | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Erythema multiforme | 1 (0.3) | 0 (0.0) | 2 (0.5) |
| Immune-mediated dermatitis | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Stevens-johnson syndrome | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Dermatitis | 0 (0.0) | 1 (0.3) | 1 (0.3) |
| Dermatitis exfoliative generalised | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| Dermatitis psoriasiform | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| Psoriasis | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| Toxic skin eruption | 0 (0.0) | 0 (0.0) | 1 (0.3) |

| System Organ Class - Preferred Term | T300 + D (N=388) n (%) | D Mono (N=388) n (%) | Sorafenib (N=374) n (%) |
|---|---|---|---|
| **Hepatobiliary disorders** | **17 (4.4)** | **11 (2.8)** | **0 (0.0)** |
| Hepatitis | 10 (2.6) | 3 (0.8) | 0 (0.0) |
| Immune-mediated hepatitis | 3 (0.8) | 0 (0.0) | 0 (0.0) |
| Autoimmune hepatitis | 2 (0.5) | 2 (0.5) | 0 (0.0) |
| Hepatic function abnormal | 1 (0.3) | 5 (1.3) | 0 (0.0) |
| Hepatotoxicity | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Drug-induced liver injury | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| **Musculoskeletal and connective tissue disorders** | **10 (2.6)** | **1 (0.3)** | **0 (0.0)** |
| Arthralgia | 4 (1.0) | 1 (0.3) | 0 (0.0) |
| Polymyalgia rheumatica | 3 (0.8) | 0 (0.0) | 0 (0.0) |
| Myositis | 2 (0.5) | 0 (0.0) | 0 (0.0) |
| Polymyositis | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| **Respiratory, thoracic and mediastinal disorders** | **5 (1.3)** | **3 (0.8)** | **0 (0.0)** |
| Pneumonitis | 4 (1.0) | 2 (0.5) | 0 (0.0) |
| Interstitial lung disease | 1 (0.3) | 1 (0.3) | 0 (0.0) |
| **Renal and urinary disorders** | **3 (0.8)** | **0 (0.0)** | **0 (0.0)** |
| Autoimmune nephritis | 2 (0.5) | 0 (0.0) | 0 (0.0) |
| Immune-mediated nephritis | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| **Cardiac disorders** | **2 (0.5)** | **1 (0.3)** | **0 (0.0)** |
| Myocarditis | 2 (0.5) | 1 (0.3) | 0 (0.0) |
| **Nervous system disorders** | **2 (0.5)** | **0 (0.0)** | **0 (0.0)** |
| Myasthenia gravis | 2 (0.5) | 0 (0.0) | 0 (0.0) |
| **Vascular disorders** | **1 (0.3)** | **0 (0.0)** | **0 (0.0)** |
| Vasculitis | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| **Eye disorders** | **0 (0.0)** | **0 (0.0)** | **1 (0.3)** |
| Uveitis | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| **Metabolism and nutrition disorders** | **0 (0.0)** | **1 (0.3)** | **0 (0.0)** |
| Type 1 diabetes mellitus | 0 (0.0) | 1 (0.3) | 0 (0.0) |

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "TREME 300 + DURVA" and SAFFL = "Y" (T300 + D); TRT01A = "DURVA MONO" and SAFFL = "Y" (D Mono); TRT01A = "SORA" and SAFFL = "Y" (Sorafenib ); TRTEMFL = "Y" and IMAEFL = "Y" (Adverse Events).

**Hepatic Adverse Events**

Data: See the Applicant's Position below.

The Applicant's Position:

The type and incidence of hepatic disorder SMQ AEs in the HCC T300+D pool were consistent with the disease under study. In the HCC T300+D pool, the most frequently reported AEs in the hepatic disorder SMQ (reported by ≥ 5% patients) were AST increased (15.4%), ALT increased (11.5%), ascites (7.6%), blood bilirubin increased (6.1%), and gamma-glutamyltransferase (5.0%), and no treatment-related AE in the hepatic disorder SMQ were reported by ≥ 5% patients. A total of 7.6% of patients in the HCC T300+D pool had treatment-related hepatic disorder SMQ AEs of CTCAE Grade 3 or Grade 4, 3.9% had hepatic

disorder SMQ AEs that led to treatment discontinuation, and less than 2% had fatal hepatic disorder SMQ AEs.

As expected based on the patient populations, the overall incidence of hepatic disorder SMQ AEs in the HCC T300+D pool (patients with uHCC; 39.2%) was greater than those in the Pan-tumor T75+D pool (predominantly patients with NSCLC and HNSCC; 22.6%).

In the HIMALAYA S arm, the most frequently reported AEs in the hepatic disorder SMQ (reported by ≥ 5% patients) were blood bilirubin increased (7.8%), AST increased (6.4%), ALT increased (5.3%), ascites (5.3%), and gamma-glutamyltransferase increased (5.1%).

T300+D did not significantly increase treatment-related hepatotoxicity, as evidenced by the incidence of hepatic disorder SMQ Grade 3 to 4 AEs: 7.6% for the HCC T300+D pool and 4.5% for the HIMALAYA S arm.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of the data and analysis. Hepatic adverse events occurred at a similar frequency across the T300+D, durvalumab and sorafenib treatment arms. The most frequently occurring hepatic adverse events were from the Liver Related Investigations SMQ and included AST increased (12% T300+D, 14% durvalumab, and 6% sorafenib), ALT increased (9% T300+D, 11% durvalumab, and 5% sorafenib), ascites (6% T300+D, 7% durvalumab, and 5% sorafenib), and GGT increased (5% T300+D, 3% durvalumab, and 5% sorafenib). While there was a numerical increase in the frequency of these events on the T300+D arm compared to the sorafenib arm, there did not appear to be a disproportionate increase of any particular hepatic adverse event that occurred on the T300+D arm compared to the sorafenib arm.

FDA notes that animal studies showed some hepatic toxicity related to tremelimumab with 2 animals displaying tremors at doses of 15 mg/kg and 50 mg/kg and another female animal treated at the 5 mg/kg dose with moderate focal liver mineralization characterized by an encapsulated mass composed of mineralized, necrotic debris.

**Table 32: Hepatic SMQ Summary of Adverse events**

| Preferred Term | T300 + D (N=388) n (%) | D Mono (N=388) n (%) | Sorafenib (N=374) n (%) |
|---|---|---|---|
| Any Grade | 144 (37) | 129 (33) | 121 (32) |
| Grade 1 | 23 (5.9) | 19 (4.9) | 29 (8) |
| Grade 2 | 61 (16) | 52 (13) | 45 (12) |
| Grade 3 | 49 (13) | 50 (13) | 39 (10) |
| Grade 4 | 5 (1.3) | 4 (1) | 0 |
| Grade 5 | 6 (1.5) | 4 (1) | 8 (2.1) |

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "TREME 300 + DURVA" and SAFFL = "Y" (T300 + D ); TRT01A = "DURVA MONO" and SAFFL = "Y" (D Mono); TRT01A = "SORA" and SAFFL = "Y" (Sorafenib ); TRTEMFL = "Y" and AEHLGT = "Hepatobiliary investigations" (Adverse Events).

**Hemorrhage Adverse Events**

Data: See the Applicant's Position below.

The Applicant's Position:
The overall incidence of hemorrhage SMQ AEs was consistent between the HCC T300+D pool and HIMALAYA S arm. Of note, no treatment-related esophageal varices hemorrhage was reported for any arm.

The overall frequency of AEs in the hemorrhage SMQ was similar in the HCC T300+D pool (12.1%) and the HIMALAYA S arm (15.0%). The frequencies of fatal AEs in the hemorrhage SMQ were also similar (1.7% vs 1.3%); however, none of these events in the HCC T300+D pool were considered treatment-related, while 2 (0.5%) patients in the HIMALAYA S arm had fatal, treatment-related AEs in the hemorrhage SMQ. T300+D was also not associated with increased bleeding risk compared to S.

The type and incidence of hemorrhage SMQ AEs in the HCC T300+D pool were generally consistent with those in the Pan-tumor T75+D pool.

The FDA's Assessment:
FDA agrees with the Applicant's presentation of the data and analysis. Hemorrhage adverse events occurred at a similar frequency across the T300+D, durvalumab, and sorafenib arms. There was not a significant rate of GI hemorrhage in the investigational arm when compared to the control arm.

**Table 33: Summary of Gastrointestinal Hemorrhage Events by PT – HIMALAYA**

| Preferred Term | T300 + D (N=388) n (%) | D Mono (N=388) n (%) | Sorafenib (N=374) n (%) |
|---|---|---|---|
| Any Grade | 44 (11) | 42 (11) | 56 (15) |
| Grade 1 | 12 (3.1) | 16 (4.1) | 24 (6.4) |
| Grade 2 | 9 (2.3) | 7 (1.8) | 11 (2.9) |
| Grade 3 | 14 (3.6) | 13 (3.4) | 15 (4.0) |
| Grade 4 | 1 (0.3) | 0 | 1 (0.3) |
| Grade 5 | 8 (2.1) | 6 (1.5) | 5 (1.3) |

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "TREME 300 + DURVA" and SAFFL = "Y" (T300 + D ); TRT01A = "DURVA MONO" and SAFFL = "Y" (D Mono); TRT01A = "SORA" and SAFFL = "Y" (Sorafenib ); TRTEMFL = "Y" and AEHLGT = "Gastrointestinal haemorrhages NEC" (Adverse Events).

**Table 34: Hemorrhage SMQ adverse events ≥1% on HIMALAYA**

| Preferred Term | T300+D (N=388) n (%) | D Mono (N=388) n (%) | Sorafenib (N=374) n (%) |
|---|---|---|---|
| Epistaxis | 6 (1.5) | 4 (1.0) | 12 (3.2) |
| Gastrointestial hemorrhage | 7 (1.8) | 5 (1.3) | 5 (1.3) |
| INR increased | 7 (1.8) | 5 (1.3) | 5 (1.3) |

| | | | |
|---|---|---|---|
| Upper gastrointestinal hemorrhage | 7 (1.8) | 3 (0.8) | 4 (1.1) |

Source: Adapted from Applicant's CSR

**Treatment-emergent Adverse Events and Adverse Reactions**

Data:

**Table 35 Adverse Events in Any Category in HIMALAYA (Safety Analysis Set)**

| AE category [a] | Number (%) of patients | | | |
|---|---|---|---|---|
| | D (N = 388) | T300+D (N = 388) | T75+D (N = 152) | S (N = 374) |
| Any AE | 345 (88.9) | 378 (97.4) | 145 (95.4) | 357 (95.5) |
| Any AE possibly related to treatment [b] | 202 (52.1) | 294 (75.8) | 106 (69.7) | 317 (84.8) |
| Any AE of CTCAE Grade 3 or 4 | 144 (37.1) | 196 (50.5) | 60 (39.5) | 196 (52.4) |
| Any AE of CTCAE Grade 3 or 4, possibly related to treatment [b] | 50 (12.9) | 100 (25.8) | 32 (21.1) | 138 (36.9) |
| Any AE with outcome of death | 26 (6.7) | 30 (7.7) | 12 (7.9) | 27 (7.2) |
| Any AE with outcome of death, possibly related to treatment [b] | 0 | 9 (2.3) | 2 (1.3) | 3 (0.8) |
| Any SAE (including events with outcome of death) | 115 (29.6) | 157 (40.5) | 52 (34.2) | 111 (29.7) |
| Any SAE (including events with outcome of death), possibly related to treatment [b] | 32 (8.2) | 68 (17.5) | 28 (18.4) | 35 (9.4) |
| Any AE leading to discontinuation of study treatment | 32 (8.2) | 53 (13.7) | 23 (15.1) | 63 (16.8) |
| Any AE leading to discontinuation of study treatment, possibly related to treatment [b] | 16 (4.1) | 32 (8.2) | 13 (8.6) | 41 (11.0) |
| Any AE leading to dose delay [c] | 95 (24.5) | 134 (34.5) | 58 (38.2) | 178 (47.6) |
| Any AE leading to dose delay, possibly related to treatment [b, c] | 54 (13.9) | 83 (21.4) | 42 (27.6) | 144 (38.5) |
| Any immune mediated AE [d] | 64 (16.5) | 139 (35.8) | 53 (34.9) | 30 (8.0) |
| Any infusion reaction AE [e] | 11 (2.8) | 20 (5.2) | 9 (5.9) | 2 (0.5) |

a. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
b. As assessed by the Investigator. Missing responses were counted as treatment-related.
c. AEs on the AE case report form with Action taken = Drug interrupted.
d. ImAEs are identified from AESIs and AEPIs using a programmatic approach.
e. As assessed by the Investigator.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurred first).
MedDRA version 23.1. CTCAE version 4.03.

Source: Table 14.3.2.1.

The nature of AEs and frequency of events within AE categories in HIMALAYA were generally consistent with the known safety profiles of each regimen. Most patients in the HIMALAYA study experienced at least 1 AE during the study, with a similar incidence across the 4 treatment arms. Treatment-related CTCAE Grade 3 or 4 AEs and Treatment-related AEs leading to discontinuation to IP were lower for IO containing regimens compared with those in arm S. The frequency of fatal AEs was similar across arms. The frequency of treatment-related fatal AEs was higher in the T300+D arm compared with the other IO arms and arm S. Seven of the 9 T300+D treatment related fatal events were attributed to disease progression, metastases or viral etiology and the role of study treatment could not be definitively ruled out.

**Table 36 Overview of AEs in the HIMALAYA T300+D and S Arms and the HCC T300+D Pool (Safety Analysis Set)**

| | Number (%) of Patients [a] | | |
|---|---|---|---|
| | HCC T300+D Pool | HIMALAYA T300+D Arm | HIMALAYA S Arm |
| **AE Category** | **(N = 462)** | **(N = 388)** | **(N = 374)** |
| Any AE | 451 (97.6) | 378 (97.4) | 357 (95.5) |
| Any AE possibly related to any study treatment [b] | 355 (76.8) | 294 (75.8) | 317 (84.8) |
| Any AE possibly related to durvalumab [b] | 349 (75.5) | 288 (74.2) | NA |
| Any AE possibly related to tremelimumab [b] | 224 (48.5) | 175 (45.1) | NA |
| Any AE possibly related to sorafenib [b] | NA | NA | 317 (84.8) |
| Any AE of CTCAE Grade 3 or 4 [c] | 240 (51.9) | 196 (50.5) | 196 (52.4) |
| Any AE of CTCAE Grade 3 or 4 [c] possibly related to any study treatment [b] | 127 (27.5) | 100 (25.8) | 138 (36.9) |
| Any AE with outcome of death | 34 (7.4) | 30 (7.7) | 27 (7.2) |
| Any SAE (including events with outcome of death) [d] | 189 (40.9) | 157 (40.5) | 111 (29.7) |
| Any AE leading to discontinuation of any study treatment | 63 (13.6) | 53 (13.7) | 63 (16.8) |
| Any AE leading to discontinuation of any study treatment, possibly related to any study treatment [b] | 41 (8.9) | 32 (8.2) | 41 (11.0) |
| Any AE leading to dose delay or interruption of any study treatment [e] | 149 (32.3) | 134 (34.5) | 178 (47.6) |
| Any AE leading to dose delay or interruption of any study treatment [e], possibly related to any study treatment [b] | NE | 83 (21.4) | 144 (38.5) |

[a] Patients with multiple events in the same category are counted only once in that category; patients with events in more than 1 category are counted once in each of those categories.

[b] As assessed by the investigator. Missing responses are counted as related.

[c] All CTCAE grades per patient, not just the maximum, are considered when identifying whether there is a Grade 3 or 4.

[d] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.

[e] Includes AEs on the AE CRF form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.

Note: Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study treatment or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Source: Table 14.3.2.1, Table 14.3.2.4, Table 14.3.2.5, and Table 14.3.2.6, HIMALAYA CSR, Module 5.3.5.1, and Table 2.7.4.2.1, Pooled Safety Outputs, Module 5.3.5.3

In the HCC T300+D pool, the most frequently reported AEs (reported by ≥ 15% patients) were pruritus (25.5%), diarrhea (25.3%), rash (24.9%), fatigue (18.0%), decreased appetite (16.5%), and AST increased (15.4%), and the most frequently reported treatment-related AEs were rash (22.1%), pruritus (19.5%), and diarrhea (15.6%). Rash, pruritus, AST increased and diarrhea are known ADRs for either durvalumab or tremelimumab. The incidence of AST increased can be attributed to the underlying liver disease. Treatment-related AEs associated with VEGF inhibitors, such as hypertension, proteinuria, and bleeding events (Finn et al 2020b), were uncommon or not observed with T300+D.

The type and incidence of AEs in the HCC T300+D pool were generally consistent with those in the Pan-tumor T75+D pool. Of the most frequently reported AEs, pruritus and rash were more common in the HCC T300+D pool (24.9% and 25.5%, respectively) than in the Pan-tumor T75+D pool (18.8% and 13.3%, respectively), and fatigue was more common in the Pan-tumor T75+D pool (23.4%) than in the HCC T300+D pool (18.0%).

In the HIMALAYA S arm, the most frequently reported AEs (reported by ≥ 15% patients) were palmar-plantar erythrodysesthesia syndrome (46.5%), diarrhea (44.7%), fatigue (19.0%), hypertension (18.2%), decreased appetite (17.9%), and abdominal pain (16.8%), and the most frequently reported treatment-related AEs were palmar-plantar erythrodysesthesia syndrome (43.9%), diarrhea (38.8%), and hypertension (15.0%).

The Applicant's Position:

Overall, the safety and tolerability of tremelimumab administered in combination with durvalumab was generally consistent with the known safety profile for each agent, and AEs were manageable according to toxicity management guidelines. CTCAE Grade 3 or 4 AEs and SAEs did not impact patient's ability to continue on T300+D treatment, as evidenced by the low rates of treatment-related AEs leading to discontinuations and dose delays or interruptions (Table 36). Incidences of treatment-related AEs of any CTCAE grade, AEs of CTCAE Grade 3 or 4, and AEs leading to treatment discontinuation or interruption were generally lower for T300+D vs S.

Adverse drug reactions related to durvalumab and tremelimumab are identified by ongoing signal evaluation based on emerging safety data from all data sources (nonclinical findings, clinical data from the ongoing clinical trial program, and post-marketing safety reports for durvalumab), as well as by comparative analyses of randomized comparator/placebo controlled pivotal trials in the target populations. The risks with durvalumab identified prior to analysis of data from HIMALAYA and the HCC tumor pools are summarized in the IMFINZI prescribing information. The identified risks for durvalumab are also considered identified risks for the durvalumab plus tremelimumab combination, including cough/productive cough, pneumonitis, interstitial lung disease, dysphonia, ALT/AST increased, hepatitis, diarrhea, abdominal pain, colitis, pancreatitis, hypothyroidism, hyperthyroidism, thyroiditis, adrenal insufficiency, Type 1 diabetes mellitus, hypophysitis/hypopituitarism, diabetes insipidus, blood creatinine increased, dysuria, nephritis, rash, pruritus, night sweats, dermatitis, pemphigoid, myocarditis, pyrexia, peripheral edema, upper respiratory tract infections, pneumonia, oral candidiasis, dental and oral soft tissue infections, influenza, myalgia, myositis, polymyositis, myasthenia gravis, infusion-related reactions, immune thrombocytopenia, and encephalitis. Additional identified risks for the durvalumab plus tremelimumab 75 mg/kg Q4W combination include lipase increased, amylase increased, intestinal perforation, and large intestine perforation. However, it should be noted that no

events of intestinal perforation or large intestine perforation were reported in the HCC T300+D pool .

Analyses were conducted to identify any new ADRs for the T300+D combination in the HCC tumor. Based on this analysis, no new ADRs were identified for the HCC T300+D pool.

It is recognized that ADRs known to occur with durvalumab alone or in combination with tremelimumab may occur during treatment with combination, even if these reactions were not reported in the HCC T300+D pool. Overall, no additional new safety concerns were identified for the combination of T300+D.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of the data and analysis. FDA analysis of TEAEs included the use of internally standardized grouped terms to evaluate frequency of clinically related adverse events. The most frequently reported (≥10% on any arm) adverse events are listed in Table 37. Overall, the frequency of all grade and grade 3-4 adverse events were similar between the T300+D and sorafenib arms.

**Table 37 - Summary of TEAEs (≥10%) – HIMALAYA**

| | T300+D N = 388 | | Durva Mono N = 388 | | Sorafenib N = 374 | |
|---|---|---|---|---|---|---|
| | All grades n (%) | Grades 3-4 n (%) | All grades n (%) | Grades 3-4 n (%) | All grades n (%) | Grades 3-4 n (%) |
| **Patients with TEAEs** | 378 (97) | 181 (47) | 345 (89) | 132 (34) | 357 (95) | 183 (49) |
| **Gastrointestinal Disorders** | | | | | | |
| Diarrhoea (GT) | 106 (27) | 23 (6) | 60 (15) | 6 (1.5) | 167 (45) | 16 (4.3) |
| Abdominal Pain (GT) | 79 (20) | 7 (1.8) | 64 (16) | 8 (2.1) | 89 (24) | 15 (4.0) |
| Nausea | 47 (12) | 0 (0.0) | 37 (10) | 0 (0.0) | 53 (14) | 0 (0.0) |
| Constipation | 36 (9) | 0 (0.0) | 42 (11) | 0 (0.0) | 35 (9) | 0 (0.0) |
| Stomatitis (GT) | 19 (4.9) | 0 (0.0) | 8 (2.1) | 1 (0.3) | 49 (13) | 3 (0.8) |
| **Vascular Disorders** | | | | | | |
| Haemorrhage (GT) | 32 (8) | 12 (3.1) | 27 (7) | 7 (1.8) | 43 (11) | 10 (2.7) |
| Hypertension (GT) | 24 (6) | 7 (1.8) | 18 (4.6) | 4 (1.0) | 69 (18) | 23 (6) |
| **Skin And Subcutaneous Tissue Disorders** | | | | | | |
| Rash (GT) | 125 (32) | 11 (2.8) | 63 (16) | 1 (0.3) | 214 (57) | 46 (12) |
| Pruritus | 89 (23) | 0 (0.0) | 56 (14) | 0 (0.0) | 24 (6) | 1 (0.3) |
| Alopecia | 2 (0.5) | 0 (0.0) | 5 (1.3) | 0 (0.0) | 53 (14) | 0 (0.0) |
| **General Disorders And Administration Site Conditions** | | | | | | |
| Fatigue (GT) | 102 (26) | 15 (3.9) | 86 (22) | 8 (2.1) | 111 (30) | 21 (6) |
| Pyrexia (GT) | 52 (13) | 1 (0.3) | 43 (11) | 7 (1.8) | 35 (9) | 1 (0.3) |
| Oedema (GT) | 41 (11) | 3 (0.8) | 29 (7) | 1 (0.3) | 25 (7) | 0 (0.0) |
| **Musculoskeletal And Connective Tissue Disorders** | | | | | | |
| Musculoskeletal Pain (GT) | 85 (22) | 10 (2.6) | 85 (22) | 4 (1.0) | 62 (17) | 3 (0.8) |

| | T300+D N = 388 | | Durva Mono N = 388 | | Sorafenib N = 374 | |
|---|---|---|---|---|---|---|
| | All grades n (%) | Grades 3-4 n (%) | All grades n (%) | Grades 3-4 n (%) | All grades n (%) | Grades 3-4 n (%) |
| **Endocrine Disorders** | | | | | | |
| Hypothyroidism (GT) | 54 (14) | 0 (0.0) | 28 (7) | 0 (0.0) | 21 (6) | 0 (0.0) |
| **Investigations** | | | | | | |
| Aspartate Aminotransferase Increased | 48 (12) | 20 (5) | 56 (14) | 26 (7) | 24 (6) | 12 (3.2) |
| Alanine Aminotransferase Increased | 36 (9) | 10 (2.6) | 44 (11) | 12 (3.1) | 20 (5) | 7 (1.9) |
| **Metabolism And Nutrition Disorders** | | | | | | |
| Decreased Appetite | 66 (17) | 5 (1.3) | 53 (14) | 2 (0.5) | 67 (18) | 3 (0.8) |
| **Psychiatric Disorders** | | | | | | |
| Insomnia | 40 (10) | 1 (0.3) | 21 (5) | 0 (0.0) | 16 (4.3) | 0 (0.0) |

Group Hypertension (GT) includes PT terms HYPERTENSION, BLOOD PRESSURE INCREASED, SYSTOLIC HYPERTENSION,
Group Haemorrhage (GT) includes PT terms OESOPHAGEAL VARICES HAEMORRHAGE, UPPER GASTROINTESTINAL HAEMORRHAGE, GASTROINTESTINAL HAEMORRHAGE, HAEMATURIA, LOWER GASTROINTESTINAL HAEMORRHAGE, GASTRIC VARICES HAEMORRHAGE, EPISTAXIS, ENTEROCOLITIS HAEMORRHAGIC, SMALL INTESTINAL HAEMORRHAGE, RECTAL HAEMORRHAGE, INTRA-ABDOMINAL HAEMORRHAGE, ANAL HAEMORRHAGE, TUMOUR HAEMORRHAGE, DUODENAL ULCER HAEMORRHAGE, HEPATIC HAEMORRHAGE, HAEMOPERITONEUM, GASTROINTESTINAL ULCER HAEMORRHAGE, HAEMOPTYSIS, HAEMORRHAGIC ASCITES, CEREBRAL HAEMORRHAGE, GASTRIC ULCER HAEMORRHAGE, GINGIVAL BLEEDING, GASTRITIS HAEMORRHAGIC, HAEMORRHOIDAL HAEMORRHAGE, HAEMORRHAGE INTRACRANIAL, INTERNAL HAEMORRHAGE, HAEMORRHAGE, POSTMENOPAUSAL HAEMORRHAGE,
Group Abdominal Pain (GT) includes PT terms ABDOMINAL PAIN, ABDOMINAL PAIN UPPER, ABDOMINAL DISCOMFORT, HEPATIC PAIN, ABDOMINAL PAIN LOWER, EPIGASTRIC DISCOMFORT, ABDOMINAL TENDERNESS, GASTROINTESTINAL PAIN,
Group Diarrhoea (GT) includes PT terms DIARRHOEA, COLITIS, ENTEROCOLITIS, ENTERITIS,
Group Fatigue (GT) includes PT terms ASTHENIA, FATIGUE,
Group Rash (GT) includes PT terms RASH, RASH MACULO-PAPULAR, ERYTHEMA MULTIFORME, PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME, DERMATITIS, ECZEMA, TOXIC SKIN ERUPTION, DERMATITIS ACNEIFORM, RASH PAPULAR, SKIN EXFOLIATION, RASH MACULAR, RASH PRURITIC, DERMATITIS BULLOUS, RASH ERYTHEMATOUS, DYSHIDROTIC ECZEMA, DRUG ERUPTION, STEVENS-JOHNSON SYNDROME, IMMUNE-MEDIATED DERMATITIS, ECZEMA ASTEATOTIC, PEMPHIGOID, DERMATITIS EXFOLIATIVE GENERALISED, AUTOIMMUNE DERMATITIS, RASH MORBILLIFORM,
Group Pyrexia (GT) includes PT terms PYREXIA, HYPERTHERMIA, BODY TEMPERATURE INCREASED,
Group Oedema (GT) includes PT terms OEDEMA PERIPHERAL, OEDEMA, FACE OEDEMA, GENERALISED OEDEMA, SCROTAL OEDEMA, PENILE OEDEMA,
Group Musculoskeletal Pain (GT) includes PT terms PAIN IN EXTREMITY, BACK PAIN, ARTHRALGIA, BONE PAIN, MYALGIA, NECK PAIN, MUSCULOSKELETAL CHEST PAIN, MUSCULOSKELETAL PAIN, NON-CARDIAC CHEST PAIN, SPINAL PAIN, ARTHRITIS, MUSCULOSKELETAL STIFFNESS,
Group Stomatitis (GT) includes PT terms STOMATITIS, MUCOSAL INFLAMMATION, MOUTH ULCERATION, CHEILITIS, GLOSSITIS, APHTHOUS ULCER,
Group Hypothyroidism (GT) includes PT terms BLOOD THYROID STIMULATING HORMONE INCREASED, HYPOTHYROIDISM, PRIMARY HYPOTHYROIDISM, SECONDARY HYPOTHYROIDISM,
Source: ADSL (Subject-Level Analysis Dataset) - 2022-02-23, ADAE (Adverse Events Analysis Dataset) - 2022-02-23.
Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER

**Patients there were rechallenged with tremelimumab:**

FDA also evaluated the safety profile in the 30 patients that were rechallenged with one additional dose of tremelimumab administered in combination with durvalumab. There were no adverse events that appeared to occur disproportionately in this population. The most common (>10%) adverse events were diarrhea 40%, fatigue 37%, pruritis 37%, rash 33%, musculoskeletal pain 30%, abdominal pain 27%, ascites 17%, hypothyroidism 17%, dry skin 13%, edema 13%, and hemorrhage 13%. Gastrointestinal hemorrhage (gastrointestinal ulcer hemorrhage) was observed in 2 patients.

The imAEs observed in the patients reported as having immune-related toxicity include hyperthyroidism (n=3), hypothyroidism (n=3), diarrhea (n=3) and pancreatic events (n=2).

| | Tremelimumab rechallenge subgroup N=30 |
|---|---|
| Any AE | 29 (97) |
| Grade 1 AE | 3 (10) |
| Grade 2 AE | 10 (33) |
| Grade 3 AE | 13 (43) |
| Grade 4 AE | 3 (10) |
| SAE | 12 (40) |
| imAE | 10 (33) |

Due to the limited number of patients who were rechallenged with tremelimumab in the HIMALAYA study, no conclusions can be made regarding the overall safety and tolerability of tremelimumab rechallenge.

**Laboratory Findings**

Data:

**Table 38 Liver Function Abnormalities (Safety Analysis Set)**

| Category | Number (%) of Patients | | | | |
|---|---|---|---|---|---|
| | HCC-tumor Pool | | Pan-tumor Pool | | |
| | T300+D (N = 462) | D (N = 492) | D (N = 4045) | T75+D (N = 3319) | T750 (N = 643) |
| **ALT or AST** | | | | | |
| ≥ 3 × to ≤ 5 × ULN | 93 (20.1) | 84 (17.1) | 242 (6.0) | 217 (6.5) | 27 (4.2) |
| > 5 × to ≤ 8 × ULN | 65 (14.1) | 56 (11.4) | 127 (3.1) | 111 (3.3) | 16 (2.5) |
| > 8 × to ≤ 10 × ULN | 26 (5.6) | 31 (6.3) | 57 (1.4) | 28 (0.8) | 7 (1.1) |
| > 10 × to ≤ 20 × ULN | 39 (8.4) | 33 (6.7) | 67 (1.7) | 66 (2.0) | 4 (0.6) |
| > 20 × ULN | 14 (3.0) | 11 (2.2) | 29 (0.7) | 36 (1.1) | 5 (0.8) |

| Category | Number (%) of Patients | | | | |
|---|---|---|---|---|---|
| | HCC-tumor Pool | | Pan-tumor Pool | | |
| | T300+D (N = 462) | D (N = 492) | D (N = 4045) | T75+D (N = 3319) | T750 (N = 643) |
| **TBL** | | | | | |
| ≥ 2 × to ≤ 3 × ULN | 29 (6.3) | 41 (8.3) | 67 (1.7) | 39 (1.2) | 6 (0.9) |
| > 3 × to ≤ 5 × ULN | 16 (3.5) | 18 (3.7) | 48 (1.2) | 33 (1.0) | 1 (0.2) |
| > 5 × ULN | 19 (4.1) | 22 (4.5) | 56 (1.4) | 32 (1.0) | 7 (1.1) |
| **Potential Hy's law** [a] | 57 (12.3) | 65 (13.2) | 131 (3.2) | 85 (2.6) | 7 (1.1) |

[a] The onset date of ALT or AST elevation should be prior to or on the date of TBL elevation.
Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurred first).
Patients were counted only once in the worst reported subcategory.
Source: Table 2.7.4.10.3, Pooled Safety Outputs, Module 5.3.5.3

The number of patients with elevated hepatic laboratory parameters is summarized in Table 38. The majority of elevations in ALT or AST were ≥3× to ≤5× ULN in the HCC T300+D pool. Most elevations in total bilirubin were ≥2× to ≤3× ULN across all treatment groups.

Cases of liver function test abnormalities meeting the biochemical criteria of Hy's Law (ALT or AST ≥3 × ULN, and total bilirubin ≥2 × ULN) were reported for 57 patients (12.3%) in the HCC T300+D pool and 65 patients (13.2%) in the HCC D pool (Table 38).

Four patients in Study 22 had liver function test abnormalities meeting the criteria for Hy's Law for whom the role of durvalumab and/or tremelimumab could not be completely excluded. In the HIMALAYA study, 2 patients in the D arm, 4 patients in the T300+D arm, and 3 patients in the T75+D arm had liver function test abnormalities meeting the criteria for Hy's Law for whom the role of durvalumab and/or tremelimumab could not be completely excluded.

The Applicant's Position:
In general, the safety profile of laboratory abnormalities in patients in the HCC T300+D pool was as expected for the studied population, the IO class and consistent with the profile of the individual agents. There were no unexpected changes or other clinically significant trends observed in laboratory parameters with T300+D. Changes from baseline in clinical laboratory evaluations in the HCC T300+D pool were generally consistent with those in the Pan-tumor T75+D pool.

The FDA's Assessment:
Overall, the majority of laboratory abnormalities were low grade (Grade 1-2) and occurred at a similar frequency between the T300+D and sorafenib arms. The majority of AST and ALT elevations in the T300+D and sorafenib arms were >3x ULN - <5x ULN (87 patients, 22.4% vs 66 patients, 17.6%, respectively.) The majority of total bilirubin increases were >2x ULN - <=3x ULN in both the T300+D and S arm (7.0% vs 7.2%, respectively).

**Table 39: Laboratory Abnormalities Occurring in ≥20% of Patients on HIMALAYA Trial**

| | T300+D N=388 | | Sorafenib N=374 | |
|---|---|---|---|---|
| **Laboratory Abnormality** | **Any grade (%)** | **Grade 3 or 4 (%)** | **Any grade (%)** | **Grade 3 or 4 (%)** |
| **Chemistry** | | | | |
| Aspartate Aminotransferase increased | 63 | 27 | 55 | 21 |
| Alanine Aminotransferase increased | 56 | 18 | 53 | 12 |
| Sodium decreased | 46 | 15 | 40 | 11 |
| Bilirubin increased | 41 | 8 | 47 | 11 |
| Alkaline Phosphatase increased | 41 | 8 | 44 | 5 |
| Glucose increased | 39 | 14 | 29 | 4 |
| Calcium decreased | 34 | 0 | 43 | 0.3 |
| Albumin decreased | 31 | 0.5 | 37 | 1.7 |
| Potassium increased | 28 | 3.8 | 21 | 2.6 |
| Creatinine increased | 21 | 1.3 | 15 | 0.9 |
| **Hematology** | | | | |
| Hemoglobin decreased | 52 | 4.8 | 40 | 6 |
| Lymphocytes decreased | 41 | 11 | 39 | 10 |
| Platelets decreased | 29 | 1.6 | 35 | 3.1 |
| Leukocytes decreased | 20 | 0.8 | 30 | 1.1 |

Source: ADSL (Subject-Level Analysis Dataset) - 2022-02-23, ADLB (Laboratory Test Results, Analysis Data) - 2022-02-23.
Variables used: USUBJID, TRT01A, SAFFL, PARAM, ABLFL, AVAL, ANRLO, ANRHI, EVLLBFL, TRTEDT, ADT, ADY, ATOXGRHN, ATOXGRLN

**Vital Signs**

Data: See the Applicant's Position below.

The Applicant's Position:
Changes from baseline in vital signs in the HCC T300+D pool were generally consistent with those in the Pan-tumor T75+D pool.

The FDA's Assessment:
Per the protocol, deteriorations in vital signs were only reported as adverse events if they fulfilled any of the SAE criteria or were the reason for treatment discontinuation.

**Electrocardiograms (ECGs)**

Data: See the Applicant's Position below.

The Applicant's Position:
Neither the HIMALAYA study nor Study 22 were designed to formally assess ECG interval, rhythm, rate, or morphology. ECGs were collected at baseline and as clinically indicated throughout the studies.

The FDA's Assessment:
The FDA agrees with the Applicant's description of ECG assessments on the HIMALAYA study. ECGs were formally assessed on Study 06.

**QT**

Data:
In Study 06, there was an in-depth assessment of digital centrally-read ECGs in 313 patients who received T + D. There was no evidence of clinically meaningful cardiac effects associated with T + D treatment. The ΔQTcF relationship was also evaluated. For this analysis, 67 and 66 patients for durvalumab and tremelimumab, respectively, had centrally read triplicate ECG and concentration-matched observations. The modeling results demonstrated no significant linear relationship between durvalumab or tremelimumab concentrations and ΔQTcF.

The Applicant's Position:
No safety concerns pertaining to and associated with the elongation QT interval were identified.

The FDA's Assessment:
Based on prior experience with monoclonal antibodies, tremelimumab is not expected to cause QTc prolongation. See Section 6 for additional discussion.

**Immunogenicity**

Data: See the Applicant's Position below.

The Applicant's Position: See Section 6.3.1 and Table 6.

The FDA's Assessment:
See Section 6 for FDA assessment.

## Safety Results – Contribution of Components

Data: See the Applicant's Position below.

The Applicant's Position:

***Contributions of Durvalumab and Tremelimumab to the Safety and Tolerability Profile of T300+D***
In the proposed treatment regimen, the primary objective of combining a single priming dose of tremelimumab with durvalumab was to derive benefit from concurrent blockade of CTLA-4 and PD-L1 immune-mediated resistance pathways. The contributions of tremelimumab to the overall safety and tolerability profile of T300+D were characterized based on the safety and tolerability profile of HCC T300+D pool vs HCC D pool. Comparison of safety data from the HCC T300+D pool and the HCC D pool gives an insight into the contribution of tremelimumab to the safety profile of T300+D.

In the HCC D pool, the most commonly reported AEs (reported by ≥ 15% patients) were pruritus, diarrhea, and AST increased, all of which are known ADRs for durvalumab. In the HCC T300+D pool, the most commonly reported AEs (reported by ≥ 15% patients) were pruritus, diarrhea, rash, fatigue, decreased appetite, and AST increased. Of these, pruritus, diarrhea, rash, and AST increased are known ADRs for either durvalumab or tremelimumab.

Adverse events by PT that were reported in a higher percentage of patients (≥5% difference between

groups) in the HCC T300+D pool compared with the HCC D pool, respectively, were pruritus (25.5% vs 15.4%), diarrhea (25.3% vs 15.9%), rash (24.9% vs 10.8%), fatigue (18.0% vs 12.6%), pyrexia (13.9% vs 8.9%), hypothyroidism (11.9% vs 6.7%), amylase increased (8.9% vs 3.5%), and hyperthyroidism (8.2% vs 2.2%).

Maximum Grade 3 or 4 AEs were reported in a higher percentage of patients in the HCC T300+D pool than in the HCC D pool (48.1% vs 38.2%, respectively). The incidence of SAEs was numerically higher in the HCC T300+D pool compared with the HCC D pool (40.9% vs 32.7%, respectively). AEs leading to death were reported in a similar percentage of patients in the HCC T300+D pool compared with the HCC D pool (7.4% vs 6.1%, respectively). There was no particular pattern in the type of AEs that lead to treatment discontinuation or death.

Overall, the type of AEs and ADRs observed in HCC T300+D and HCC D pools were similar and consistent with the known safety profiles of durvalumab and tremelimumab. The frequencies and severity of the AEs were generally higher in the HCC T300+D combination as compared to the durvalumab monotherapy, which is consistent with other PDx/CTLA-4 combinations. These events were manageable according to the toxicity management guidelines.

Overall, the incidence of imAEs was higher in the HCC T300+D pool than in the HCC D pool. Although the majority of imAEs were CTCAE Grade 1 or 2, there was a higher incidence of maximum Grade 3 or 4 imAEs in the HCC T300+D pool than in the HCC D pool. The higher incidence of maximum Grade 3 or 4 imAEs in the HCC T300+D pool compared to the HCC D pool was mainly driven by diarrhea/colitis and dermatitis/rash.

A higher percentage of patients had an imAE that required treatment intervention with systemic corticosteroids, high-dose steroids, immunosuppressants, and/or endocrine therapy in the HCC T300+D pool compared with the HCC D pool. The discontinuation rate due to imAEs was low in both treatments groups but higher in HCC T300+D pool (5.6%) than in HCC D pool (3.3%), suggesting that imAEs were successfully managed according to the toxicity management guidelines allowing the majority of patients with imAEs to continue on treatment.

The FDA's Assessment:
The evaluation of the safety and tolerability of tremelimumab in combination with durvalumab for the treatment of adult patients with unresectable HCC was based primarily on the 762 patients randomized in the HIMALAYA trial who received at least one dose of study treatment (T300+D: 388 patients; sorafenib: 374 patients). To support the safety analysis, the Applicant included pooled safety data from patients with HCC who received T300+D or who received durvalumab monotherapy. FDA notes that as these were pooled studies and the proposed analysis involves cross trial comparisons, no definitive conclusions can be made from this data regarding the safety, tolerability, or necessity of tremelimumab in the T300+D regimen for the treatment of unresectable HCC. There was a nominal increase in some adverse events in the T300+D population compared to the durvalumab population, however, there did not appear to be a disproportionate increase in adverse events and no new safety signals were identified.

### 8.2.5. Analysis of Submission-Specific Safety Issues

Data: Not applicable.

The Applicant's Position: Not applicable.

The FDA's Assessment:
See above discussion regarding immune-mediated, hepatic and hemorrhage adverse events.

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

Data:
Patient-reported symptoms, function, and HRQoL were collected in the HIMALAYA study using the EORTC QLQ C30 and its HCC module (EORTC QLQ HCC18) as secondary efficacy endpoints. Other PRO assessments were exploratory endpoints and are reported in the CSR.

The Applicant's Position:
T300+D demonstrated a clinically meaningful delay in time to deterioration in a broad range of patient-reported symptoms, function, and global health status/QoL compared with S and lower patient-reported symptom, functional, and HRQoL burden over time as evidenced by the change from baseline scores compared with S in patient-reported symptoms, function, and global health status/QoL.

The FDA's Assessment:
The analyses of PRO data were considered exploratory and were not formally evaluated in the HIMALAYA trail because there was no pre-specified statistical testing procedure or alpha allocation for any PRO endpoints.

### 8.2.7. Safety Analyses by Demographic Subgroups

Data: See the Applicant's Position below.

The Applicant's Position:
There were no clinically meaningful differences in the safety profile of T300+D vs D with respect to of sex, race, or geographic region.

The FDA's Assessment:
The FDA performed safety group analysis using the safety population dataset to evaluate and confirm the safety profile of T300+D vs S across certain subgroups: age, sex, race, and region. The respective tables are below.

In general, patients who received T300+D and were over the age of 75 had a similar rate of adverse events to the 65-<75 group but a higher incidence of adverse events compared to patients younger than 65 who also received T300+D, particularly with anemia (9.4% vs 0.5%), hypertension (3.8% vs 0.5%), fatigue (3.8% vs 0.5%) and diarrhea (7.5% vs 4.7%).

There was a disproportionate enrollment of males to females as expected due to the epidemiology of hepatocellular carcinoma and overall, there were no clinically significant difference in the safety profile of T300+D administration across the two groups.

Given the low number of Black (T300+D=7, S=8), Native Hawaiian/Pacific Islander (T300+D=1, S=0), and American Indian/Alaskan Native (no patients enrolled) participants enrolled in the HIMALAYA trial, no

conclusions can be drawn regarding the safety profile in these subgroups. In general, there was not an increased rate of toxicity between White or Asian patients who received T300+D, though patients of Asian descent were more likely to experience hyponatremia compared to White patients (6.7% vs 1.7%).

**Table 40: Summary of TEAEs by Maximum Severity-Toxicity by Age (≥5%)**

| System Organ Class - Preferred Term | T300 + D <65 (N=193) Grade 3 to 5 n (%) | T 300 + D >=65-<75 (N=142) Grade 3 to 5 n (%) | T300 + D >=75 (N=53) Grade 3 to 5 n (%) | D Mono <65 (N=201) Grade 3 to 5 n (%) | D Mono >=65-<75 (N=130) Grade 3 to 5 n (%) | D Mono Age >=75 (N=57) Grade 3 to 5 n (%) | S Age <65 (N=188) Grade 3 to 5 n (%) | S >=65-<75 (N=130) Grade 3 to 5 n (%) | S >=75 (N=56) Grade 3 to 5 n (%) |
|---|---|---|---|---|---|---|---|---|---|
| **Investigations** | **32 (16.6)** | **26 (18.3)** | **11 (20.8)** | **30 (14.9)** | **18 (13.8)** | **8 (14.0)** | **20 (10.6)** | **22 (16.9)** | **11 (19.6)** |
| Lipase increased | 10 (5.2) | 9 (6.3) | 5 (9.4) | 7 (3.5) | 7 (5.4) | 2 (3.5) | 2 (1.1) | 6 (4.6) | 3 (5.4) |
| Aspartate aminotransferase increased | 8 (4.1) | 9 (6.3) | 3 (5.7) | 15 (7.5) | 6 (4.6) | 5 (8.8) | 5 (2.7) | 5 (3.8) | 2 (3.6) |
| Amylase increased | 8 (4.1) | 3 (2.1) | 3 (5.7) | 2 (1.0) | 1 (0.8) | 0 (0.0) | 1 (0.5) | 2 (1.5) | 1 (1.8) |
| Platelet count decreased | 2 (1.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (1.1) | 0 (0.0) | 3 (5.4) |
| **Gastrointestinal disorders** | **29 (15.0)** | **20 (14.1)** | **7 (13.2)** | **16 (8.0)** | **10 (7.7)** | **3 (5.3)** | **25 (13.3)** | **18 (13.8)** | **5 (8.9)** |
| Diarrhoea | 9 (4.7) | 4 (2.8) | 4 (7.5) | 5 (2.5) | 1 (0.8) | 0 (0.0) | 8 (4.3) | 5 (3.8) | 3 (5.4) |
| **Metabolism and nutrition disorders** | **17 (8.8)** | **17 (12.0)** | **8 (15.1)** | **13 (6.5)** | **10 (7.7)** | **5 (8.8)** | **11 (5.9)** | **16 (12.3)** | **7 (12.5)** |
| **Infections and infestations** | **16 (8.3)** | **13 (9.2)** | **4 (7.5)** | **9 (4.5)** | **7 (5.4)** | **2 (3.5)** | **12 (6.4)** | **6 (4.6)** | **3 (5.4)** |
| **Hepatobiliary disorders** | **9 (4.7)** | **10 (7.0)** | **3 (5.7)** | **4 (2.0)** | **7 (5.4)** | **1 (1.8)** | **8 (4.3)** | **5 (3.8)** | **2 (3.6)** |
| **Skin and subcutaneous tissue disorders** | **9 (4.7)** | **2 (1.4)** | **4 (7.5)** | **1 (0.5)** | **0 (0.0)** | **0 (0.0)** | **22 (11.7)** | **14 (10.8)** | **13 (23.2)** |
| Rash maculo-papular | 0 (0.0) | 1 (0.7) | 1 (1.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.8) | 3 (5.4) |
| Palmar-plantar erythrodysaesthesia syndrome | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 17 (9.0) | 7 (5.4) | 10 (17.9) |
| **General disorders and administration site conditions** | **7 (3.6)** | **12 (8.5)** | **3 (5.7)** | **12 (6.0)** | **8 (6.2)** | **4 (7.0)** | **12 (6.4)** | **10 (7.7)** | **5 (8.9)** |
| Asthenia | 3 (1.6) | 4 (2.8) | 0 (0.0) | 3 (1.5) | 4 (3.1) | 2 (3.5) | 5 (2.7) | 2 (1.5) | 3 (5.4) |
| Fatigue | 1 (0.5) | 5 (3.5) | 2 (3.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (1.6) | 7 (5.4) | 1 (1.8) |
| **Nervous system disorders** | **6 (3.1)** | **7 (4.9)** | **4 (7.5)** | **6 (3.0)** | **1 (0.8)** | **2 (3.5)** | **3 (1.6)** | **2 (1.5)** | **2 (3.6)** |
| **Blood and lymphatic system disorders** | **3 (1.6)** | **5 (3.5)** | **5 (9.4)** | **11 (5.5)** | **5 (3.8)** | **0 (0.0)** | **8 (4.3)** | **6 (4.6)** | **4 (7.1)** |
| Anaemia | 1 (0.5) | 5 (3.5) | 5 (9.4) | 7 (3.5) | 2 (1.5) | 0 (0.0) | 4 (2.1) | 6 (4.6) | 2 (3.6) |
| **Vascular disorders** | **3 (1.6)** | **6 (4.2)** | **3 (5.7)** | **5 (2.5)** | **3 (2.3)** | **0 (0.0)** | **4 (2.1)** | **10 (7.7)** | **9 (16.1)** |
| Hypertension | 1 (0.5) | 4 (2.8) | 2 (3.8) | 3 (1.5) | 1 (0.8) | 0 (0.0) | 4 (2.1) | 10 (7.7) | 9 (16.1) |

Source: OCS Analysis Studio, Safety Explorer. Adverse events missing severity/toxicity grades are not included in the above table.

Filters: TRT01A = "TREME 300 + DURVA" and AGEGR1 = "< 65" and SAFFL = "Y" (T300 + D <65); AGEGR1 = ">=65 - <75" and TRT01A = "TREME 300 + DURVA" and SAFFL = "Y" (T 300 + D >=65-<75); TRT01A = "TREME 300 + DURVA" and AGEGR1 = ">=75" and SAFFL = "Y" (T300 + D >=75); AGEGR1 = "< 65" and TRT01A = "DURVA MONO" and SAFFL = "Y" (D Mono <65); AGEGR1 = ">=65 - <75" and TRT01A = "DURVA MONO" and SAFFL = "Y" (D Mono >=65-<75); TRT01A = "DURVA MONO" and AGEGR1 = ">=75" and SAFFL = "Y" (D Mono Age >=75); TRT01A =

| System Organ Class - Preferred Term | T300 + D <65 | T 300 + D >=65-<75 | T300 + D >=75 | D Mono <65 | D Mono >=65-<75 | D Mono Age >=75 | S Age <65 | S >=65-<75 | S >=75 |
|---|---|---|---|---|---|---|---|---|---|
| | (N=193) | (N=142) | (N=53) | (N=201) | (N=130) | (N=57) | (N=188) | (N=130) | (N=56) |
| | Grade 3 to 5 | Grade 3 to 5 | Grade 3 to 5 | Grade 3 to 5 | Grade 3 to 5 | Grade 3 to 5 | Grade 3 to 5 | Grade 3 to 5 | Grade 3 to 5 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |

"SORA" and AGEGR1 = "< 65" and SAFFL = "Y" (S Age <65); TRT01A = "SORA" and AGEGR1 = ">=65 - <75" and SAFFL = "Y" (S >=65-<75); TRT01A = "SORA" and AGEGR1 = ">=75" and SAFFL = "Y" (S >=75); TRTEMFL = "Y" and AETOXGRN = "Grade 3 to 5" (Adverse Events).
Percent Threshold: Any Column ≥ 5%.

**Table 41: Summary of TEAEs by Maximum Severity-Toxicity by Sex (≥5%)**

| System Organ Class - Preferred Term | T300 + D - Males (N=323) | T 300 + D - Females (N=65) | D Mono - Male (N=322) | D Mono - Female (N=66) | S - Male (N=323) | S - Female (N=51) |
|---|---|---|---|---|---|---|
| | Grade 3 to 5 | Grade 3 to 5 | Grade 3 to 5 | Grade 3 to 5 | Grade 3 to 5 | Grade 3 to 5 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Investigations** | **57 (17.6)** | **12 (18.5)** | **46 (14.3)** | **10 (15.2)** | **43 (13.3)** | **10 (19.6)** |
| Lipase increased | 20 (6.2) | 4 (6.2) | 14 (4.3) | 2 (3.0) | 8 (2.5) | 3 (5.9) |
| Aspartate aminotransferase increased | 17 (5.3) | 3 (4.6) | 22 (6.8) | 4 (6.1) | 11 (3.4) | 1 (2.0) |
| **Gastrointestinal disorders** | **47 (14.6)** | **9 (13.8)** | **27 (8.4)** | **2 (3.0)** | **43 (13.3)** | **5 (9.8)** |
| Diarrhoea | 13 (4.0) | 4 (6.2) | 5 (1.6) | 1 (1.5) | 14 (4.3) | 2 (3.9) |
| **Metabolism and nutrition disorders** | **32 (9.9)** | **10 (15.4)** | **25 (7.8)** | **3 (4.5)** | **29 (9.0)** | **5 (9.8)** |
| Hyponatraemia | 10 (3.1) | 6 (9.2) | 4 (1.2) | 1 (1.5) | 11 (3.4) | 0 (0.0) |
| Hyperkalaemia | 6 (1.9) | 0 (0.0) | 8 (2.5) | 0 (0.0) | 6 (1.9) | 3 (5.9) |
| **Infections and infestations** | **29 (9.0)** | **4 (6.2)** | **17 (5.3)** | **1 (1.5)** | **19 (5.9)** | **2 (3.9)** |
| **Hepatobiliary disorders** | **18 (5.6)** | **4 (6.2)** | **11 (3.4)** | **1 (1.5)** | **13 (4.0)** | **2 (3.9)** |
| **General disorders and administration site conditions** | **17 (5.3)** | **5 (7.7)** | **21 (6.5)** | **3 (4.5)** | **23 (7.1)** | **4 (7.8)** |
| **Blood and lymphatic system disorders** | **13 (4.0)** | **0 (0.0)** | **15 (4.7)** | **1 (1.5)** | **14 (4.3)** | **4 (7.8)** |
| Anaemia | 11 (3.4) | 0 (0.0) | 8 (2.5) | 1 (1.5) | 9 (2.8) | 3 (5.9) |
| **Skin and subcutaneous tissue disorders** | **13 (4.0)** | **2 (3.1)** | **1 (0.3)** | **0 (0.0)** | **41 (12.7)** | **8 (15.7)** |
| Rash | 6 (1.9) | 0 (0.0) | 1 (0.3) | 0 (0.0) | 1 (0.3) | 3 (5.9) |
| Palmar-plantar erythrodysaesthesia syndrome | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 30 (9.3) | 4 (7.8) |
| **Vascular disorders** | **11 (3.4)** | **1 (1.5)** | **8 (2.5)** | **0 (0.0)** | **19 (5.9)** | **4 (7.8)** |
| Hypertension | 6 (1.9) | 1 (1.5) | 4 (1.2) | 0 (0.0) | 19 (5.9) | 4 (7.8) |
| **Respiratory, thoracic and mediastinal disorders** | **8 (2.5)** | **1 (1.5)** | **8 (2.5)** | **1 (1.5)** | **6 (1.9)** | **3 (5.9)** |

Source: OCS Analysis Studio, Safety Explorer. Adverse events missing severity/toxicity grades are not included in the above table.
Filters: TRT01A = "TREME 300 + DURVA" and SEX = "M" and SAFFL = "Y" (T300 + D - Males); TRT01A = "TREME 300 + DURVA" and SEX = "F" and SAFFL = "Y" (T 300 + D - Females ); TRT01A = "DURVA MONO" and SEX = "M" and SAFFL = "Y" (D Mono - Male); TRT01A = "DURVA MONO" and SEX = "F" and SAFFL = "Y" (D Mono - Female); TRT01A = "SORA" and SEX = "M" and SAFFL = "Y" (S - Male); TRT01A = "SORA" and SEX = "F" and SAFFL = "Y" (S - Female); TRTEMFL = "Y" and AETOXGRN = "Grade 3 to 5" (Adverse Events).
Percent Threshold: Any Column ≥ 5%.

**Table 42: Summary of TEAEs by Maximum Severity-Toxicity by Race (≥5%)**

| System Organ Class - Preferred Term | T300 + D - White (N=177) | T 300 + D - Black (N=7) | T300 + D - Asian (N=195) | D Mono White (N=160) | D Mono - Black (N=2) | D Mono - Asian (N=210) | S - White (N=171) | S - Black (N=8) | S - Asian (N=184) |
|---|---|---|---|---|---|---|---|---|---|
| | Grade 3 to 5 n (%) | Grade 3 to 5 n (%) | Grade 3 to 5 n (%) | Grade 3 to 5 n (%) | Grade 3 to 5 n (%) | Grade 3 to 5 n (%) | Grade 3 to 5 n (%) | Grade 3 to 5 n (%) | Grade 3 to 5 n (%) |
| **Investigations** | **34 (19.2)** | **1 (14.3)** | **31 (15.9)** | **24 (15.0)** | **1 (50.0)** | **28 (13.3)** | **26 (15.2)** | **1 (12.5)** | **26 (14.1)** |
| Aspartate aminotransferase increased | 13 (7.3) | 0 (0.0) | 7 (3.6) | 12 (7.5) | 1 (50.0) | 13 (6.2) | 4 (2.3) | 1 (12.5) | 7 (3.8) |
| Alanine aminotransferase increased | 8 (4.5) | 0 (0.0) | 2 (1.0) | 3 (1.9) | 0 (0.0) | 9 (4.3) | 2 (1.2) | 1 (12.5) | 4 (2.2) |
| Lipase increased | 7 (4.0) | 1 (14.3) | 14 (7.2) | 8 (5.0) | 0 (0.0) | 7 (3.3) | 6 (3.5) | 0 (0.0) | 5 (2.7) |
| Amylase increased | 5 (2.8) | 1 (14.3) | 7 (3.6) | 1 (0.6) | 0 (0.0) | 2 (1.0) | 1 (0.6) | 0 (0.0) | 3 (1.6) |
| Blood bilirubin increased | 3 (1.7) | 0 (0.0) | 0 (0.0) | 3 (1.9) | 1 (50.0) | 3 (1.4) | 5 (2.9) | 1 (12.5) | 2 (1.1) |
| Blood alkaline phosphatase increased | 1 (0.6) | 0 (0.0) | 0 (0.0) | 1 (0.6) | 1 (50.0) | 0 (0.0) | 2 (1.2) | 0 (0.0) | 0 (0.0) |
| **Gastrointestinal disorders** | **28 (15.8)** | **0 (0.0)** | **27 (13.8)** | **13 (8.1)** | **0 (0.0)** | **15 (7.1)** | **21 (12.3)** | **2 (25.0)** | **23 (12.5)** |
| Diarrhoea | 10 (5.6) | 0 (0.0) | 7 (3.6) | 2 (1.3) | 0 (0.0) | 3 (1.4) | 5 (2.9) | 1 (12.5) | 10 (5.4) |
| Intestinal obstruction | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (12.5) | 0 (0.0) |
| **General disorders and administration site conditions** | **14 (7.9)** | **0 (0.0)** | **8 (4.1)** | **11 (6.9)** | **0 (0.0)** | **13 (6.2)** | **18 (10.5)** | **0 (0.0)** | **8 (4.3)** |
| Asthenia | 5 (2.8) | 0 (0.0) | 2 (1.0) | 8 (5.0) | 0 (0.0) | 1 (0.5) | 9 (5.3) | 0 (0.0) | 0 (0.0) |
| **Infections and infestations** | **13 (7.3)** | **0 (0.0)** | **18 (9.2)** | **6 (3.8)** | **0 (0.0)** | **8 (3.8)** | **8 (4.7)** | **1 (12.5)** | **11 (6.0)** |
| Pneumonia | 3 (1.7) | 0 (0.0) | 2 (1.0) | 1 (0.6) | 0 (0.0) | 2 (1.0) | 5 (2.9) | 1 (12.5) | 2 (1.1) |
| **Metabolism and nutrition disorders** | **12 (6.8)** | **0 (0.0)** | **28 (14.4)** | **11 (6.9)** | **0 (0.0)** | **15 (7.1)** | **15 (8.8)** | **3 (37.5)** | **14 (7.6)** |
| Hyponatraemia | 3 (1.7) | 0 (0.0) | 13 (6.7) | 0 (0.0) | 0 (0.0) | 4 (1.9) | 4 (2.3) | 2 (25.0) | 5 (2.7) |
| Dehydration | 1 (0.6) | 0 (0.0) | 1 (0.5) | 2 (1.3) | 0 (0.0) | 0 (0.0) | 1 (0.6) | 1 (12.5) | 1 (0.5) |
| Hypoalbuminaemia | 0 (0.0) | 0 (0.0) | 1 (0.5) | 0 (0.0) | 0 (0.0) | 1 (0.5) | 1 (0.6) | 1 (12.5) | 0 (0.0) |
| **Hepatobiliary disorders** | **10 (5.6)** | **0 (0.0)** | **11 (5.6)** | **6 (3.8)** | **0 (0.0)** | **6 (2.9)** | **7 (4.1)** | **0 (0.0)** | **8 (4.3)** |
| **Musculoskeletal and connective tissue disorders** | **10 (5.6)** | **1 (14.3)** | **2 (1.0)** | **1 (0.6)** | **0 (0.0)** | **3 (1.4)** | **4 (2.3)** | **0 (0.0)** | **1 (0.5)** |
| Pain in extremity | 0 (0.0) | 1 (14.3) | 1 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.6) | 0 (0.0) | 1 (0.5) |
| **Nervous system disorders** | **10 (5.6)** | **0 (0.0)** | **6 (3.1)** | **4 (2.5)** | **0 (0.0)** | **3 (1.4)** | **6 (3.5)** | **0 (0.0)** | **1 (0.5)** |
| **Vascular disorders** | **8 (4.5)** | **0 (0.0)** | **4 (2.1)** | **3 (1.9)** | **0 (0.0)** | **2 (1.0)** | **12 (7.0)** | **2 (25.0)** | **6 (3.3)** |
| Hypertension | 5 (2.8) | 0 (0.0) | 2 (1.0) | 1 (0.6) | 0 (0.0) | 2 (1.0) | 12 (7.0) | 2 (25.0) | 6 (3.3) |
| **Blood and lymphatic system disorders** | **5 (2.8)** | **0 (0.0)** | **7 (3.6)** | **8 (5.0)** | **0 (0.0)** | **7 (3.3)** | **13 (7.6)** | **0 (0.0)** | **4 (2.2)** |

| System Organ Class - Preferred Term | T300 + D - White (N=177) Grade 3 to 5 n (%) | T 300 + D - Black (N=7) Grade 3 to 5 n (%) | T300 + D - Asian (N=195) Grade 3 to 5 n (%) | D Mono White (N=160) Grade 3 to 5 n (%) | D Mono - Black (N=2) Grade 3 to 5 n (%) | D Mono - Asian (N=210) Grade 3 to 5 n (%) | S - White (N=171) Grade 3 to 5 n (%) | S - Black (N=8) Grade 3 to 5 n (%) | S - Asian (N=184) Grade 3 to 5 n (%) |
|---|---|---|---|---|---|---|---|---|---|
| **Cardiac disorders** | **5 (2.8)** | **0 (0.0)** | **3 (1.5)** | **3 (1.9)** | **0 (0.0)** | **3 (1.4)** | **5 (2.9)** | **1 (12.5)** | **2 (1.1)** |
| Supraventricular tachycardia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.5) | 0 (0.0) | 1 (12.5) | 0 (0.0) |
| **Renal and urinary disorders** | **4 (2.3)** | **0 (0.0)** | **3 (1.5)** | **1 (0.6)** | **1 (50.0)** | **2 (1.0)** | **3 (1.8)** | **0 (0.0)** | **3 (1.6)** |
| Acute kidney injury | 1 (0.6) | 0 (0.0) | 2 (1.0) | 0 (0.0) | 1 (50.0) | 2 (1.0) | 1 (0.6) | 0 (0.0) | 1 (0.5) |
| **Skin and subcutaneous tissue disorders** | **3 (1.7)** | **0 (0.0)** | **12 (6.2)** | **1 (0.6)** | **0 (0.0)** | **0 (0.0)** | **20 (11.7)** | **0 (0.0)** | **28 (15.2)** |
| Palmar-plantar erythrodysaesthesia syndrome | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 9 (5.3) | 0 (0.0) | 25 (13.6) |

Source: OCS Analysis Studio, Safety Explorer. Adverse events missing severity/toxicity grades are not included in the above table.
Filters: TRT01A = "TREME 300 + DURVA" and RACESGR = "WHITE" and SAFFL = "Y" (T300 + D - White ); TRT01A = "TREME 300 + DURVA" and RACESGR = "BLACK OR AFRICAN AMERICAN" and SAFFL = "Y" (T 300 + D - Black); TRT01A = "TREME 300 + DURVA" and RACESGR = "ASIAN" and SAFFL = "Y" (T300 + D - Asian); TRT01A = "DURVA MONO" and RACESGR = "WHITE" and SAFFL = "Y" (D Mono White); TRT01A = "DURVA MONO" and RACESGR = "BLACK OR AFRICAN AMERICAN" and SAFFL = "Y" (D Mono - Black); TRT01A = "DURVA MONO" and RACESGR = "ASIAN" and SAFFL = "Y" (D Mono - Asian); TRT01A = "SORA" and RACESGR = "WHITE" and SAFFL = "Y" (S - White ); TRT01A = "SORA" and RACESGR = "BLACK OR AFRICAN AMERICAN" and SAFFL = "Y" (S - Black ); TRT01A = "SORA" and RACESGR = "ASIAN" and SAFFL = "Y" (S - Asian); TRTEMFL = "Y" and AETOXGRN = "Grade 3 to 5" (Adverse Events).
Percent Threshold: Any Column ≥ 5%.

**Table 43: Summary of TEAEs by Maximum Severity-Toxicity by Region (≥5%)**

| System Organ Class - Preferred Term | T300 + D - Asia (N=156) Grade 3 to 5 n (%) | T 300 + D - Rest of World (ROW) (N=232) Grade 3 to 5 n (%) | D Mono Asia (N=165) Grade 3 to 5 n (%) | D Mono - ROW (N=223) Grade 3 to 5 n (%) | S - Asia (N=151) Grade 3 to 5 n (%) | S - ROW (N=223) Grade 3 to 5 n (%) |
|---|---|---|---|---|---|---|
| **Investigations** | **25 (16.0)** | **44 (19.0)** | **26 (15.8)** | **30 (13.5)** | **16 (10.6)** | **37 (16.6)** |
| Lipase increased | 10 (6.4) | 14 (6.0) | 5 (3.0) | 11 (4.9) | 4 (2.6) | 7 (3.1) |
| Aspartate aminotransferase increased | 7 (4.5) | 13 (5.6) | 12 (7.3) | 14 (6.3) | 4 (2.6) | 8 (3.6) |
| **Metabolism and nutrition disorders** | **25 (16.0)** | **17 (7.3)** | **12 (7.3)** | **16 (7.2)** | **11 (7.3)** | **23 (10.3)** |
| Hyponatraemia | 12 (7.7) | 4 (1.7) | 5 (3.0) | 0 (0.0) | 4 (2.6) | 7 (3.1) |
| **Gastrointestinal disorders** | **22 (14.1)** | **34 (14.7)** | **12 (7.3)** | **17 (7.6)** | **22 (14.6)** | **26 (11.7)** |
| Diarrhoea | 5 (3.2) | 12 (5.2) | 2 (1.2) | 4 (1.8) | 8 (5.3) | 8 (3.6) |
| **Infections and infestations** | **15 (9.6)** | **18 (7.8)** | **8 (4.8)** | **10 (4.5)** | **11 (7.3)** | **10 (4.5)** |
| **Skin and subcutaneous tissue disorders** | **9 (5.8)** | **6 (2.6)** | **0 (0.0)** | **1 (0.4)** | **21 (13.9)** | **28 (12.6)** |
| Palmar-plantar erythrodysaesthesia syndrome | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 19 (12.6) | 15 (6.7) |

| System Organ Class - Preferred Term | T300 + D - Asia (N=156) | T 300 + D - Rest of World (ROW) (N=232) | D Mono Asia (N=165) | D Mono - ROW (N=223) | S - Asia (N=151) | S - ROW (N=223) |
|---|---|---|---|---|---|---|
| | Grade 3 to 5 n (%) | Grade 3 to 5 n (%) | Grade 3 to 5 n (%) | Grade 3 to 5 n (%) | Grade 3 to 5 n (%) | Grade 3 to 5 n (%) |
| **Blood and lymphatic system disorders** | **7 (4.5)** | **6 (2.6)** | **7 (4.2)** | **9 (4.0)** | **3 (2.0)** | **15 (6.7)** |
| **Hepatobiliary disorders** | **7 (4.5)** | **15 (6.5)** | **2 (1.2)** | **10 (4.5)** | **6 (4.0)** | **9 (4.0)** |
| **General disorders and administration site conditions** | **6 (3.8)** | **16 (6.9)** | **12 (7.3)** | **12 (5.4)** | **6 (4.0)** | **21 (9.4)** |
| **Nervous system disorders** | **4 (2.6)** | **13 (5.6)** | **3 (1.8)** | **6 (2.7)** | **1 (0.7)** | **6 (2.7)** |
| **Vascular disorders** | **4 (2.6)** | **8 (3.4)** | **0 (0.0)** | **8 (3.6)** | **4 (2.6)** | **19 (8.5)** |
| Hypertension | 2 (1.3) | 5 (2.2) | 0 (0.0) | 4 (1.8) | 4 (2.6) | 19 (8.5) |
| **Musculoskeletal and connective tissue disorders** | **1 (0.6)** | **12 (5.2)** | **2 (1.2)** | **3 (1.3)** | **1 (0.7)** | **4 (1.8)** |

Source: OCS Analysis Studio, Safety Explorer. Adverse events missing severity/toxicity grades are not included in the above table.
Filters: TRT01A = "TREME 300 + DURVA" and REGION1 = "ASIA (EXCLUDING JAPAN" and SAFFL = "Y" (T300 + D - Asia ); TRT01A = "TREME 300 + DURVA" and REGION1 = "REST OF THE WORLD (INCLUDING JAPAN" and SAFFL = "Y" (T 300 + D - Rest of World (ROW)); TRT01A = "DURVA MONO" and REGION1 = "ASIA (EXCLUDING JAPAN" and SAFFL = "Y" (D Mono Asia); TRT01A = "DURVA MONO" and REGION1 = "REST OF THE WORLD (INCLUDING JAPAN" and SAFFL = "Y" (D Mono - ROW); TRT01A = "SORA" and REGION1 = "ASIA (EXCLUDING JAPAN" and SAFFL = "Y" (S - Asia ); TRT01A = "SORA" and REGION1 = "REST OF THE WORLD (INCLUDING JAPAN" and SAFFL = "Y" (S - ROW); TRTEMFL = "Y" and AETOXGRN = "Grade 3 to 5" (Adverse Events).
Percent Threshold: Any Column ≥ 5%.

### 8.2.8. Specific Safety Studies/Clinical Trials

Data: See the Applicant's Position below.

The Applicant's Position: No safety specific clinical studies were conducted to evaluate a specific safety concern.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

### 8.2.9. Additional Safety Explorations

**Human Carcinogenicity or Tumor Development**

Data: No studies were conducted.

The Applicant's Position: No studies were conducted.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

**Human Reproduction and Pregnancy**

Data: No studies were conducted.

The Applicant's Position: No studies were conducted.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

**Pediatrics and Assessment of Effects on Growth**

Data: Not applicable.

The Applicant's Position: Not applicable.

The FDA's Assessment:
See Sections 10 and 13 for information on the pediatrics development program.

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

Data: See the Applicant's Position below.

The Applicant's Position:

**Overdose:** Neither durvalumab nor tremelimumab have any particular effect or characteristic that might increase the likelihood of intentional overdose. There is no specific treatment in the event of durvalumab or tremelimumab overdose, and symptoms of overdose have not been established.

**Drug abuse:** Based on the clinical setting of use, mode of action, physiological and pharmacological activity, and lack of stimulant properties, durvalumab and tremelimumab are unlikely to be abused.

**Withdrawal and rebound:** Because durvalumab and tremelimumab have no known potential for dependence and are not dosed continuously, withdrawal or rebound events are not relevant to treatment with durvalumab or tremelimumab.

The FDA's Assessment:
FDA agrees with the Applicant's position.

### 8.2.10. Safety in the Postmarket Setting

**Safety Concerns Identified Through Postmarket Experience**

Data:
As of the date of this application, tremelimumab is not approved in any region. As of 05 October 2021, durvalumab is approved in 75 countries for Stage III, unresectable, NSCLC, in 64 countries for ES-SCLC, and 17 countries for metastatic UC. The cumulative global post-marketing patient exposure to durvalumab (10 mg/kg) since launch to 30 June 2021 has been estimated to be 52006 patient-years.

The Applicant's Position:
No new safety concern was identified based on the post-marketing safety reports.
Tremelimumab is not yet approved for use in any country.

The FDA's Assessment:
Tremelimumab plus durvalumab is not an approved regimen for marketing in any country to date and there is no postmarket data available for safety analyses of the combination regimen. The safety profile

of durvalumab has been well characterized in clinical trials and in the post-marketing database. The observed safety profile of T300+D in HIMALAYA appears generally consistent with the known safety profile of durvalumab in regard to the type of adverse events observed.

**Expectations on Safety in the Postmarket Setting**

Data: See the Applicant's Position below.

The Applicant's Position:
AstraZeneca has comprehensive processes for signal detection, regular safety reviews identifying and evaluating issues potentially affecting patient safety, and developing safety recommendations (including changes to the reference safety information). In addition, these processes enable the identification of safety topics that need to be kept under close surveillance. The safety signal detection activities include review of reported AEs from postmarketed sources, and a review of the published literature relevant to durvalumab. The postmarket data for durvalumab are regularly reviewed for new findings or trends. The Applicant will employ the same measures for tremelimumab.

The FDA's Assessment:Potential safety concerns beyond the risks observed in clinical trials of tremelimumab and durvalumab and described in product labeling are not expected. Routine pharmacovigilance will also be conducted by FDA to monitor for unexpected adverse events. The review teams determined that a REMS is not required to ensure safe and effective use of tremelimumab in combination with -durvalumab. Tremelimumab in combination with durvalumab will be prescribed by oncologists who are trained on how to monitor, diagnose, and manage serious adverse reactions caused by immune checkpoint inhibitor drugs in accordance with FDA-approved labeling. Additionally, standard practice in oncology dictates informed consent prior to prescribing or administering antineoplastic drugs.

### 8.2.11. Integrated Assessment of Safety

Data: Not applicable.

The Applicant's Position:
Overall, the safety and tolerability of tremelimumab administered in combination with durvalumab was consistent with the known safety profile for each agent, and AEs were well tolerated and manageable according to toxicity management guidelines.

Although more toxicity was observed with the T300+D, the safety profile was as expected, and AEs were manageable according to toxicity management guidelines. Importantly, the addition of tremelimumab to durvalumab therapy did not cause any meaningful increase in discontinuation due to toxicity, and the majority of patients continued treatment with durvalumab after a single loading dose of tremelimumab, supporting the tolerability of the regimen. The most common AEs in the HCC T300+D pool were pruritus, diarrhea, rash, fatigue, decreased appetite, and AST increased.

Further, the safety profile for HIMALAYA T300+D was differentiated from sorafenib and was not associated with increased bleeding risk and lower treatment discontinuation rate, suggesting that T300+D offers a different safety profile from agents that are currently available.

In totality, the safety and tolerability data demonstrated that durvalumab in combination with tremelimumab has a manageable safety profile in the target patient population.

The FDA's Assessment:
The evaluation of the safety of tremelimumab in combination with durvalumab at the proposed dosage in adult patients with unresectable hepatocellular carcinoma was based primarily on the 388 patients randomized to the T300+D arm and the 374 patients randomized to the sorafenib arm in the HIMALAYA study who received at least one dose each of the study drug. The Applicant provided an integrated safety analysis that incorporated data from the supportive trial Study 22 which included

Overall, the safety profile of tremelimumab in combination with durvalumab in the HIMALAYA study is consistent with the types of AEs expected from an immune-oncology combination regimen containing an anti-PD-L1 and anti-CTLA-4 therapy. There were no new safety signals observed. When compared to sorafenib, however, there was a higher incidence of grade 3-4 AEs and SAEs with tremelimumab in combination with durvalumab. While there was a slight numerical increase in the incidence of adverse events on the T300+D arm, there did not appear to be a disproportionate occurrence of any specific AEs on the T300+D arm and there were fewer dose interruptions and discontinuations resulting in a higher relative dose intensity in patients on the T300+D arm compared to the sorafenib arm.

# SUMMARY AND CONCLUSIONS

## 8.3.Statistical Issues

The FDA's Assessment:
No major statistical issues were identified during review of this application. HIMALAYA showed a statistically significant and clinically meaningful improvement in overall survival for the T300+D arm compared to sorafenib. Key secondary endpoints included evaluating overall survival non-inferiority and superiority for D compared to sorafenib; results showed that durvalumab achieved statistical non-inferiority relative to sorafenib based on the Applicant's pre-specified non-inferiority margin of 1.08. However, given that the Applicant is not seeking an indication for durvalumab monotherapy, FDA did not conduct a detailed assessment of the appropriateness of a non-inferiority claim. Results also showed that durvalumab failed to achieve overall survival superiority relative to sorafenib with a 2-sided p-value of 0.0674, which was greater than the pre-specified alpha level of 0.049; these results provided supportive evidence that both components of the T300+D combination regimen are needed to achieve a statistically significant OS effect compared to sorafenib. Analyses of all other endpoints in HIMALAYA, including PRO analyses, were descriptive and exploratory.

Results of Study 22 provided additional support for the contribution of each component of the proposed T300+D regimen. However, the results of Study 22 should be interpreted with caution given that Study 22 pooled efficacy results from multi-part of the study, which contained both randomized and non-randomized patients, did not include formal testing of efficacy endpoints (which were secondary endpoints) and enrolled a study population that differed from the proposed indication in this application (i.e., 1L uHCC); FDA considers Study 22 to be supportive only.

## 8.4.Conclusions and Recommendations

The FDA's Assessment:
FDA concludes that the results of the HIMALAYA trial demonstrate that T300+D provides a statistically significant and clinically meaningful improvement in OS in patients with unresectable HCC who were randomized to receive T300+D compared to patients randomized to receive sorafenib. OS is an acceptable endpoint to demonstrate the effectiveness of a new therapeutic in this patient population. The safety profile of T300+D at the proposed recommended dosage of tremelimumab 300 mg administered as a single dose IV followed by durvalumab 1500 mg IV on Day 1 of Cycle 1, with durvalumab 1500 mg continued as a single agent every 4 weeks is acceptable in the context of patients with a serious and life-threatening condition and is manageable with guidelines provided in product labeling. Overall, the review team concludes that the data in the application support a favorable benefit:risk assessment for T300+D in the indicated population and recommends traditional approval for the following indication:

Tremelimumab in combination with durvalumab is indicated for the treatment of adult patients with unresectable HCC.

X X

Primary Statistical Reviewer Statistical Team Leader

X X

Primary Clinical Reviewer Clinical Team Leader

# 9. Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The Division did not refer the application to the Oncologic Drug Advisory Committee (ODAC) or seek input from Special Government Employees (SGEs) for this BLA as no significant review issues were identified during the review of this application.

# 10. Pediatrics

The Applicant's Position:
Agreed Initial Pediatric Study Plans are in place for durvalumab as a single agent and for tremelimumab in combination with durvalumab for the 1L treatment of patients with uHCC not eligible for loco-regional therapy.

HCC occurs almost exclusively in the adult population and has limited applicability to the pediatric patient population. The Sponsor has included a request for a full waiver from conducting studies of durvalumab or tremelimumab in combination with durvalumab in patients with HCC across all pediatric age groups. The Sponsor considers that necessary studies in pediatrics are impossible or highly impractical in this indication.

A request for deferral for molecularly targeted pediatric cancer investigation in newborns and pediatric patients 29 days and older is planned for tremelimumab. This deferral is necessary as the establishment of a positive benefit-risk of the tremelimumab and durvalumab combination is needed from ongoing pivotal studies like HIMALAYA before a pediatric study can be initiated.

The FDA's Assessment:
The Applicant was granted a deferral for the conduct of molecularly targeted pediatric cancer studies for tremelimumab. The studies required under the FDARA provisions of PREA are intended to evaluate safety, dosing, PK, PD, and preliminary activity. A PMR was issued for Study 1, A Phase I/II, open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of tremelimumab in combination with durvalumab in pediatric patients, as proposed in the Agreed Initial Pediatric Study Plan. The proposed Study 2 and Study 3 are not required under FDARA and were issued as Pediatric PMCs.

The Applicant's Agreed Initial Pediatric Study Plan included a proposal to address the FDARA provisions of PREA, therefore a full waiver from conducting studies of tremelimumab in combination with durvalumab in patients with HCC across all pediatric age groups is not needed. See Section 13 for additional information.

# 11. Labeling Recommendations

Data:
This is an original application. Please see annotated label in Module 1.14.1.2 for proposed labeling.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Table 44 summarizes changes to the proposed prescribing information (PI) made by FDA. See the final approved prescribing information for IMJUDO (tremelimumab-actl) accompanying the approval letter for more information.

Table 44: Summary of Significant Labeling Changes

| Summary of Significant Labeling Changes (High level changes and not direct quotations) | | |
|---|---|---|
| Section | Applicant's Proposed Labeling | FDA's proposed Labeling |
| Highlights | Applicant provided overview of PI | Most common laboratory abnormalities added |
| Full Prescribing Information | | |
| Section 1: Indications and Usage | IMJUDO in combination with durvalumab is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC). | None |
| Section 2: Dosage and Administration | Recommended weight-based dosing described for IMJUDO and durvalumab in uHCC as (b) (4) | Elimination (b) (4) Additional edits to clarify the order of infusion and observation period following infusion of IMJUDO |
| Section 5: Warnings and Precautions | Immune-mediated adverse reactions<br>Infusion-related reactions<br>Embryo-fetal toxicity | Description of (b) (4) removed |
| Section 6: Adverse Reactions | Data from HIMALAYA and study 22 described. | Description of events limited to HIMALAYA study. Immunogenicity sub-section moved to 12.6 per 2022 draft Immunogenicity Guidance |
| Section 8: Use in Specific | | Added statement on presence of maternal IgG in human milk and unknown effects on breastfed child |



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

| | | |
|---|---|---|
| Populations | | added to 8.2 |
| Section 12: Clinical Pharmacology | | Pharmacodynamics sub-section added |
| Section 14: Clinical Studies | Efficacy results described for HIMALAYA and Study 22.<br>Efficacy results for HIMALAYA included durvalumab-only arm | Description of efficacy results limited to HIMALAYA<br>Description of efficacy results limited to tremelimumab plus durvalumab and sorafenib arms only |

# 12. Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The clinical review team determined that a risk evaluation and mitigation strategy (REMS) was not required to ensure safe and effective use of tremelimumab in combination with durvalumab for the indicated population given the consistency of the safety profile with that of durvalumab and other anti-PD-1 and anti-CTLA-4 combination regimen, and the experience of the medical oncology community in managing immune-mediated adverse reactions. Recommendations for the safe and effective use of tremelimumab in combination with durvalumab, including monitoring for immune-related adverse events, are provided in the US prescribing information as well as in the patient medication guide.

# 13. Postmarketing Requirements and Commitment

The FDA's Assessment:

The FDA review team recommends issuing the following postmarketing requirements and postmarketing commitments:

Pediatric PMR:

4333-1: Conduct Study D419EC00001 (A Phase I/II, open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of tremelimumab in combination with durvalumab in pediatric patients) to further characterize the safety, pharmacokinetics, and efficacy of tremelimumab in combination with durvalumab in patients from birth to <18 years of age with relapsed/refractory malignant solid tumors or a relapsed/refractory hematological malignancy including lymphomas for whom no standard treatment is available. Include at least 12 patients in the dose escalation cohort and at least 45 evaluable patients in the dose expansion cohort.

Pediatric PMC:

4333-2: Conduct a study, Study 2, to evaluate the efficacy and safety of tremelimumab used in combination with durvalumab in children from birth to less than 18 years of age with a pediatric solid tumor, to further characterize the efficacy and safety of tremelimumab in combination with durvalumab in pediatric solid tumors.

4333-3: Conduct a study, Study 3, to evaluate the efficacy and safety of tremelimumab in combination with durvalumab in children from birth to less than 18 years of age with a pediatric hematological malignancy, to further characterize the efficacy and safety of tremelimumab in combination with durvalumab in pediatric hematologic malignancies.

CMC PMC:

4333-4: To perform a shipping validation study under real time shipping conditions (i.e. temperature, mode of transport, shipping duration, and shipping containers and packing

representative of the minimum and maximum load) using a representative commercial tremelimumab drug product lot in the final commercial container closure and packaging systems to evaluate the ability of the shipping containers to maintain the recommended temperature and to evaluate the impact of shipping from the AstraZeneca Sweden labeling and packaging site to the US Distribution Center on the physical integrity and product quality of tremelimumab drug product. The shipping validation data will be submitted in accordance with 21 CFR 601.12.

4333-5: Implement (b) (4) monitoring (b) (4) validated by the microbial retention study.

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

X

## 15. Division Director (OCP)

X

## 16. Division Director (OB)

X

## 17. Division Director (Clinical)

I concur with the review team's assessment of the CMC, non-clinical pharmacology/toxicology, clinical pharmacology, clinical, statistical, review teams with
respect to the approvability of this BLA. The submitted data package meets the evidentiary requirements for approval for the indication, based on a favorable benefit:risk assessment. The Applicant submitted data from an adequate and well controlled study (HIMALAYA; NCT03298451) which demonstrated improvement in overall survival (OS) in patients randomized to receive treatment with tremelimumab 300 mg as a one-time single dose administered intravenously (IV) in combination with durvalumab 1500 mg on the same day, followed by durvalumab 1500 mg Q4W (T300+D), compared to patients randomized to the sorafenib 400 mg given orally twice daily, arm. The trial demonstrated hazard ratio of 0.78 [95% CI: 0.66, 0.92]; p=0.0035) which corresponds to a 2.6-month improvement in median OS; these effects were statistically significant and considered clinically meaningful. The benefits of tremelimumab in combination with durvalumab were observed in the context of an acceptable safety profile that is consistent with the well-characterized effects of dual checkpoint inhibition. Overall, the benefit:risk assessment is favorable for the indicated population.

Lola A. Fashoyin-Aje, MD, MPH
Deputy Director, Division of Oncology III

X _____

## 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 _____

# 19. Appendices

## 19.1. References

The Applicant's References:

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The FDA's References:
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## 19.2. Financial Disclosure

The Applicant's Position:
Financial interests or arrangements with clinical investigators have been disclosed in the table for the 2 covered studies. No concerns were raised regarding the overall integrity of the data.

The FDA's Assessment:
Below are the covered clinical studies from HIMALAYA study. FDA agrees with he Applicant's assessment. Additional information regarding investigator financial disclosures is provided in Section 8.

**Covered Clinical Study (Name and/or Number):* HIMALAYA (D419CC00002)**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 1829 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 18 | | |
| 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: 0<br>Significant payments of other sorts: 18 | | |

| | | |
|---|---|---|
| Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in study: 0<br>Sponsor of covered study: 0 | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 8 | | |
| Is an attachment provided with the reason: | Yes ☒ | No ☐ (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):* STUDY 22 (D4190C00022)**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 507 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| 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 ☐ | No ☐ (Request details from Applicant) |

| | | |
|---|---|---|
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3 | | |
| Is an attachment provided with the reason: | Yes ☒ | No ☐ (Request explanation from Applicant) |

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

## 19.3. Nonclinical Pharmacology/Toxicology

Data: Not applicable.

The Applicant's Position: No new information concerning nonclinical pharmacology/toxicology.

The FDA's Assessment:
FDA agrees.

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

### 19.4.1. Population PK Analysis

#### 19.4.1.1. Executive Summary

The FDA's Assessment:

In support of this BLA, the Applicant submitted reports of the updated population pharmacokinetic (PPK) analyses for durvalumab and tremelimumab by pooling additional data from the pivotal trial D419CC00002 (HIMALAYA) and supportive trial D419CC00002 (Study 22). The Applicant claimed that a 2-compartment PPK model with time-dependent elimination best described durvalumab PK and a 2-compartment PPK model with both linear and time-dependent elimination (for monotherapy, elimination was linear only) best described tremelimumab PK. The PPK analyses showed no clinically significant differences in the pharmacokinetics of durvalumab and tremelimumab were found based on body weight (34 to 149 kg), age (18 to 87 years), sex, race (White, Black, Asian, Native Hawaiian, Pacific Islander, or American Indian), serum albumin levels (0.3 to 396 g/L), lactate dehydrogenase levels (12 to 5570 U/L), soluble PD-L1 (67 to 349 pg/mL), varying degrees of organ dysfunctions including mild to moderate renal impairment (CLcr 30 to 89 mL/min), and mild to moderate hepatic impairment (bilirubin <3x ULN and any AST).

In general, the Applicant's PPK analyses for durvalumab and tremelimumab are deemed acceptable for the purpose of supporting the analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

Specifically, the developed model was acceptable to be used to derive exposure metrics for exposure

response analyses, and to support the Applicant's proposed labeling statements regarding general PK information including intrinsic and extrinsic factors in the current submission.

### 19.4.1.2.PPK Assessment Summary

The Applicant's Position:

| General Information – Durvalumab PPK Model | | |
|---|---|---|
| Objectives of PPK Analysis | | • Characterize the PK of **Durvalumab** in various indications<br>• Assess the correlation between pre-defined categorical and continuous covariates and individual EBEs<br>• Predict individual exposure metrics of durvalumab for ER assessment<br>• Justify the durvalumab fixed dosing of 1500 mg Q4W |
| Study Included | | HIMALAYA, Study 22 (both studies in uHCC), ATLANTIC, PACIFIC, POSEIDON (3 studies in NSCLC), Study 1108 (a study in various advanced solid tumors), and CASPIAN (a study in extensive disease SCLC) |
| Dose(s) Included | | 3, 10 mg/kg Q2W<br>15 mg/kg, 1500 mg Q3W<br>20 mg/kg, 1500 mg Q4W |
| Population Included | | Patients with uHCC, NSCLC, various advanced solid tumors, and SCLC |
| Population Characteristics (See Tables 5 to 6, Population PK and Exposure-Response Report, Module 5.3.3.5) | General | Age (years) median (range, % subj ≥65 yr, % subj ≥75 yr): 63 (18-96, 45.1%, 11.1%);<br>Weight (kg) median (range): 69.1 (31.0-175);<br>n (%) male: 2852 (70.4%);<br>n (%) in each race: White 2467 (60.9%), Black 104 (2.57%), Asian 1289 (31.8%), Native Hawaiian or Other Pacific Islander 10 (0.247%), American Indian/Alaskan Native 34 (0.840%), other 143 (3.53%), multiple 2 (0.0494%), missing 1 (0.0247%) |
| | Organ Impairment | Hepatic (NCI) - n (%) in each category: Normal 2876 (71.0%), mild 1078 (26.6%), moderate 51 (1.26%), severe 1 (0.0247%), missing 44 (1.09%)<br>Renal (CrCL in mL/min) - median (range): 85.6 (25.7-279) |
| | Pediatrics (if any) | None |
| No. of Patients, PK Samples, and BLQ | | • 4043 patients with 14760 PK samples for durvalumab available; 216 (1.45%) BLQ and 49 (0.33%) incorrect PK sampling time were excluded. |
| Sampling Schedule | Rich Sampling | Pre-dose: Days 1, 3, 4, 10, 15 (Dose 1), Days 1, 8 (Dose 2), W9, W15 (Q3W)<br>Post-dose (end of infusion): Weeks 0, 3, 9, 15 (Q3W) |
| | In ITT Population | Pre-dose: W0, W4, W12<br>Post-dose: W12 (end of infusion) |
| Covariates Evaluated | Static | Sex, body weight, age, race, region of enrollment, albumin at baseline, LDH, creatinine clearance, combination therapy, hepatic function NCI, baseline neutrophil to lymphocyte ratio, ECOG, primary indication, ADA status post-baseline |

| | | |
|---|---|---|
| Time-varying | NA | |
| **Final Model** | **Summary** | **Acceptability [FDA's comments]** |
| Software and Version | NONMEM v7.3.0 | Yes |
| Model Structure | Two-compartment model with time-varying clearance | Yes |
| Model Parameter Estimates | See Table 9, Population PK and Exposure-Response Report, Module 5.3.3.5 | Yes |
| Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap) | All fixed and random effects were estimated with good precision (< 30% RSE except COMB2 and tumor types). The IIV was 8.96%, 3.89%, 5.24%, and 6.65% for CL, V1, V2, and $T_{max}$, respectively. Shrinkage was <20% for CL, and high for V1 (30%) and $T_{max}$ -maximum change of CL over time (59%). | Yes |
| BLQ for Parameter Accuracy | 216 (1.45%) durvalumab concentrations BLQ during active treatment were excluded, corresponding to the M1 method, and the minimum impact of BLQ on PK is anticipated due to the low BLQ percentage (<5%). | Yes |
| GOF, VPC | See Figure 2, Population PK and Exposure-Response Report, Module 5.3.3.5 (GOF); See Figure 3 and Appendix 3, Population PK and Exposure-Response Report, Module 5.3.3.5 (VPC) | Yes |
| Significant Covariates and Clinical Relevance | See Figure 4-5, Population PK and Exposure-Response Report, Module 5.3.3.5 (tornado plots of covariates on exposure) | Yes<br>Albumin levels (ALB), creatinine clearance (CL), ECOG status, LDH, sex, body weight (WT), tumor types and combination therapy were identified as statistical significant covariates on clearance. WT and sex had a statistically significant impact on central volume of distribution. None of the covariates were considered as clinically relevant i.e. impact on durvalumab PK was less than or about |

| | | |
|---|---|---|
| | | 20% in univariate testing. |
| Analysis Based on Simulation (optional) | None | |
| **Labeling Language** | **Description** | **Acceptability [FDA's comments]** |
| 12.3 PK | The PK of durvalumab as a single agent was studied in patients with doses ranging from 0.1 mg/kg (0.01 times the approved recommended dosage) to 20 mg/kg (2 times the approved recommended dosage) administered once every 2, 3, or 4 weeks.<br>PK exposure increased more than dose-proportionally at doses < 3 mg/kg (0.3 times the approved recommended dosage) and dose proportionally at doses ≥ 3 mg/kg Q2W. Steady state was achieved at approximately 16 weeks.<br>The PK of durvalumab is similar when assessed as a single agent, when in combination with chemotherapy and when in combination with tremelimumab.<br>Distribution<br>The geometric mean (CV%) Vss was 5.6 (18%) L.<br>Elimination<br>Durvalumab clearance decreases over time, with a mean maximal reduction (CV%) from baseline values of approximately 23% (57%) resulting in a geometric mean (CV%) CLss of 8.2 mL/h (39%) at day 365; the decrease in CLss is not considered clinically relevant. The geometric mean (CV%) terminal half-life, based on baseline CL was approximately 18 (24%) days.<br>Specific Populations<br>Age (19–96 years), body weight (31-149 kg), sex, albumin levels, LDH levels, creatinine levels, soluble PD-L1, tumor type, race, mild renal impairment (CrCL 60 to 89 mL/min), moderate renal impairment (CrCL 30 to 59 mL/min), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1 to 1.5x ULN and any AST), moderate hepatic impairment (bilirubin > 1.5 to 3x ULN and any AST) or ECOG/WHO performance | Yes |

| | | |
|---|---|---|
| | status had no clinically significant effect on the pharmacokinetics of durvalumab. The effect of severe renal impairment (CrCL 15 to 29 mL/min) or severe hepatic impairment (bilirubin > 3x ULN and any AST) on the PK of durvalumab is unknown. | |

| **General Information – Tremelimumab PPK Model** | | |
|---|---|---|
| Objectives of PPK Analysis | | • Characterize the PK of **Tremelimumab** in various indications<br>• Assess the correlation between pre-defined categorical and continuous covariates and individual EBEs<br>• Predict individual exposure metrics of tremelimumab for ER assessment<br>• Justify the tremelimumab fixed dosing of 300 mg single dose |
| Study Included | | HIMALAYA, Study 22 (both studies in uHCC), D4884C00001, Study 10, Japanese Study 02 (all 3 studies in various advanced solid tumors), POSEIDON, Study 06 (both studies in NSCLC), and DETERMINE (study in unresectable pleural or peritoneal malignant mesothelioma). |
| Dose(s) Included | | 1 mg/kg, 3 mg/kg, 10 mg/kg. 75 mg, 750 mg Q4W<br>75 mg Q3W, 300 mg single dose |
| Population Included | | patients with uHCC and different types of solid tumors |
| Population Characteristics (See Table 12-13, Population PK and Exposure-Response Report, Module 5.3.3.5) | General | Age (years) median (range, % subj ≥65 yr, % subj ≥75 yr): 64 (18-87, 48.2%, 11.8%);<br>Weight (kg) median (range): 70.0 (34.0-149);<br>n (%) male: 1772 (71.6%);<br>n (%) in each race: White 1485 (61.7%), Black 54 (2.24%), Asian 773 (32.1%), Native Hawaiian or Other Pacific Islander 8 (0.333%), American Indian/Alaskan Native 15 (0.623%), other 69 (2.87%), multiple 1 (0.0416%), missing 1 (0.0416%) |
| | Organ Impairment | Hepatic (NCI) - n (%) in each category: Normal 1734 (72.1%), mild 630 (26.2%), moderate 19 (0.790%), missing 23 (0.956%)<br>Renal (CrCL in mL/min) - median (range): 82.6 (22.5-299) |
| | Pediatrics (if any) | None |
| No. of Patients, PK Samples, and BLQ | | • 2406 patients with 7039 PK samples for tremelimumab available: 280 (3.8%) BLQ and 54 (0.7%) incorrect PK sampling time were excluded. |
| Sampling Schedule | Rich Sampling | Pre-dose: Weeks 0, 1, 2, 4, 8, 12, 24, 36, 48<br>Post-dose (end of infusion): Weeks 0, 4, 8, 12, 24 |
| | In ITT Population | Pre-dose: W0, W4<br>Post-dose: W0 (end of infusion) |
| Covariates Evaluated | Static | Sex, body weight, age, race, region of enrollment, albumin at baseline, LDH, creatinine clearance, combination therapy, hepatic function NCI, baseline neutrophil to lymphocyte ratio, ECOG, primary indication, ADA status post-baseline |
| | Time-varying | NA |

| Final Model | Summary | Acceptability [FDA's comments] |
|---|---|---|
| Software and Version | NONMEM v7.3.0 | Yes |
| Model Structure | Two-compartmental distribution model with both linear and time-varing clearance (for monotherapy, elimination was linear only) | Yes |
| Model Parameter Estimates | See Table 16, Population PK and Exposure-Response Report, Module 5.3.3.5 | Yes<br>See Table 47 |
| Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap) | All fixed and random effects were estimated with good precision (< 20% RSE). The IIV was 10.8%, 6.19%, 21.2% and 142% for CL, V1, V2, and Tmax, respectively. Shrinkage was <25% for CL and V1, and high for V2 (28%) and Tmax -maximum change of CL over time (65%). | Yes<br>See Table 5 |
| BLQ for Parameter Accuracy | 280 (3.8%) tremelimumab concentrations BLQ during active treatment were excluded, corresponding to the M1 method, and the minimum impact of BLQ on PK is anticipated due to the low BLQ percentage (<5%). | Yes |
| GOF, VPC | See Figure 8, Population PK and Exposure-Response Report, Module 5.3.3.5 (GOF); See Figure 9 and Appendix 6, Population PK and Exposure-Response Report, Module 5.3.3.5 (VPC) | Yes<br>See Figure 17 and Figure 18 |
| Significant Covariates and Clinical Relevance | See Figure 10-11, Population PK and Exposure-Response Report, Module 5.3.3.5. (tornado plots of covariates on exposure) | Yes<br>See Figure 3 and Figure 4. Covariate analysis results showed WT, ALB, sex, combination therapy and primary indication had a statistically significant impact on clearance; WT and sex had a statistically significant impact on central volume of distribution. Again, none of the covariates were considered as |

| | | |
|---|---|---|
| | | clinically relevant i.e. impact on tremelimumab PK was less than or about 20% in univariate testing. |
| Analysis Based on Simulation (optional) | None | NA |
| **Labeling Language** | **Description** | **Acceptability [FDA's comments]** |
| 12.3 PK | The PK of tremelimumab as a single agent was studied in patients with doses ranging from 75 mg to 750 mg or 10 mg/kg administered Q4W or Q4W x 7 then every 12 weeks.<br>PK exposure increased dose proportionally at doses ≥ 75 mg Q4W. Steady state was achieved at approximately 12 weeks.<br>The PK of tremelimumab was similar when assessed as a single agent and when in combination with durvalumab.<br><u>Distribution</u><br>From a final 2-compartmental tremelimumab population PK model, the geometric mean (CV%) for central (V1) and peripheral (V2) volume of distribution was 3.45 (27.3%) and 2.47 (43.3%) L, respectively.<br><u>Elimination</u><br>Tremelimumab clearance decreases over time, with a mean maximal reduction (CV%) from baseline values of approximately 22.7% (26.1%) resulting in a geometric mean (CV%) CLss of 0.202 L/day (19.2%); the decrease in CLss is not considered clinically relevant. The geometric mean (CV%) terminal half-life was approximately 20.4 (34.7%) days.<br><u>Specific Populations</u><br>Age (22–87 years), body weight (34-149 kg), sex, serum albumin levels, LDH levels, creatinine levels, soluble PD-L1, tumor type, race, mild renal impairment (CrCL 60 to 89 mL/min), moderate renal impairment (CrCL 30 to 59 mL/min), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1 to 1.5x ULN and any AST),moderate hepatic impairment | Yes<br>See comments in FDA's assessment below |

| | | |
|---|---|---|
| | (bilirubin > 1.5 to 3x ULN and any AST) or ECOG/WHO PS had no clinically significant effect on the PK of tremelimumab.<br>The effect of severe renal impairment (CrCL 15 to 29 mL/min) or severe hepatic impairment (bilirubin > 3x ULN and any AST) on the PK of tremelimumab is unknown. | |

**Table 45. Summary Statistics for the Continuous Covariates in the Population PK Analysis for Durvalumab**

| | Total | Previous Studies | Study 22 | HIMALAYA |
|---|---|---|---|---|
| N | 4050 | 2827 | 295 | 928 |
| **Age (years)** | | | | |
| Mean (SD) | 62.2 (10.7) | 61.9 (10.4) | 63.3 (10.7) | 62.9 (11.6) |
| Median (IQR) | 63.0 (56.0-69.0) | 63.0 (56.0-69.0) | 64.0 (57.0-70.0) | 64.0 (57.0-71.0) |
| Min-max | 18.0-96.0 | 19.0-96.0 | 26.0-89.0 | 18.0-86.0 |
| Missing | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Bodyweight (kg)** | | | | |
| Mean (SD) | 71.0 (16.4) | 71.2 (16.7) | 70.4 (15.2) | 70.5 (15.8) |
| Median (IQR) | 69.1 (59.0-80.4) | 69.4 (59.3-81.0) | 68.5 (59.2-78.9) | 68.7 (59.0-79.0) |
| Min-max | 31.0-175 | 31.0-175 | 39.9-125 | 38.5-140 |
| | Total | Previous | Study 22 | HIMALAYA |
| Missing | 4 (0.0988%) | 4 (0.141%) | 0 (0%) | 0 (0%) |
| **Creatinine clearance (mL/min)** | | | | |
| Mean (SD) | 90.5 (31.5) | 90.5 (31.6) | 91.0 (28.9) | 90.2 (32.0) |
| Median (IQR) | 85.6 (68.3-106) | 85.7 (68.4-106) | 88.1 (68.9-109) | 84.6 (67.3-106) |
| Min-max | 25.7-279 | 25.7-279 | 35.6-180 | 29.5-248 |
| Missing | 65 (1.60%) | 63 (2.23%) | 0 (0%) | 2 (0.216%) |
| **Albumin (g/L)** | | | | |
| Mean (SD) | 38.4 (5.19) | 38.1 (5.31) | 37.8 (4.65) | 39.3 (4.85) |
| Median (IQR) | 39.0 (35.0-42.0) | 39.0 (35.0-42.0) | 38.0 (34.0-41.0) | 39.4 (36.0-43.0) |
| Min-max | 4.10-57.1 | 4.10-57.1 | 26.0-50.0 | 19.0-54.0 |
| Missing | 73 (1.80%) | 71 (2.51%) | 0 (0%) | 2 (0.216%) |
| **Lactate Dehydrogenase (U/L)** | | | | |
| Mean (SD) | 337 (429) | 359 (487) | 314 (301) | 278 (225) |

| | | | | |
|---|---|---|---|---|
| Median (IQR) | 239 (186-361) | 247 (186-387) | 240 (188-364) | 224 (185-294) |
| Min-max | 18.0-15800 | 18.0-15800 | 50.0-4380 | 92.0-3720 |
| Missing | 137 (3.38%) | 121 (4.28%) | 3 (1.02%) | 13 (1.40%) |
| **Neutrophil-to-Lymphocyte Ratio** | | | | |
| Mean (SD) | 3.99 (6.33) | 4.41 (3.62) | 5.08 (16.7) | 3.32 (2.38) |
| Median (IQR) | 3.13 (2.19-4.62) | 3.46 (2.50-5.20) | 3.19 (2.40-4.91) | 2.77 (1.94-3.98) |
| Min-max | 0.00300-253 | 0.00600-58.8 | 0.733-253 | 0.00300-27.3 |
| Missing | 2037 (50.3%) | 1968 (69.6%) | 67 (22.7%) | 2 (0.216%) |
| **s-PDL1 (pg/mL)** | | | | |
| Mean (SD) | 138 (103) | 138 (103) | NA (NA) | NA (NA) |
| Median (IQR) | 125 (95.1-161) | 125 (95.1-161) | NA (NA-NA) | NA (NA-NA) |
| Min-max | 67.1-3470 | 67.1-3470 | - | - |
| Missing | 2366 (58.4%) | 1143 (40.4%) | 295 (100%) | 928 (100%) |

*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Table5.*

**Table 46. Summary Statistics for the Categorical Covariates in the Population PK Analysis**

| | **Total** | **Previous Studies** | **HIMALAYA** | **Study 22** |
|---|---|---|---|---|
| N | 4050 | 2827 | 928 | 295 |
| **Sex** | | | | |
| Male | 2852 (70.4%) | 1837 (65.0%) | 765 (82.4%) | 250 (84.7%) |
| Female | 1198 (29.6%) | 990 (35.0%) | 163 (17.6%) | 45 (15.3%) |
| **Race** | | | | |
| White | 2467 (60.9%) | 1956 (69.2%) | 407 (43.9%) | 104 (35.3%) |
| Black | 104 (2.57%) | 70 (2.48%) | 13 (1.40%) | 21 (7.12%) |
| Asian | 1289 (31.8%) | 646 (22.9%) | 480 (51.7%) | 163 (55.3%) |
| Native Hawaiian or Other Pacific Islander | 10 (0.247%) | 8 (0.283%) | 1 (0.108%) | 1 (0.339%) |
| American Indian/Alaskan Native | 34 (0.840%) | 30 (1.06%) | -- | 4 (1.36%) |
| Other | 143 (3.53%) | 115 (4.07%) | 26 (2.80%) | 2 (0.678%) |
| Multiple | 2 (0.0494%) | 2 (0.0707%) | -- | -- |
| Missing | 1 (0.0247%) | -- | 1 (0.108%) | -- |
| **Region of enrollment** | | | | |
| South America | 76 (1.88%) | 76 (2.69%) | -- | -- |
| Africa | 25 (0.617%) | 25 (0.884%) | -- | -- |

| | | | | |
|---|---|---|---|---|
| Asia | 1199 (29.6%) | 568 (20.1%) | 476 (51.3%) | 155 (52.5%) |
| Europe | 1520 (37.5%) | 1096 (38.8%) | 374 (40.3%) | 50 (16.9%) |
| North America | 1198 (29.6%) | 1030 (36.4%) | 78 (8.41%) | 90 (30.5%) |
| Other | 32 (0.790%) | 32 (1.13%) | -- | -- |
| **Tumor Type** | | | | |
| Lung | 2165 (53.5%) | 2165 (76.6%) | -- | -- |
| Bladder | 191 (4.72%) | 191 (6.76%) | -- | -- |
| Liver | 1263 (31.2%) | 40 (1.41%) | 928 (100%) | 295 (100%) |
| Solid | 431 (10.6%) | 431 (15.2%) | -- | -- |
| **Age Group** | | | | |
| <65 | 2220 (54.8%) | 1596 (56.5%) | 468 (50.4%) | 156 (52.9%) |
| 65-75 | 1379 (34.0%) | 954 (33.7%) | 327 (35.2%) | 98 (33.2%) |
| >=75 | 451 (11.1%) | 277 (9.80%) | 133 (14.3%) | 41 (13.9%) |
| **Renal Status** | | | | |
| Normal | 1761 (43.5%) | 1216 (43.0%) | 403 (43.4%) | 142 (48.1%) |
| Mild | 1637 (40.4%) | 1136 (40.2%) | 389 (41.9%) | 112 (38.0%) |
| Moderate | 586 (14.5%) | 412 (14.6%) | 133 (14.3%) | 41 (13.9%) |
| Severe | 66 (1.63%) | 63 (2.23%) | 3 (0.323%) | -- |

*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Table6.*

**Table 47. Population PK Parameters of Durvalumab from the Applicant's Final PK Model**

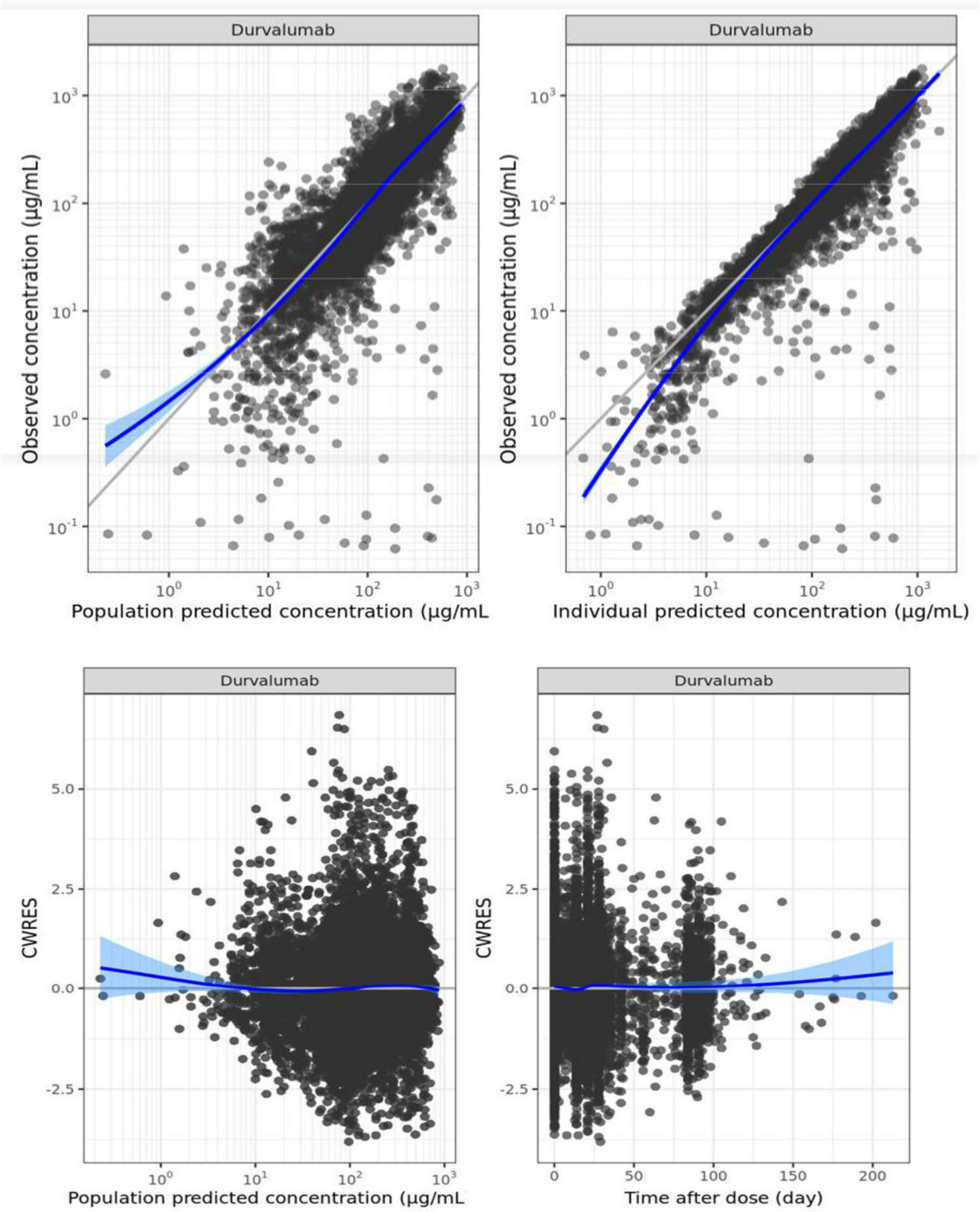
| Parameter | Estimate | RSE (%) | bootstrap 95%CI | Shrinkage (%) | Unit |
|---|---|---|---|---|---|
| **Population Parameter** | | | | | |
| CL | 0.277 | 2.01 | [0.263 ; 0.292] | -- | L/day |
| V1 | 3.45 | 0.807 | [3.40 ; 3.49] | -- | L |
| V2 | 2.13 | 2.02 | [1.98 ; 2.29] | -- | L |
| Q | 0.469 | 5.15 | [0.411 ; 0.535] | -- | L/day |
| Tmax | -0.372 | 4.99 | [-0.419 ; -0.327] | -- | L/day |
| $TC_{50}$ | 88.7 | 9.92 | [58.3 ; 150] | -- | day |
| LAM | 1.00 | -- | -- | -- | - |
| **Covariate** | | | | | |
| Albumin on CL | -0.659 | 2.87 | [-0.834 ; -0.506] | -- | -- |
| Creatinine clearance on CL | 0.121 | 15.6 | [0.0800 ; 0.162] | -- | -- |
| ECOG status on CL | -0.0516 | 20.7 | [-0.0720 ; -0.0278] | -- | -- |
| LDH on CL | 0.0442 | 23.3 | [0.0208 ; 0.0642] | -- | -- |

| | | | | | |
|---|---|---|---|---|---|
| Sex on CL | -0.149 | 7.95 | [-0.172 ; -0.126] | -- | -- |
| COMB1 on CL | -0.0459 | 27.0 | [-0.0688 ; -0.0195] | -- | -- |
| COMB2 on CL | -0.0417 | 43.2 | [-0.0886 ; 0.00746] | -- | -- |
| Body weight on CL | 0.376 | 8.32 | [0.317 ; 0.443] | -- | -- |
| Tumor type 1 on CL | -0.0393 | 46.1 | [-0.0750 ; -0.00306] | -- | -- |
| Tumor type 2 on CL | 0.0622 | 55.8 | [-0.0131 ; 0.137] | -- | -- |
| Tumor type 3 on CL | 0.0472 | 46.1 | [0.00497 ; 0.0932] | -- | -- |
| Sex on V1 | -0.140 | 7.60 | [-0.163 ; -0.118] | -- | -- |
| Body weight on V1 | 0.499 | 5.01 | [0.449 ; 0.549] | -- | -- |
| **Interindividual Variability** | | | | | |
| ETA CL | 0.0896 | 2.85 | [0.0803 ; 0.0982] | 17.6 | -- |
| Cov CL-V1 | 0.0389 | 5.34 | [0.0338 ; 0.0441] | - | -- |
| ETA V1 | 0.0524 | 3.32 | [0.0451 ; 0.0598] | 29.9 | -- |
| ETA $T_{max}$ | 0.0665 | 9.03 | [0.0436 ; 0.109] | 59.3 | -- |
| **Residual Variability** | | | | | |
| Proportional component | 0.250 | 0.541 | [0.241 ; 0.258] | 15.0 | -- |
| Additive component | 4.28 | 6.70 | [3.39 ; 5.29] | 15.0 | µg/mL |

Abbreviations: CI=confidence interval, COMB1=durvalumab+SOC or treme, COMB2=durvalumab+tremelimumab+SOC, Cov=Covariance, ECOG=Eastern Cooperative Oncology Group, Tumor type 1= NSCLC, Tumor type 2= bladder cancer, Tumor type 3 = HCC, ETA=random effect, LAM=Hill factor, LDH=lactate dehydrogenase, RSE=relative standard error, CL=clearance, V1=central volume of distribution, Q=inter-compartmental clearance, PK=pharmacokinetics, SOC=standard of care, V2=peripheral volume of distribution, Tmax=maximum change of CL over time, TC50: time to 50% change of CL over time. Source: az-durvalumab-pk-model-himalaya-V1.0.Rmd, Reference: 04e0e5:2e52f0

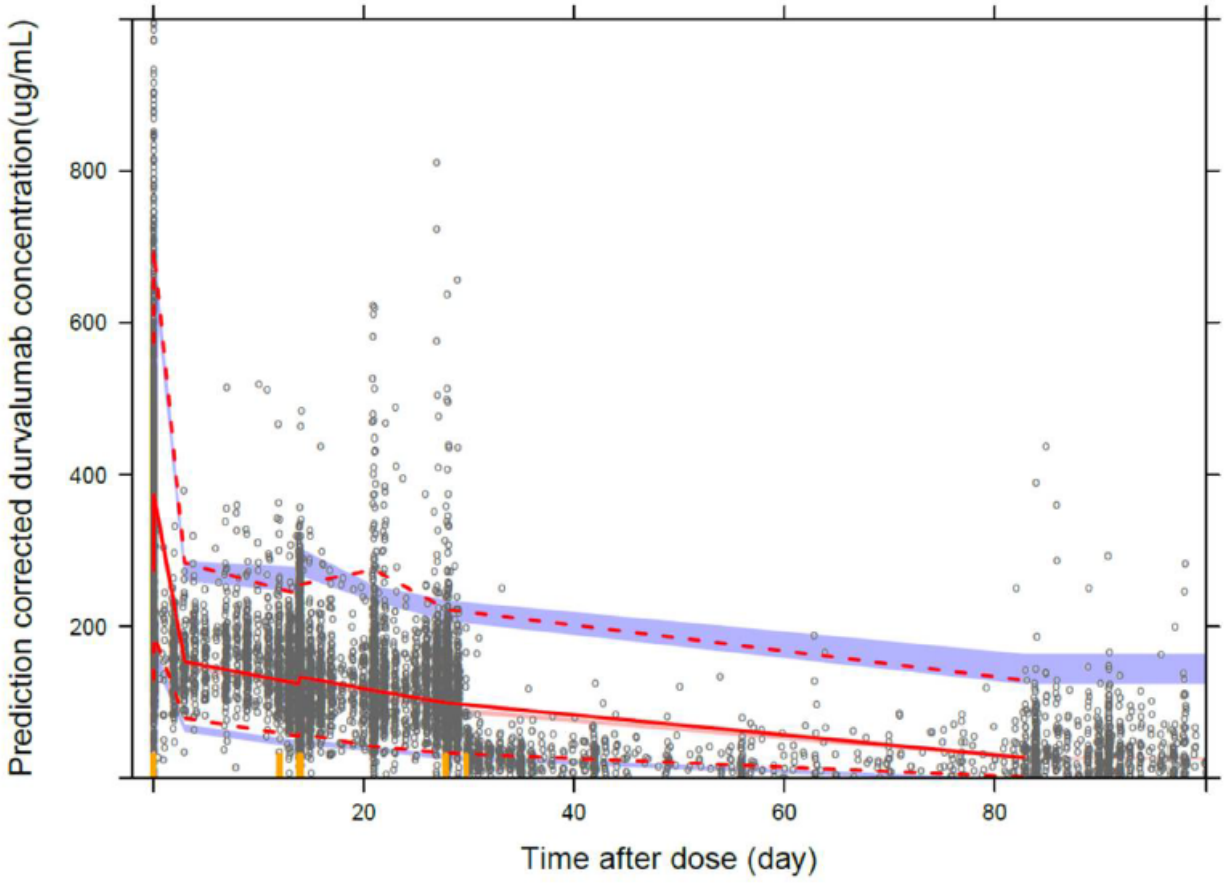
*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Table9.*

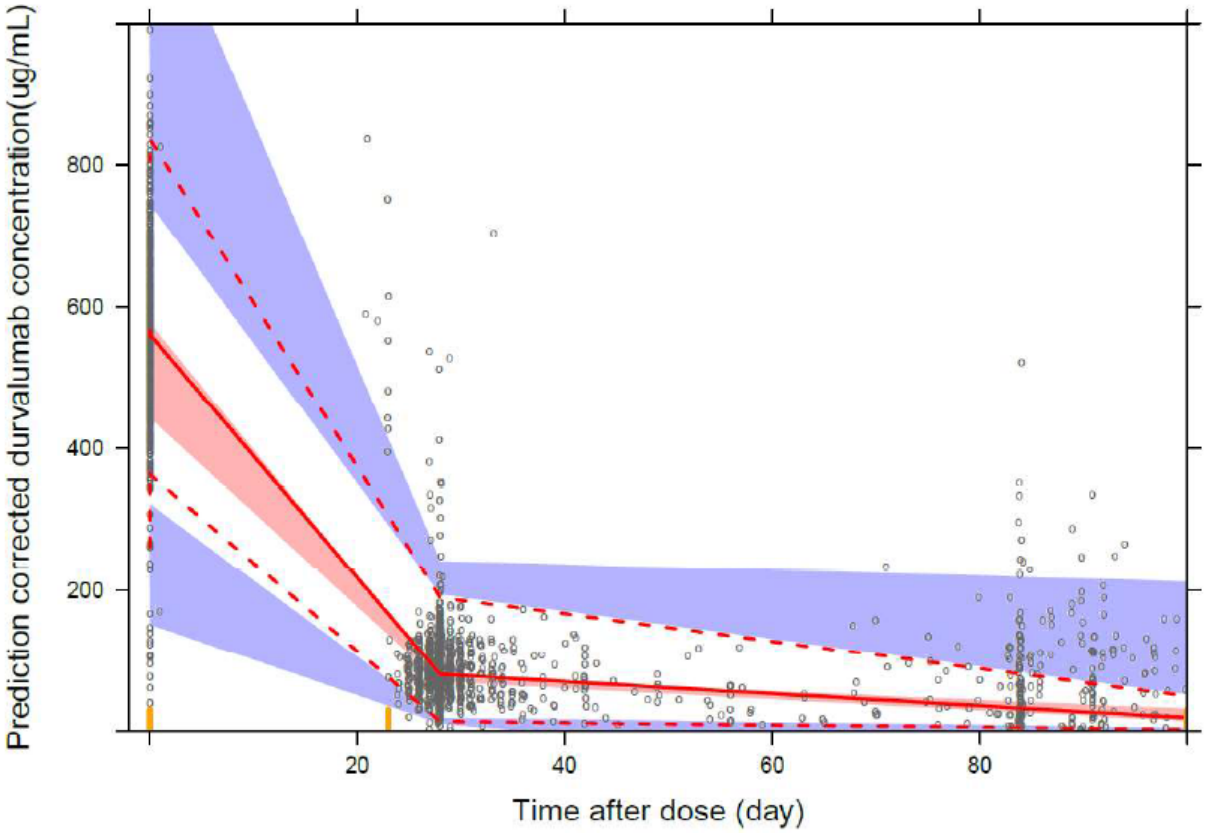
## Figure 17. Goodness-of-fit Plots for the Applicant's Final Population PK Model for Durvalumab




*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Figure2.*

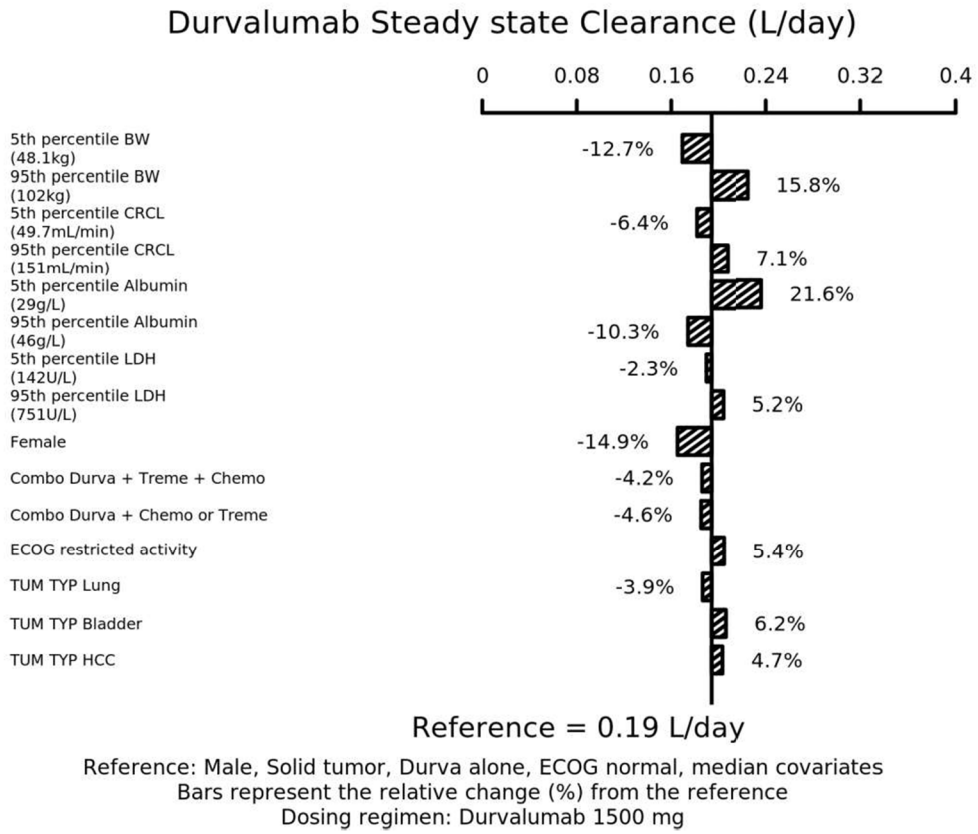
**Figure 18. The Prediction-Corrected Visual Predictive Check (pcVPC) for the Applicant's Final Durvalumab Model (upper: all the studies; lower: HIMALAYA study)**





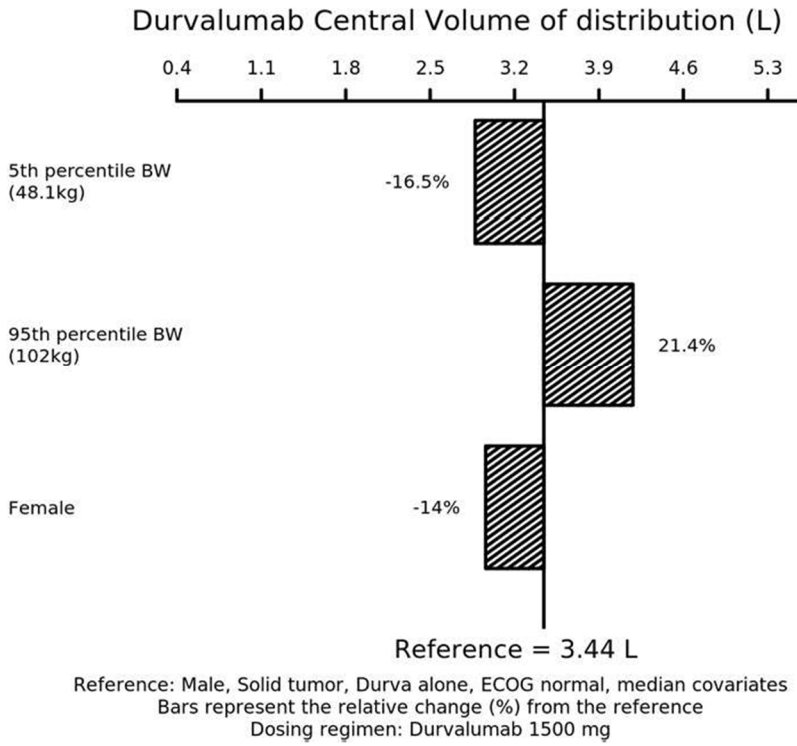

*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Appendix3.Figure 1.8(upper:all the studies) Figure 3(lower:HIMALAYA study).*

**Figure 19. Impact of Covariates on Durvalumab Clearance at Steady State**




*Note: The dashed area represents the percentage change of model parameter for the 5th and 95th percentile of the relevant covariates relative to the median parameter estimates (for continuous covariates), or relative to the most frequent category (for categorical covariates).*
*Abbreviations: Chemo=chemotherapy, CRCL=creatinine clearance, Durva=durvalumab, ECOG=Eastern Cooperative Oncology Group, LDH=lactate dehydrogenase, NSCLC=non-small cell lung cancer, Treme=tremelimumab*
*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Figure 4*

**Figure 20. Impact of Covariates on Central Volume of Distribution of Durvalumab**




*Note: The dashed area represents the percentage change of model parameter for the 5th and 95th percentile of the relevant covariates relative to the median parameter estimates (for continuous covariates), or relative to the most frequent category (for categorical covariates).*
*Abbreviations: Durva=durvalumab, ECOG=Eastern Cooperative Oncology Group*
*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Figure 5*

**Table 48. Summary of Continuous Covariates in the Population PK Analysis of Tremelimumab**

| | Total | Previous Studies | Study 22 | HIMALAYA |
|---|---|---|---|---|
| **Individuals** | | | | |
| N | 2406 | 1605 | 262 | 539 |
| **Body weight (kg)** | | | | |
| Mean (SD) | 71.8 (16.6) | 72.4 (17.2) | 69.9 (14.7) | 70.9 (15.5) |
| Median (IQR) | 70.0 (60.0-81.5) | 70.2 (60.1-82.4) | 68.0 (59.4-77.0) | 69.8 (59.3-80.0) |
| Min-max | 34.0-149 | 34.0-149 | 39.0-119 | 40.5-140 |
| Missing | 6 (0.249%) | 6 (0.374%) | 0 (0%) | 0 (0%) |
| **Age (years)** | | | | |
| Mean (SD) | 62.7 (10.8) | 62.6 (10.5) | 62.6 (10.7) | 63.1 (11.8) |
| Median (IQR) | 64.0 (57.0-70.0) | 64.0 (57.0-70.0) | 63.0 (56.3-70.0) | 65.0 (57.5-71.0) |
| Min-max | 18.0-87.0 | 22.0-87.0 | 26.0-87.0 | 18.0-86.0 |

| | | | | |
|---|---|---|---|---|
| Missing | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Albumin (g/L)** | | | | |
| Mean (SD) | 38.5 (9.13) | 38.3 (10.6) | 37.5 (4.66) | 39.3 (4.95) |
| Median (IQR) | 39.0 (35.0-42.0) | 39.0 (35.0-42.0) | 37.0 (34.0-41.0) | 40.0 (36.0-43.0) |
| Min-max | 0.300-396 | 0.300-396 | 26.3-50.0 | 19.0-54.0 |
| Missing | 33 (1.37%) | 31 (1.93%) | 0 (0%) | 2 (0.371%) |
| **Lactate Dehydrogenase (U/L)** | | | | |
| Mean (SD) | 300 (271) | 308 (290) | 313 (313) | 270 (171) |
| Median (IQR) | 228 (180-340) | 230 (177-356) | 244 (189-358) | 223 (186-293) |
| Min-max | 12.0-5570 | 12.0-5570 | 50.0-4380 | 98.0-2010 |
| Missing | 58 (2.41%) | 46 (2.87%) | 2 (0.763%) | 10 (1.86%) |
| **Creatinine clearance (mL/min)** | | | | |
| Mean (SD) | 88.0 (32.0) | 86.6 (32.6) | 91.9 (28.6) | 90.2 (31.6) |
| Median (IQR) | 82.6 (64.8-105) | 80.3 (63.0-103) | 88.2 (69.5-109) | 85.4 (67.5-106) |
| Min-max | 22.5-299 | 22.5-299 | 38.0-180 | 29.5-221 |
| Missing | 32 (1.33%) | 30 (1.87%) | 0 (0%) | 2 (0.371%) |
| **s-PDL1 (pg/mL)** | | | | |
| Mean (SD) | 136 (51.8) | 136 (51.8) | -- | -- |
| Median (IQR) | 128 (98.7-168) | 128 (98.7-168) | -- | -- |
| Min-max | 67.1-349 | 67.1-349 | -- | -- |
| Missing | 1979 (82.3%) | 1178 (73.4%) | 262 (100%) | 539 (100%) |
| **Neutrophil-to-Lymphocyte Ratio** | | | | |
| Mean (SD) | 4.81 (6.68) | 5.27 (4.68) | 5.15 (17.5) | 3.38 (2.55) |
| Median (IQR) | 3.53 (2.41-5.56) | 4.00 (2.70-6.21) | 3.25 (2.37-4.91) | 2.77 (1.92-4.03) |
| Min-max | 0-253 | 0-66.3 | 0.561-253 | 0.00300-27.3 |
| Missing | 123 (5.11%) | 67 (4.17%) | 54 (20.6%) | 2 (0.371%) |

*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Table12.*

## Table 49. Summary Statistics for the Categorical Covariates in the Population PK Analysis of Tremelimumab

| | Total | Previous Studies | Study 22 | HIMALAYA |
|---|---|---|---|---|
| **Individuals** | | | | |
| N | 2406 | 1605 | 262 | 539 |
| **Sex** | | | | |

| | | | | |
|---|---|---|---|---|
| Male | 1722 (71.6%) | 1063 (66.2%) | 217 (82.8%) | 442 (82.0%) |
| Female | 684 (28.4%) | 542 (33.8%) | 45 (17.2%) | 97 (18.0%) |
| **Race** | | | | |
| White | 1485 (61.7%) | 1143 (71.2%) | 96 (36.6%) | 246 (45.6%) |
| Black | 54 (2.24%) | 29 (1.81%) | 14 (5.34%) | 11 (2.04%) |
| Asian | 773 (32.1%) | 357 (22.2%) | 146 | 270 (50.1%) |
| Native Hawaiian or Other Pacific Islander | 8 (0.333%) | 6 (0.374%) | 1 (0.382%) | 1 (0.186%) |
| American Indian/Alaskan Native | 15 (0.623%) | 12 (0.748%) | 3 (1.15%) | -- |
| Other | 69 (2.87%) | 57 (3.55%) | 2 (0.763%) | 10 (1.86%) |
| Multiple | 1 (0.0416%) | 1 (0.0623%) | -- | -- |
| Missing | 1 (0.0416%) | -- | -- | 1 (0.186%) |
| **Region of enrollment** | | | | |
| Europe | 804 (33.4%) | 534 (33.3%) | 47 (17.9%) | 223 (41.4%) |
| Asia | 732 (30.4%) | 328 (20.4%) | 138 (52.7%) | 266 (49.4%) |
| North America | 788 (32.8%) | 661 (41.2%) | 77 (29.4%) | 50 (9.28%) |
| South America | 33 (1.37%) | 33 (2.06%) | -- | -- |
| Africa | 15 (0.623%) | 15 (0.935%) | -- | -- |
| Other | 34 (1.41%) | 34 (2.12%) | -- | -- |
| **Primary indication** | | | | |
| Advanced Non-small Cell Lung Cancer | 707 (29.4%) | 707 (44.0%) | -- | -- |
| Bladder Cancer | 213 (8.85%) | 213 (13.3%) | -- | -- |
| Triple-negative breast-cancer | 43 (1.79%) | 43 (2.68%) | -- | -- |
| Pleural | 358 (14.9%) | 358 (22.3%) | -- | -- |
| BTC | 64 (2.66%) | 64 (3.99%) | -- | -- |
| EC | 58 (2.41%) | 58 (3.61%) | -- | -- |
| HPV positive anogenital cancer, MSI-H CRC, Ovarian, STS | 146 (6.07%) | 146 (9.10%) | -- | -- |
| Peritoneal | 16 (0.665%) | 16 (0.997%) | -- | -- |
| HCC | 801 (33.3%) | -- | 262 (100%) | 539 (100%) |
| **Tumor type** | | | | |
| Lung | 676 (28.1%) | 676 (42.1%) | -- | -- |
| Bladder | 213 (8.85%) | 213 (13.3%) | -- | -- |
| Missing | 12 (0.499%) | 12 (0.748%) | -- | -- |
| Liver | 801 (33.3%) | -- | 262 (100%) | 539 (100%) |

| | | | | |
|---|---|---|---|---|
| Solid | 330 (13.7%) | 330 (20.6%) | -- | -- |
| Malignant mesothelioma | 374 (15.5%) | 374 (23.3%) | -- | -- |
| **Eastern Cooperative Oncology Group performance status** | | | | |
| Normal activity | 1052 (43.7%) | 556 (34.6%) | 158 (60.3%) | 338 (62.7%) |
| Restricted activity | 1350 (56.1%) | 1046 (65.2%) | 104 (39.7%) | 200 (37.1%) |
| In bed less than or equal to 50% of the time | 2 (0.0831%) | 1 (0.0623%) | -- | 1 (0.186%) |
| Missing | 2 (0.0831%) | 2 (0.125%) | -- | -- |
| **Smoking status** | | | | |
| Current | 147 (6.11%) | 147 (9.16%) | -- | -- |
| Former | 647 (26.9%) | 647 (40.3%) | -- | -- |
| Never | 213 (8.85%) | 213 (13.3%) | -- | -- |
| Missing | 1399 (58.1%) | 598 (37.3%) | 262 (100%) | 539 (100%) |
| **Age Group** | | | | |
| <65 | 1246 (51.8%) | 834 (52.0%) | 146 (55.7%) | 266 (49.4%) |
| 65-75 | 875 (36.4%) | 595 (37.1%) | 83 (31.7%) | 197 (36.5%) |
| >=75 | 285 (11.8%) | 176 (11.0%) | 33 (12.6%) | 76 (14.1%) |
| **Renal Status** | | | | |
| Normal | 966 (40.1%) | 602 (37.5%) | 126 (48.1%) | 238 (44.2%) |
| Mild | 970 (40.3%) | 646 (40.2%) | 105 (40.1%) | 219 (40.6%) |
| Moderate | 434 (18.0%) | 324 (20.2%) | 31 (11.8%) | 79 (14.7%) |
| Severe | 36 (1.50%) | 33 (2.06%) | -- | 3 (0.557%) |
| **Anti-drug antibody status post-baseline** | | | | |
| Negative | 1476 (61.3%) | 1109 (69.1%) | 127 (48.5%) | 240 (44.5%) |
| Positive | 165 (6.86%) | 104 (6.48%) | 13 (4.96%) | 48 (8.91%) |
| Missing | 765 (31.8%) | 392 (24.4%) | 122 (46.6%) | 251 (46.6%) |
| **NCI scale - hepatic function** | | | | |
| Normal | 1734 (72.1%) | 1435 (89.4%) | 99 (37.8%) | 200 (37.1%) |
| Mild | 630 (26.2%) | 146 (9.10%) | 158 (60.3%) | 326 (60.5%) |
| Moderate | 19 (0.790%) | 3 (0.187%) | 5 (1.91%) | 11 (2.04%) |
| Missing | 23 (0.956%) | 21 (1.31%) | -- | 2 (0.371%) |
| **Combination therapy** | | | | |
| Tremelimumab | 504 (20.9%) | 435 (27.1%) | 69 (26.3%) | -- |
| Tremelimumab + Durvalumab | 1576 (65.5%) | 844 (52.6%) | 193 (73.7%) | 539 (100%) |
| Tremelimumab + Durvalumab + Chemo | 326 (13.5%) | 326 (20.3%) | -- | -- |

*Abbreviations: Chemo=chemotherapy, Durva=durvalumab, BTC=biliary tract carcinoma, EC=esophagus carcinoma, HCC= hepatocellular carcinoma*
*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Table13.*

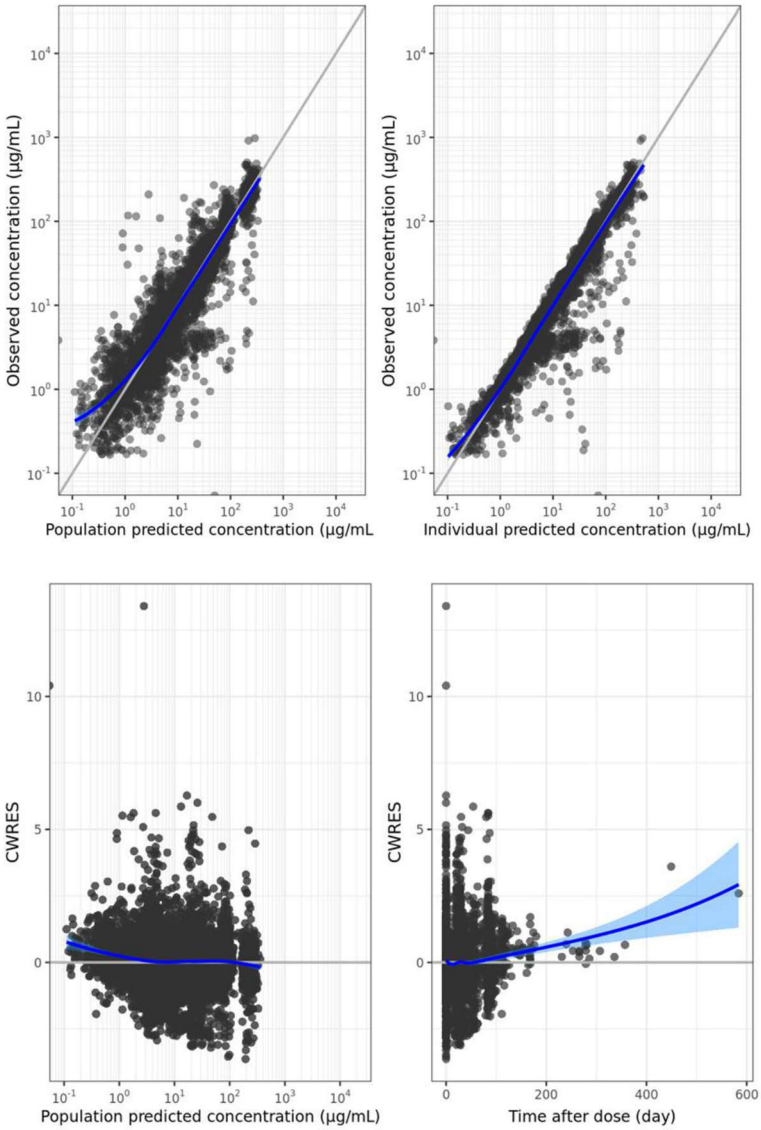
**Table 50. Population PK Parameters of Tremelimumab from the Applicant's Final PK Model**

| Parameter | Estimate | RSE (%) | bootstrap 95%CI | Shrinkage (%) | Unit |
|---|---|---|---|---|---|
| **Population Parameter** | | | | | |
| CL | 0.295 | 1.35 | [0.283 ; 0.308] | -- | L/day |
| V1 | 3.59 | 1.11 | [3.54 ; 3.65] | -- | L |
| Q | 0.480 | 6.94 | [0.383 ; 0.624] | -- | L/day |
| V2 | 2.69 | 3.55 | [2.48 ; 2.98] | -- | L |
| Tmax change CL | -0.134 | 15.3 | [-0.283 ; -0.0219] | -- | L/day |
| TC50 change CL | 63.1 | 7.22 | [4.06 ; 468] | -- | days |
| **Covariate** | | | | | |
| Body weight on V1 | 0.467 | 7.99 | [0.404 ; 0.539] | -- | -- |
| Sex on V1 | -0.116 | 15.4 | [-0.144 ; -0.0892] | -- | -- |
| Body weight on CL | 0.384 | 10.5 | [0.304 ; 0.469] | -- | -- |
| Albumin on CL | -0.780 | 5.74 | [-0.896 ; -0.669] | -- | -- |
| Sex on CL | -0.0985 | 18.4 | [-0.135 ; -0.0634] | -- | -- |
| Comb2 on CL | -0.124 | 15.2 | [-0.166 ; -0.0772] | -- | -- |
| Primary tumor 6-7 on CL | -0.146 | 17.2 | [-0.202 ; -0.0872] | -- | -- |
| **Interindividual Variability** | | | | | |
| ETA CL | 0.108 | 3.67 | [0.0873 ; 0.131] | 21.8 | -- |
| Covariance CL-V1 | 0.0621 | 3.84 | [0.0420 ; 0.0862] | -- | -- |
| ETA V1 | 0.0619 | 1.71 | [0.0377 ; 0.0932] | 24.3 | -- |
| Covariance CL-V2 | 0.0898 | 9.68 | [0.0468 ; 0.138] | -- | -- |
| Covariance V1-V2 | 0.112 | 7.48 | [0.0694 ; 0.158] | -- | -- |
| ETA V2 | 0.212 | 12.3 | [0.119 ; 0.312] | 28.3 | -- |
| ETA $T_{max}$ | 1.42 | 10.6 | [0.784 ; 8.14] | 65.2 | -- |
| **Residual Variability** | | | | | |
| Proportional component | 0.285 | 0.799 | [0.271 ; 0.300] | 18.3 | -- |
| Additive component | 0.369 | 0.915 | [0.134 ; 0.506] | 18.3 | µg/mL |

*Abbreviations: CI=confidence interval, CL=clearance, Comb2=durvalumab, tremelimumab and chemotherapy (standard of care), as compared to treatment arms without chemotherapy, ETA=random effect, IIV=inter-individual variability, PK=pharmacokinetics, V1=central volume of distribution, primary indication 6=biliary tract*

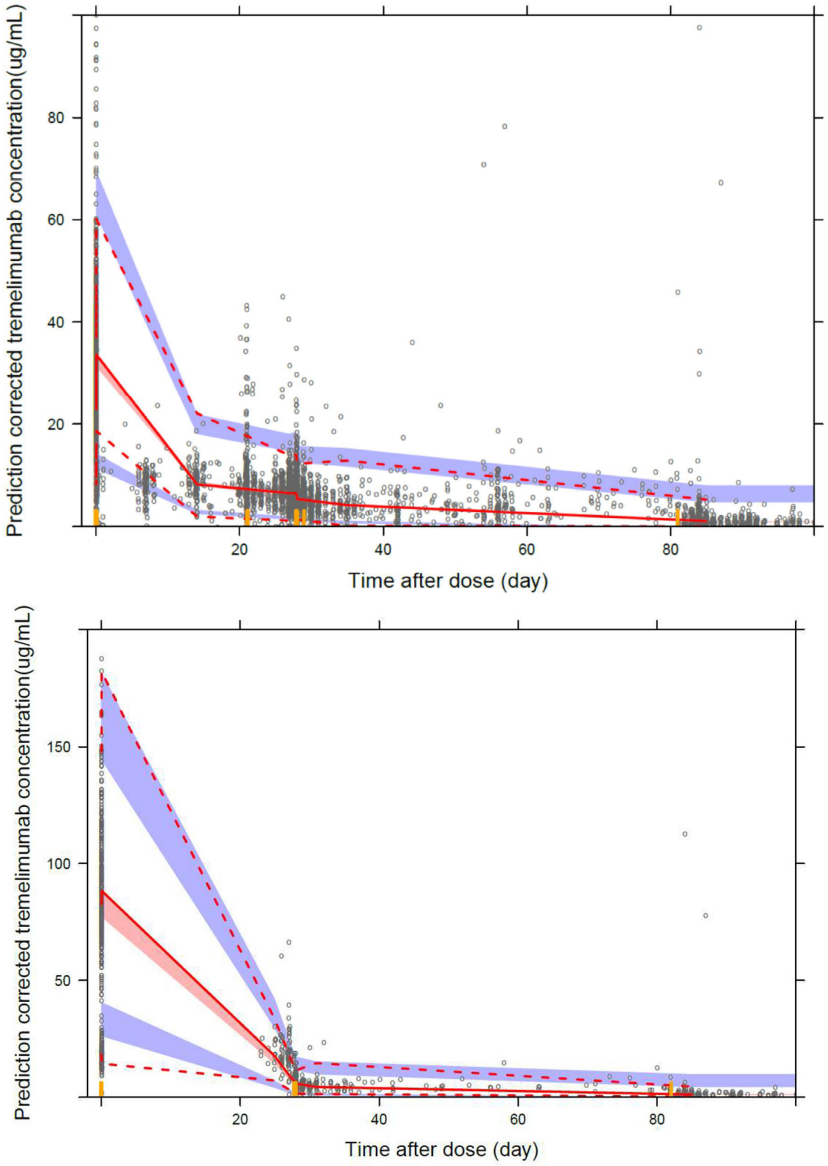
*carcinoma, primary indication 7=esophagus carcinoma, Q=inter-compartmental clearance, V2=peripheral volume of distribution, RSE=relative standard error, TC50=time to 50% clearance reduction, Tmax=maximum change of CL over time.*
*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Table16.*

**Figure 21. Goodness-of-fit Plots for the Applicant's Final Population PK Model for Tremelimumab**




*Note: the blue line is a trend line through the data points, the blue area is the 95% confidence interval around it.*
*Abbreviations: CWRES=conditional weighted residuals.*
*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Figure8.*

**Figure 22. The Prediction Corrected Visual Predictive Check (pcVPC) for the Applicant's Final Tremelimumab Model (upper: all the studies; lower: HIMALAYA study)**

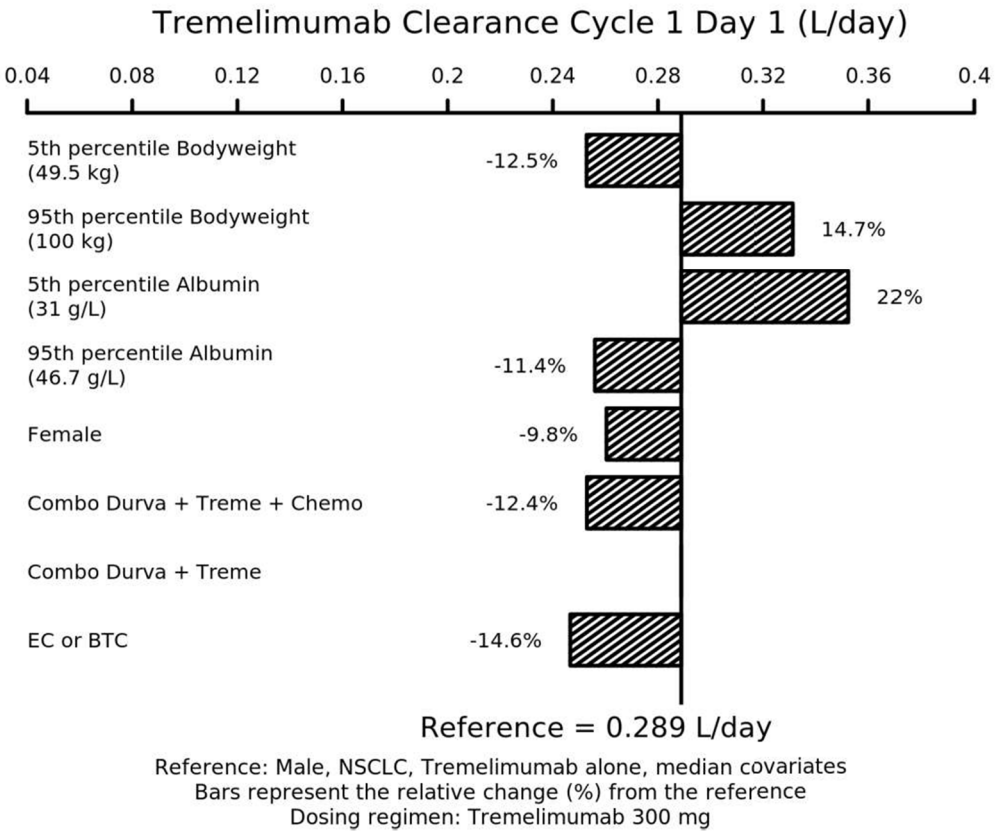



*Note: The solid and dashed lines represent the median, 5th, and 95th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model.*

*Abbreviations: CI=confidence interval, pcVPC=prediction-corrected visual predictive check*

*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Appendix6.Figure 1.8(upper:all the studies) and Figure 9(lower:HIMALAYA study).*

**Figure 23. Impact of Covariates on Clearance at Cycle 1 of Tremelimumab**

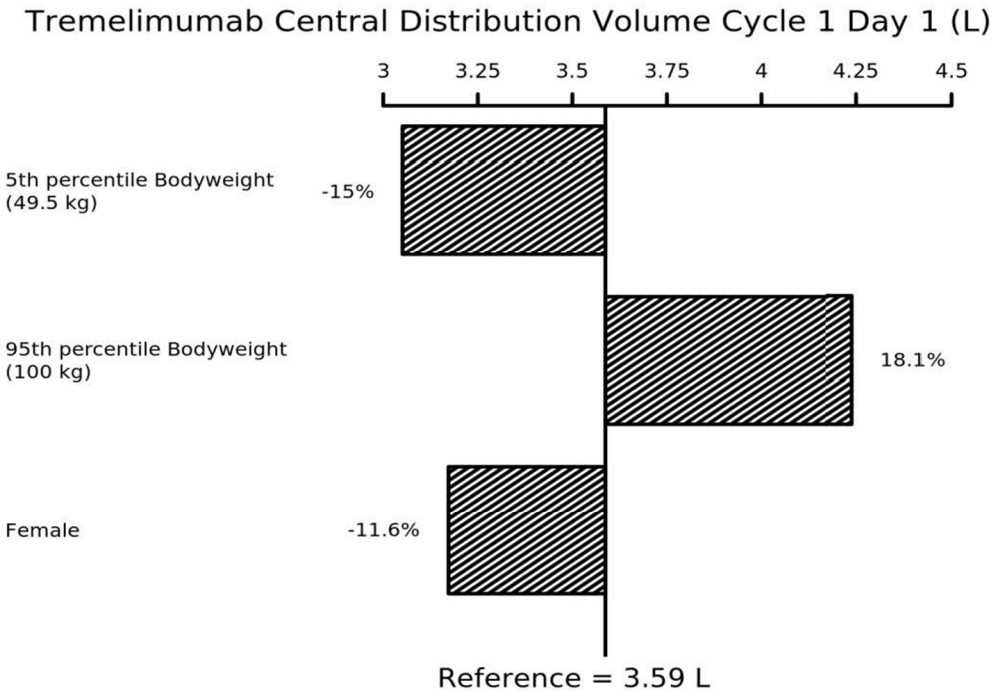



*Note: Covariate effects were expressed as a percentage change from the typical value of the reference patient. For continuous covariates, bars represent the range of individual clearance values between the $5^{th}$ and $95^{th}$ percentiles, respectively, of the median observed covariate values.*

*Abbreviations: Chemo=chemotherapy, BTC=biliary tract carcinoma, Durva=durvalumab, EC=esophagus carcinoma, NSCLC=non-small cell lung cancer, Treme=tremelimumab*

*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Figure10.*

**Figure 24. Impact of Covariates on Central Volume of Distribution of Tremelimumab**




Reference: Male, NSCLC, Tremelimumab alone, median covariates
Bars represent the relative change (%) from the reference
Dosing regimen: Tremelimumab 300 mg

*Note: Covariate effects were expressed as a percentage change from the typical value of the reference patient. For continuous covariates, bars represent the range of individual central volumes of distribution between the 5$^{th}$ and 95$^{th}$ percentiles, respectively of median observed covariate values.*
*Abbreviations: NSCLC=non-small cell lung cancer*
*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Figure11.*

**Table 51. Durvalumab PK Parameters Derived from the PPK Model (N=4043)**

| | $C_{min,dosel}$ (µg/mL) | $C_{max,dosel}$ (µg/mL) | $AUC_{dosel}$ (µg•day/mL) | $C_{min,ss}$ (µg/mL) | $C_{max,ss}$ (µg/mL) | $AUC_{ss}$ (µg•day/mL) |
|---|---|---|---|---|---|---|
| Geometric Mean (CV%) | 69.7 (38.6) | 455 (22.1) | 4270 (22.0) | 153 (52.6) | 616 (26.2) | 7760 (35.1) |
| Mean (SD) | 74.5 (27.3) | 466 (110) | 4380 (964) | 173 (95.3) | 638 (180) | 8240 (3150) |
| Median (Min-Max) | 71.2 (4.58-290) | 448 (219-1220) | 4270 (1360-11000) | 155 (7.40-1320) | 607 (266-2510) | 7700 (1640-43600) |

CV=Coefficient of variation; SD=Standard Deviation

* parameters were estimated at 28 days cycle

*Source: Response to 01 June 2022 Information Request, Table 2*

**Table 52. Tremelimumab PK Parameters for Single dose Derived from the PPK Model (N=2406)**

| | 75 mg | | | 300 mg | | |
|---|---|---|---|---|---|---|
| | $C_{min,dose1}$ (µg/mL) | $C_{max,dose1}$ (µg/mL) | $AUC_{dose1}$ (µg•day/mL) | $C_{min,dose1}$ (µg/mL) | $C_{max,dose1}$ (µg/mL) | $AUC_{dose1}$ (µg•day/mL) |
| Geometric Mean (CV%) | 2.99 (40.4) | 21.6 (23.9) | 191 (28.0) | 11.9 (40.4) | 86.5 (23.9) | 763 (28.0) |
| Mean (SD) | 3.23 (1.67) | 22.4 (12.8) | 200 (132) | 12.9 (6.70) | 89.7 (51.0) | 801 (528) |
| Median (Min-Max) | 3.04 (0.499-49.0) | 21.3 (9.26-581) | 189 (73.8-5930) | 12.2 (2.00-196) | 85.1 (37.0-2330) | 756 (295-23700) |

CV=Coefficient of variation; SD=Standard Deviation

* parameters were estimated at 28 days cycle

*Source: Response to 01 June 2022 Information Request, Table 3*

**Table 53. Tremelimumab PK Parameters for Multiple doses of 75 mg Derived from the PPK Model (N=2406)**

| | $C_{min,ss}$ (µg/mL) | $C_{max,ss}$ (µg/mL) | $AUC_{ss}$ (µg•day/mL) |
|---|---|---|---|
| Geometric Mean (CV%) | 4.14 (43.5) | 24.4 (24.7) | 245 (30.9) |
| Mean (SD) | 4.52 (2.27) | 25.4 (13.3) | 258 (152) |
| Median (Min-Max) | 4.21 (0.610-58.5) | 24.1 (10.2-593) | 243 (85.3-6400) |

CV=Coefficient of variation; SD=Standard Deviation

* parameters were estimated at 28 days cycle

*Source: Response to 01 June 2022 Information Request, Table 4*

**Table 54. Other Tremelimumab PK Parameters Derived from PPK Model (N=2406)**

| | $CL_{dose1}$ (L/day) | Half-life,dose1 (day) | CLss (L/day) | Half-life,ss (day) | V1 (L) | V2 (L) |
|---|---|---|---|---|---|---|
| Geometric Mean (CV%) | 0.286 (32.3) | 16.9 (18.5) | 0.263 (32.3) | 18.2 (18.6) | 3.45 (24.0) | 2.66 (33.9) |
| Mean (SD) | 0.300 (0.0940) | 17.2 (3.12) | 0.276 (0.0863) | 18.5 (3.38) | 3.54 (0.769) | 2.77 (0.726) |
| Median (Min-Max) | 0.286 (0.0117-0.903) | 17.1 (6.41-52.8) | 0.263 (0.0108-0.829) | 18.4 (6.98-57.1) | 3.51 (0.125-8.08) | 2.76 (0.00575-8.90) |

CV=Coefficient of variation; SD=Standard Deviation

*Source: Response to 01 June 2022 Information Request, Table 5*

The FDA's Assessment:

In general, the Applicant's population PK analyses for durvalumab and tremelimumab are deemed acceptable.

In addition, to support labeling statements mentioned above, the Applicant also provided the single dose and multiple dose PK information derived from population PK models (Table 51,Table 52,Table 53, and Table 54), which were based on HIMALAYA and Study 22 data combined with data in various indications (D4190C00002, D4190C00006, D4190C00010, DETERMINE, D4884C00001 and POSEIDON).

Therefore, the following labeling statements in section 12.3 are upded based on current PPK model:

Distribution

The geometric mean (% coefficient of variation [CV%]) of tremelimumab-actl for central (V1) and peripheral (V2) volume of distribution was 3.45 (27%) and 2.47 (43%) L, respectively.

Elimination

The geometric mean (CV%) terminal half-life of tremelimumab-actl was 16.9 days (19%) after a single dose and 18.2 days (19%) during steady state. The geometric mean (CV%) clearance of tremelimumab-actl was 0.286 L/day (32%) after a single dose and 0.263 L/day (32%) during steady state."

### 19.4.1.3.PPK Review Issues

None

#### 19.4.1.4.Reviewer's Independent Analysis

None

### 19.4.2. Exposure-Response Analysis

#### 19.4.2.1.ER (efficacy) Executive Summary

The FDA's Assessment:

In support of this BLA, the Applicant submitted reports of exposure-response (E-R) analyses for efficacy based on data from durvalumab 1500 mg Q4W + tremelimumab 300 mg single dose arm (T300+D) of the Phase III study HIMALAYA (D419CC00002). The Applicant's E-R for efficacy analysis was conducted in 388 patients only from durvalumab + tremelimumab (T300+D) group. The E-R analysis dataset covered a body weight range between 59.6 and 80 kg and an age range of 58 and 71 years old and was based on individual PK exposures derived from an Applicant's PopPK model. For the efficacy analysis, the relationship of overall survival (OS) or progression-free survival (PFS) of HCC patients to first dose and/or steady-state Cmax, Cmin, and AUC of durvalumab or tremelimumab was assessed based on data from durvalumab 1500mg Q4W + tremelimumab 300 mg single dose arm (T300+D) of HIMALAYA study. Kaplan-Meier estimates stratified by the quartile exposure for any of the exposure metrics indicated no exposure-response relationship. A Cox proportional hazard analysis identified AST and NLR as the significant factors ($p<0.001$) for the OS hazard and no covariate was identified as a significant factor ($p<0.001$) for the PFS hazard. Overall, Kaplan-Meir survival analysis and COXPH multivariate regression results showed that there was no significant E-R relationship for OS and PFS vs. any of durvalumab and tremelimumab PK exposure metrix. E-R for efficacy analysis showed no significant E-R relationship for efficacy at the proposed dose of T300+D regimen. The flat E-R relationship for efficacy endpoints may imply that the effectiveness of durvalumab reached the plateau, supporting the proposed dose (durvalumab 1500mg Q4W + tremelimumab 300 mg single dose).

The Applicant's E-R efficacy analysis appears to be adequate. Therefore, E-R for efficacy supports that no dose adjustment for durvalumab or tremelimumab is needed.

#### 19.4.2.2.ER (efficacy) Assessment Summary

The Applicant's Position:

| General Information | |
|---|---|
| Goal of ER analysis | • Assess the durvalumab/tremelimumab ER (efficacy) relationship using HIMALAYA study data<br>• Support the evidence of effectiveness and justify the dosages and dosing regimens in the ITT population (T300+D)<br>• Evaluate the intrinsic and extrinsic factors, and identify important covariates if any |

| | | |
|---|---|---|
| Study Included | | HIMALAYA (Individual predicted exposure metrics of patients and efficacy data from HIMALAYA study) |
| Endpoint | | Primary: OS<br>Secondary: PFS |
| No. of Patients (total, and with individual PK) | | Total: 388 (T300+D), 388 patients with durvaluab PK and 387 patients with tremelimumab PK |
| Population Characteristics (See Table 18, 19 Population PK and Exposure-Response Report, Module 5.3.3.5) | General | Age (years) median (range): 65 (22-86)<br>Weight (kg) median (range): 70.0 (40.5-140)<br>n (%) male: 323 (83.2%)<br>n (%) race: White 177 (45.6%), Black 7 (1.80%), Asian 195 (50.3%), Native Hawaiian or Other Pacific Islander 1 (0.258%), Other 7 (1.80%), missing 1 (0.258%) |
| | Pediatrics (if any) | None |
| Dose(s) Included | | Durvalumab 1500 mg Q4W, Tremelimumab 300 mg single dose |
| Exposure Metrics Explored (range) | | <u>Durvalumab exposure:</u><br>$C_{min,dose\ 1}$ Durva (µg/mL): 11.2-255<br>$C_{max,dose\ 1}$ Durva (µg/mL): 270-1030<br>$AUC_{dose\ 1}$ Durva (µg.day/mL): 1740-9930<br>$C_{min,ss}$ Durva (µg/mL): 13.2-1050<br>$C_{max,ss}$ Durva (µg/mL): 283-2060<br>$AUC_{ss}$ Durva (µg.day/mL): 1930-35600<br><u>Tremelimumab exposure:</u><br>$C_{min,dose\ 1}$ Treme (µg/mL): 3.70-74.8<br>$C_{max,dose\ 1}$ Treme (µg/mL): 45.8-174<br>$AUC_{dose\ 1}$ Treme (µg.day/mL): 373-2320<br>$AUC_{inf}$ Treme (µg.day/mL): 460-2130 |
| Covariates Evaluated | | Age, body weight, BMI, AST, ALT, albumin, bilirubin, creatinine, baseline LDH, baseline neutrophil-to-lymphocyte ratio, baseline tumor size per investigator, sex, race, baseline ECOG, ADA post-baseline to durva, ADA post-baseline to treme, PD-L1 TC (<1%), NCI scale for hepatic function, BCLC Stage, hepatitis type, exposure metrics |

| **Final Model Parameters** | **Summary** | **Acceptability [FDA's comments]** |
|---|---|---|
| Model Structure | <u>Primary endpoint OS:</u><br>CPH Model with AST and neutrophil-to-lymphocyte ratio as significant covariates;<br><u>Secondary endpoint PFS:</u><br>CPH Model with no significant covariate | Yes |
| Model Parameter Estimates | See Table 20-22, Population PK and Exposure-Response Report, Module 5.3.3.5 (for primary and major secondary endpoints) | Yes |
| Model Evaluation | OS and PFS: graphical exploration of OS and PFS by exposure metrics of durvalumab and tremelimumab; evaluated by the change of objective function values and significant p-value for CPH model when incorporating covariates. | Yes<br>See Figure 25, Figure 26, Figure 27, Figure 28, Figure 29, and Figure 30 |

| | | |
|---|---|---|
| Covariates and Clinical Relevance | No relationship between durvalumab or tremelimumab exposure and OS or PFS was identified in the HIMALAYA T300+D arm.<br>There appears to be no association between durvalumab or tremelimumab exposure vs the body weight (quartiles) or ADA status (positive or negative). | Yes<br>See Figure 27, Figure 28 |
| Simulation for Specific Population | NA | NA |
| Visualization of ER relationships | See Figure 13-15 (OS vs Exposure quartiles KM plots), Figure 18-20 (PFS vs Exposure quartiles KM plots), Appendix 7-Figure 1.8, 1.9, 1.10 (OS vs Body weight quartiles or ADA Status KM plots), Population PK and Exposure-Response Report, Module 5.3.3.5.<br>See Appendix 7, Population PK and Exposure-Response Report, Module 5.3.3.5. for baseline demographics stratified by quartiles) | Yes<br>See Figure 25, Figure 26, Figure 27, Figure 28, Figure 29, and Figure 30 |
| Overall Clinical Relevance for ER | No need for adjustments of dose regimen as no clinical relevant ER (efficacy) relationship identified at the dose regime in HIMALAYA | Yes |
| **Labeling Language** | **Description** | **Acceptability [FDA's comments]** |
| 12.2 Pharmacodynamics | NA | NA |

### 19.4.2.3.ER (safety) Executive Summary

The FDA's Assessment:

In support of the dosing recommendation in this BLA, the Applicant also submitted reports of exposure-response (E-R) for safety analyses. The Applicant's E-R for safety analysis of Durvalumab was conducted with same dataset in E-R for efficacy analysis, which contains 388 patients from the durvalumab 1500 mg Q4W + tremelimumab 300mg x1 (T300+D) arm in the Phase III study HIMALAYA. The E-R analysis dataset covered a body weight range between 59.6 and 80 kg and an age range of 58 and 71 years old. There was no missing safety endpoint data.

Assessment of durvalumab/tremelimumab E-R relationships for safety included the following safety endpoints: Grade 3+ (i.e. including Grade 3, 4 and 5) treatment-related adverse events (AE), Grade 3+ drug-related AE of special interest (AEOSI), and AE leading to treatment discontinuation using data collected from HIMALAYA. No clinically relevant E-R relationship was observed for durvalumab or tremelimumab PK exposure and the above listed safety endpoints in patients treated with T300+D. The Applicant's E-R analyses for safety appear to be adequate. No dose adjustment for durvalumab or tremelimumab is needed based on exposure-response analyses

### 19.4.2.4.ER (safety) Assessment Summary

The Applicant's Position:

| General Information | | |
|---|---|---|
| Goal of ER analysis | | • Assess the durvalumab/tremelimumab ER (safety) relationship using HIMALAYA study data<br>• Support the acceptance of safety profile and justify the dosages and dosing regimens in the ITT population (T300+D)<br>• Evaluate the intrinsic and extrinsic factors, and identify important covariates if any |
| Study Included | | HIMALAYA (Individual predicted exposure metrics of patients and safety data from HIMALAYA study) |
| Population Included | | T300+D |
| Endpoints | | Grade 3 and above drug-related AEs, Grade 3 and above drug-related AESIs, and AEs leading to durvalumab treatment discontinuation |
| No. of Patients (total, and with individual PK) | | Total: 388 (T300+D), 388 patients with durvaluab PK and 387 patients with tremelimumab PK |
| Population Characteristics (See Table 18, 19 Poppulation PK and Exposure-Response Report, Module 5.3.3.5) | General | Age (years) median (range): 65 (22-86)<br>Weight (kg) median (range): 70.0 (40.5-140)<br>n (%) male: 323 (83.2%)<br>n (%) race: White 177 (45.6%), Black 7 (1.80%), Asian 195 (50.3%), Native Hawaiian or Other Pacific Islander 1 (0.258%), Other 7 (1.80%), missing 1 (0.258%) |
| | Organ impairment | Hepatic (NCI) - n (%) in each category: Normal 149 (38.4%), mild 232 (59.8%), moderate 6 (1.55%), missing 1 (0.258%)<br>Renal (CrCL in mL/min) - median (range): 84.8 (29.5-221) |
| | Pediatrics (if any) | None |
| | Geriatrics (if any) | Age (years) median (range, % subj ≥65 yr, % subj ≥75 yr): 65 (22-86), 53.3%, 13.7%) |
| Dose(s) Included | | Durvalumab 1500 mg Q4W, Tremelimumab 300 mg single dose |
| Exposure Metrics Explored (range) | | Durvalumab exposure:<br>$C_{min,dose\ 1}$ Durva (µg/mL): 11.2-255<br>$C_{max,dose\ 1}$ Durva (µg/mL): 270-1030<br>$AUC_{dose\ 1}$ Durva (µg.day/mL): 1740-9930<br>$C_{min,ss}$ Durva (µg/mL): 13.2-1050<br>$C_{max,ss}$ Durva (µg/mL): 283-2060<br>$AUC_{ss}$ Durva (µg.day/mL): 1930-35600<br>Tremelimumab exposure:<br>$C_{min,dose\ 1}$ Treme (µg/mL): 3.70-74.8<br>$C_{max,dose\ 1}$ Treme (µg/mL): 45.8-174<br>$AUC_{dose\ 1}$ Treme (µg.day/mL): 373-2320<br>$AUC_{inf}$ Treme (µg.day/mL): 460-2130 |
| Covariates Evaluated | | Age, body weight, BMI, AST, ALT, albumin, bilirubin, creatinine, baseline LDH, baseline neutrophil-to-lymphocyte ratio, baseline tumor size per investigator, sex, race, baseline ECOG, ADA post-baseline to durva, ADA post-baseline to treme, PD-L1 TC (<1%), NCI |

| | scale for hepatic function, BCLC Stage, hepatitis type, exposure metrics | |
|---|---|---|
| **Final Model Parameters** | **Summary** | **Acceptability [FDA's comments]** |
| Model Structure | The safety endpoints (Grade 3+ AE, Grade 3+ AEOSI, AE leading to treatment discontinuation) were converted to binary responses and analyzed with linear logistic regression models relating the probability of responses to durvalumab or tremelimumab exposure metrics. | **Yes** |
| Model Parameter Estimates | See Table 23-25, Population PK and Exposure-Response Report, Module 5.3.3.5 (logistic regressions for probability of safety endpoints vs exposure quartiles) | **Yes** |
| Model Evaluation | The probability of safety endpoints (Grade 3+ AE, Grade 3+ AEOSI, AE leading to treatment discontinuation) calculated in quartiles of the various durvalumab and tremelimumab exposure metrics were graphically explored with overlaid model predictions from the logistic regression model fit.<br>The logistic regression results assessing the impact of exposure on the probability of safety endpoints were tabulated with P values associated with exposure effects in comparison to the pre-specified significance level of $\alpha$ =0.001. | **Yes**<br>**See Figure 31** |
| Covariates and Clinical Relevance | In general, there appears to be no clear trend between increasing exposure of durvalumab or tremelimumab and the probability of all safety endpoints.<br>The P values associated with exposure effects were relatively large (in comparison to the pre-specified significance level of $\alpha$ =0.001), indicating that the relationship was not statistically significant.<br>In addition, there appears to be no association between covariates (e.g., among baseline bodyweight quartiles, ADA status and other covariates explored) and the percentages of patients having safety endpoints (Grade 3+ AE, Grade 3+ AEOSI, AE leading to treatment discontinuation). | **Yes** |
| Simulation for Specific Population | NA | |
| Visualization of ER relationships | See Figure 23-25, Population PK and Exposure-Response Report, Module 5.3.3.5 | **Yes**<br>**See Figure 31** |

| | | |
|---|---|---|
| | (logistic regression of probabilities of AEs vs exposure plots)<br>See Appendix 8-Figure 1.14-1.19, Population PK and Exposure-Response Report, Module 5.3.3.5 (additional covariates exploratory analysis) | |
| Overall Clinical Relevance for ER | No need for adjustments of dose regimen as no clinical relevant ER (safety) relationship identified at the dose regime in HIMALAYA | **Yes** |
| **Labeling Language** | **Description** | **Acceptability [FDA's comments]** |
| 12.2 Pharmacodynamics | NA | NA |

**Table 55. Summary of Continuous Covariates for the Efficacy E-R Dataset for Durvalumab and Tremelimumab**

| | D alone | T75+D | T300+D | SoC |
|---|---|---|---|---|
| **Individuals** | | | | |
| N | 388 | 152 | 388 | 374 |
| **Age (years)** | | | | |
| Mean (SD) | 62.7 (11.5) | 63.2 (12.0) | 63.0 (11.7) | 63.5 (11.1) |
| Median (IQR) | 64.0 (56.0-71.0) | 65.0 (56.0-72.0) | 65.0 (58.0-71.0) | 64.0 (58.3-71.0) |
| Min-max | 20.0-86.0 | 18.0-85.0 | 22.0-86.0 | 18.0-88.0 |
| Missing | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Body weight (kg)** | | | | |
| Mean (SD) | 70.0 (16.3) | 69.9 (14.3) | 71.3 (15.9) | 71.4 (15.6) |
| Median (IQR) | 67.5 (58.4-78.0) | 68.6 (59.1-77.7) | 70.0 (59.6-80.0) | 69.0 (60.0-80.2) |
| Min-max | 38.5-140 | 42.1-115 | 40.5-140 | 37.2-139 |
| Missing | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Body Mass Index (kg/m²)** | | | | |
| Mean (SD) | 25.0 (4.83) | 25.0 (4.22) | 25.2 (4.92) | 25.0 (4.56) |
| Median (IQR) | 24.3 (21.8-27.3) | 24.4 (22.0-27.4) | 24.7 (21.8-27.7) | 24.5 (21.8-27.3) |
| Min-max | 15.9-55.7 | 16.9-41.3 | 15.4-45.2 | 15.1-48.2 |
| Missing | 3 (0.773%) | 0 (0%) | 2 (0.515%) | 3 (0.802%) |
| **Aspartate transaminase (AST) (IU/L)** | | | | |
| Mean (SD) | 62.3 (43.6) | 62.6 (42.6) | 59.7 (38.9) | 62.7 (46.8) |
| Median (IQR) | 47.0 (31.0-80.3) | 50.0 (35.0-78.0) | 49.0 (30.2-77.0) | 48.5 (33.0-76.0) |
| Min-max | 12.0-279 | 5.00-293 | 9.00-240 | 11.0-459 |

| | | | | |
|---|---|---|---|---|
| Missing | 0 (0%) | 0 (0%) | 1 (0.258%) | 0 (0%) |
| **Alanine transaminase (ALT) (IU/L)** | | | | |
| Mean (SD) | 46.5 (33.9) | 45.8 (31.4) | 47.0 (34.7) | 46.6 (34.5) |
| Median (IQR) | 36.5 (24.0-60.0) | 35.0 (23.8-62.3) | 37.0 (23.0-60.1) | 37.0 (22.0-60.8) |
| Min-max | 5.00-262 | 6.00-200 | 5.00-217 | 7.00-233 |
| Missing | 0 (0%) | 0 (0%) | 1 (0.258%) | 0 (0%) |
| **Albumin (g/L)** | | | | |
| Mean (SD) | 39.4 (4.72) | 38.7 (5.14) | 39.5 (4.86) | 39.0 (4.68) |
| | D alone | T75+D | T300+D | SoC |
| Median (IQR) | 39.0 (36.2-43.0) | 39.0 (35.2-42.0) | 40.0 (36.0-43.0) | 39.0 (36.0-42.3) |
| Min-max | 24.0-52.0 | 19.0-49.8 | 25.6-54.0 | 24.0-54.7 |
| Missing | 0 (0%) | 1 (0.658%) | 1 (0.258%) | 0 (0%) |
| **Bilirubin (mg/dL)** | | | | |
| Mean (SD) | 0.879 (0.457) | 0.831 (0.477) | 0.786 (0.362) | 0.836 (0.447) |
| Median (IQR) | 0.800 (0.585-1.08) | 0.700 (0.558-0.965) | 0.700 (0.501-1.00) | 0.746 (0.501-1.04) |
| Min-max | 0.160-3.10 | 0.200-3.90 | 0.175-2.40 | 0.140-4.40 |
| Missing | 0 (0%) | 1 (0.658%) | 1 (0.258%) | 0 (0%) |
| **Creatinine (mg/dL)** | | | | |
| Mean (SD) | 0.853 (0.202) | 0.838 (0.212) | 0.869 (0.228) | 0.877 (0.209) |
| Median (IQR) | 0.820 (0.720-0.964) | 0.820 (0.698-0.933) | 0.860 (0.710-0.980) | 0.840 (0.724-1.00) |
| Min-max | 0.390-1.73 | 0.362-1.63 | 0.362-2.27 | 0.440-1.78 |
| Missing | 0 (0%) | 0 (0%) | 2 (0.515%) | 0 (0%) |
| **Baseline Lactate Dehydrogenase (U/L)** | | | | |
| Mean (SD) | 288 (282) | 275 (150) | 268 (179) | 258 (136) |
| Median (IQR) | 226 (181-294) | 233 (188-306) | 218 (186-286) | 216 (180-288) |
| Min-max | 92.0-3720 | 123-1200 | 98.0-2010 | 125-1170 |
| Missing | 3 (0.773%) | 2 (1.32%) | 8 (2.06%) | 4 (1.07%) |
| **Baseline Neutrophil-to-Lymphocyte Ratio** | | | | |
| Mean (SD) | 3.25 (2.12) | 3.36 (2.93) | 3.39 (2.39) | 3.34 (2.45) |
| Median (IQR) | 2.77 (1.97-3.91) | 2.76 (1.90-3.63) | 2.78 (1.93-4.18) | 2.71 (1.86-4.09) |
| Min-max | 0.619-25.3 | 0.00300-27.3 | 0.146-21.8 | 0.589-23.8 |
| Missing | 0 (0%) | 2 (1.32%) | 0 (0%) | 1 (0.267%) |
| **Baseline Tumor Size per Investigator (mm)** | | | | |
| Mean (SD) | 93.7 (61.9) | 94.7 (62.2) | 92.2 (64.6) | 101 (78.7) |

| | | | | |
|---|---|---|---|---|
| Median (IQR) | 79.0 (44.0-131) | 82.0 (42.0-144) | 79.0 (43.0-121) | 76.5 (42.8-143) |
| Min-max | 10.0-383 | 10.0-267 | 10.0-477 | 10.0-790 |
| Missing | 1 (0.258%) | 1 (0.658%) | 0 (0%) | 2 (0.535%) |

*Abbreviations: IQR=interquartile range, SoC=standard of care, D - Durvalumab, T75+D-Durvalumab + tremelimumab 75mg x4, T300+D-Durvalumab + tremelimumab 300mg x1*

*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Table18.*

**Table 56. Summary of Categorical Covariates for the Efficacy E-R Dataset for Durvalumab and Tremelimumab**

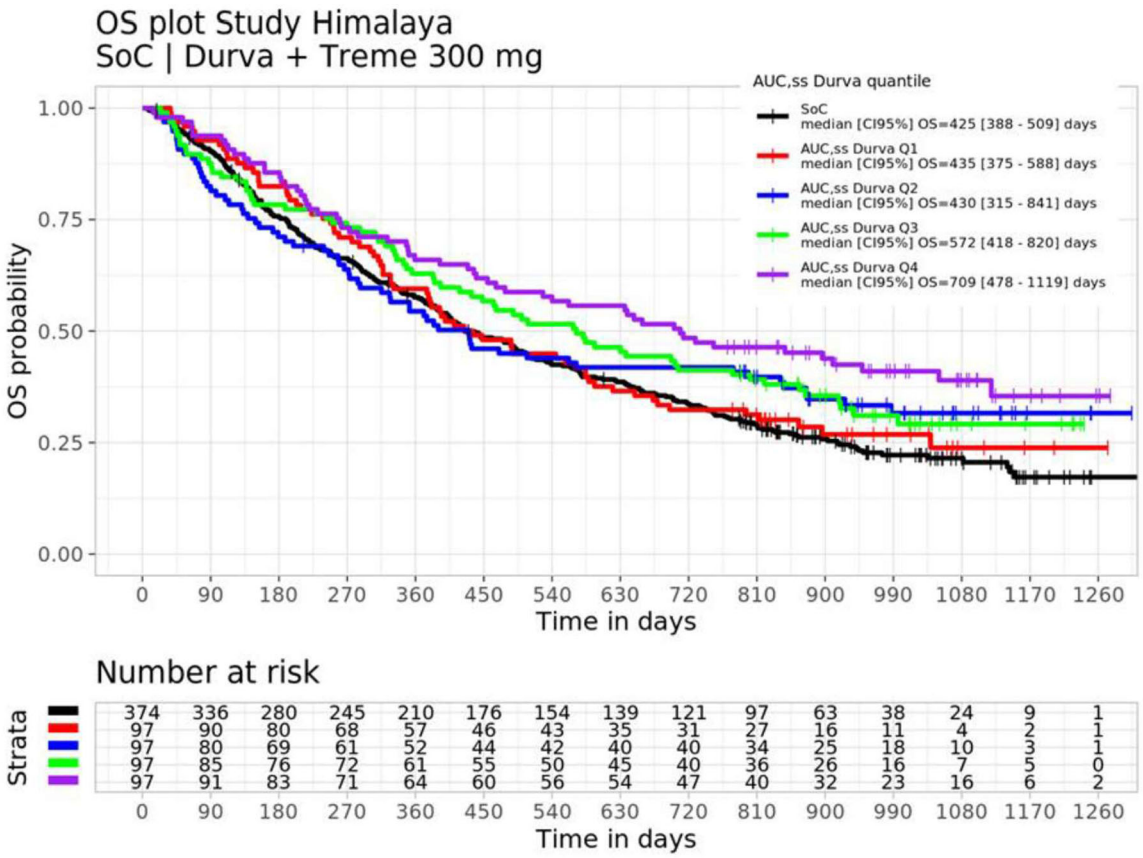
| | D alone | T75+D | T300+D | SoC |
|---|---|---|---|---|
| **Individuals** | | | | |
| N | 388 | 152 | 388 | 374 |
| **Sex** | | | | |
| Male | 322 (83.0%) | 120 (78.9%) | 323 (83.2%) | 323 (86.4%) |
| Female | 66 (17.0%) | 32 (21.1%) | 65 (16.8%) | 51 (13.6%) |
| **Race** | | | | |
| White | 160 (41.2%) | 70 (46.1%) | 177 (45.6%) | 171 (45.7%) |
| Black | 2 (0.515%) | 4 (2.63%) | 7 (1.80%) | 8 (2.14%) |
| Asian | 210 (54.1%) | 75 (49.3%) | 195 (50.3%) | 184 (49.2%) |
| Native Hawaiian or Other Pacific Islander | -- | -- | 1 (0.258%) | -- |
| Other | 16 (4.12%) | 3 (1.97%) | 7 (1.80%) | 5 (1.34%) |
| Missing | -- | -- | 1 (0.258%) | 6 (1.60%) |
| **Baseline Eastern Cooperative Oncology Group performance status** | | | | |
| Normal activity | 236 (60.8%) | 98 (64.5%) | 241 (62.1%) | 235 (62.8%) |
| Restricted activity | 150 (38.7%) | 54 (35.5%) | 146 (37.6%) | 139 (37.2%) |
| Missing | 2 (0.515%) | -- | 1 (0.258%) | -- |
| **Anti-drug antibody status post-baseline Durva** | | | | |
| Positive | 8 (2.06%) | 5 (3.29%) | 11 (2.84%) | -- |
| Negative | 279 (71.9%) | 104 (68.4%) | 283 (72.9%) | 1 (0.267%) |
| Missing | 101 (26.0%) | 43 (28.3%) | 94 (24.2%) | 373 (99.7%) |
| **Anti-drug antibody status post-baseline Treme** | | | | |
| Positive | -- | 25 (16.4%) | 23 (5.93%) | -- |
| Negative | 1 (0.258%) | 77 (50.7%) | 163 (42.0%) | -- |
| Missing | 387 (99.7%) | 50 (32.9%) | 202 (52.1%) | 374 (100%) |
| **PD-L1 TC <1%** | | | | |

| | | | | |
|---|---|---|---|---|
| Yes | 191 (49.2%) | 79 (52.0%) | 188 (48.5%) | 181 (48.4%) |
| No | 155 (39.9%) | 64 (42.1%) | 148 (38.1%) | 148 (39.6%) |
| Missing | 42 (10.8%) | 9 (5.92%) | 52 (13.4%) | 45 (12.0%) |
| **NCI scale for hepatic function** | | | | |
| Normal | 139 (35.8%) | 51 (33.6%) | 149 (38.4%) | 128 (34.2%) |
| Mild | 232 (59.8%) | 95 (62.5%) | 232 (59.8%) | 234 (62.6%) |
| Moderate | 17 (4.38%) | 5 (3.29%) | 6 (1.55%) | 12 (3.21%) |
| Missing | -- | 1 (0.658%) | 1 (0.258%) | -- |
| | D alone | T75+D | T300+D | SoC |
| **Tumor type** | | | | |
| HCC | 388 (100%) | 152 (100%) | 388 (100%) | 374 (100%) |
| **Barcelona Clinic Liver Cancer Stage** | | | | |
| stage B | 80 (20.6%) | 31 (20.4%) | 77 (19.8%) | 66 (17.6%) |
| stage C | 308 (79.4%) | 121 (79.6%) | 311 (80.2%) | 308 (82.4%) |
| **Hepatitis type** | | | | |
| HBV | 123 (31.7%) | 49 (32.2%) | 125 (32.2%) | 120 (32.1%) |
| HCV | 103 (26.5%) | 39 (25.7%) | 104 (26.8%) | 98 (26.2%) |
| HDV | 162 (41.8%) | 64 (42.1%) | 159 (41.0%) | 156 (41.7%) |

*Abbreviations: IQR=interquartile range, SoC=standard of care, D - Durvalumab, D + T75-Durvalumab + tremelimumab 75mg x4, D + T300-Durvalumab + tremelimumab 300mg x1*

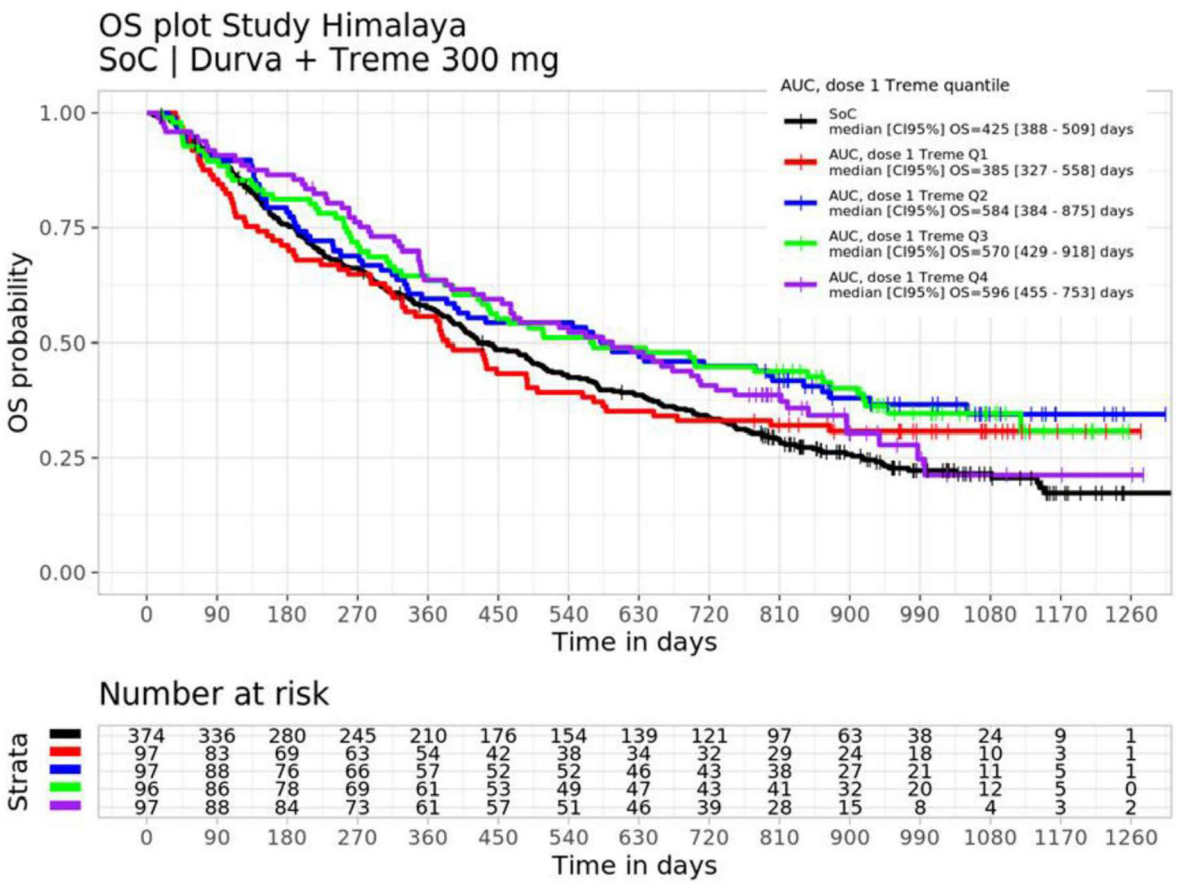
*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Table19.*

**Figure 25. Overall Survival (OS) Kaplan-Meier Plots for Durvalumab Exposure Metrics AUCss by Quartiles at Steady-State**



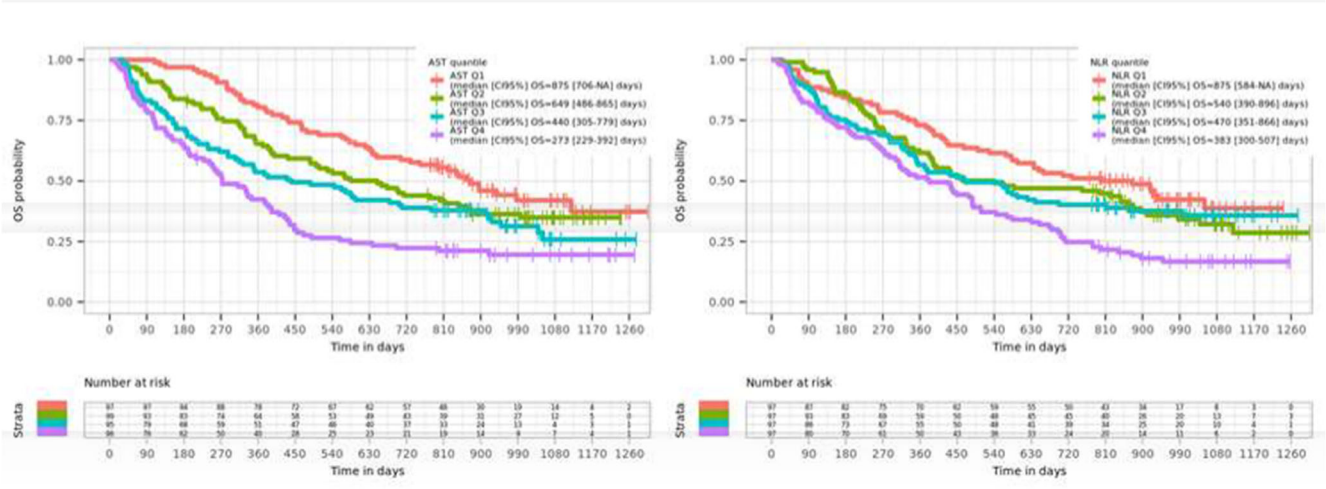

*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Figure14.*

**Figure 26. Overall Survival (OS) Kaplan-Meier Plots for Tremelimumab Exposure Metrics AUC by Quartiles at Dose 1**



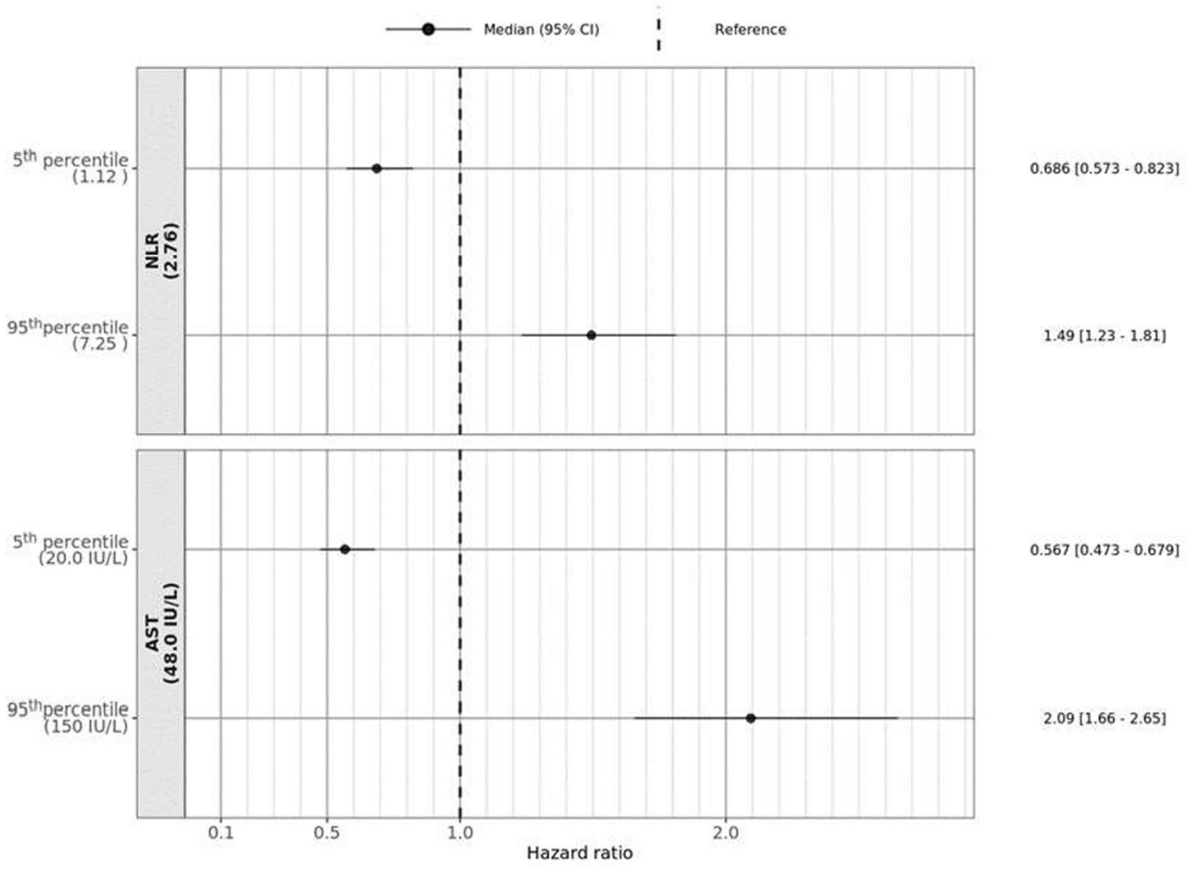

*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Figure15.*

**Figure 27. Overall Survival (OS) Kaplan Meier Plots Stratified by Significant Covariates**



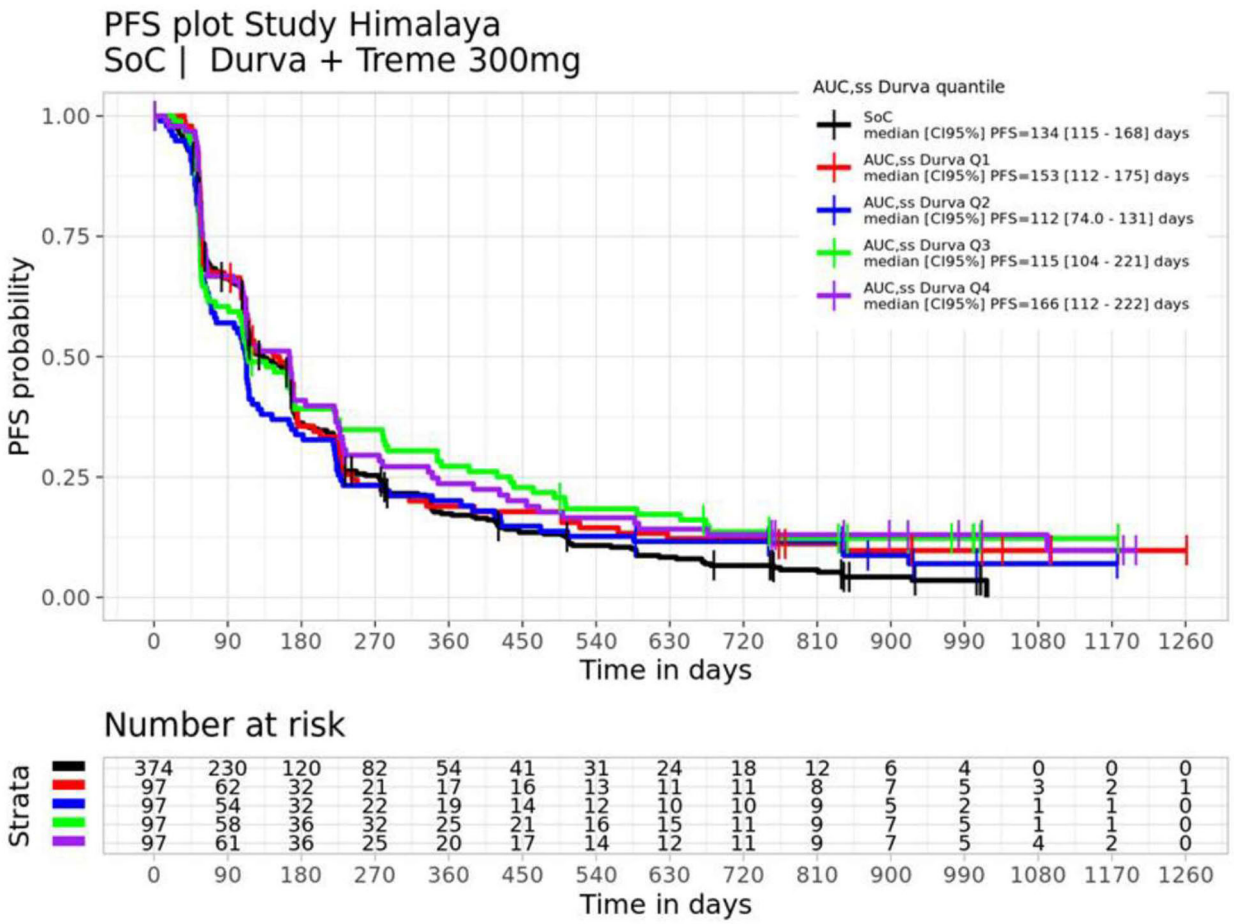

*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Figure16.*

**Figure 28. Forest Plot of the Final Cox PH Model for Overall Survival (OS)**



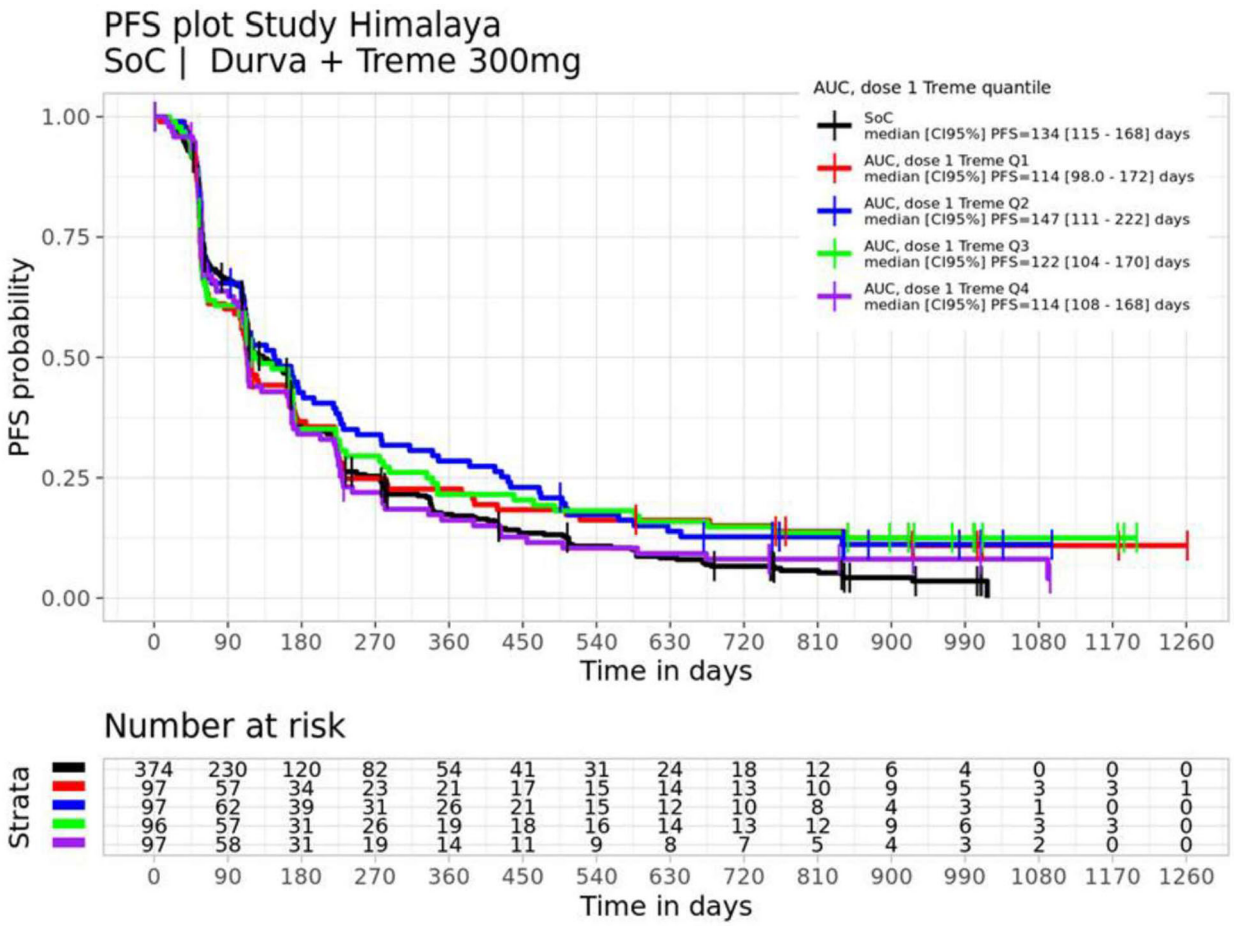

*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Figure17.*

**Figure 29. PFS Kaplan-Meier Plots for Durvalumab Exposure Metrics - AUCss by Quartiles at Steady-state**



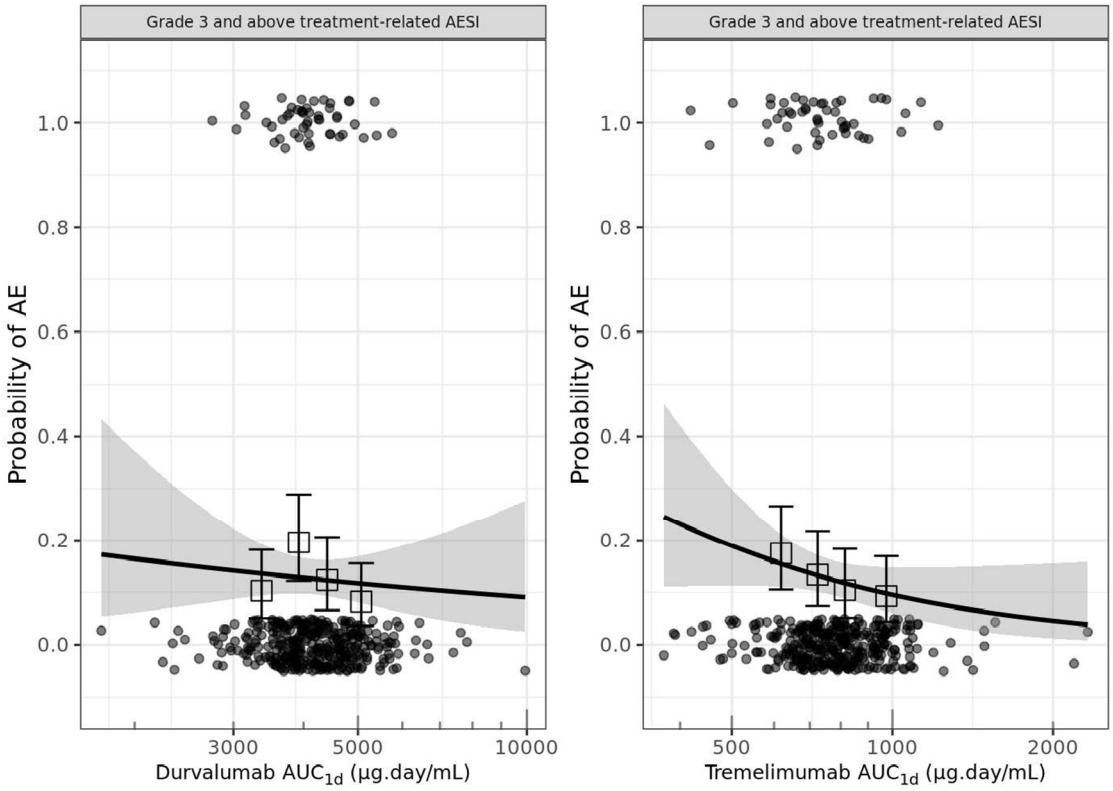

*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Figure18.*

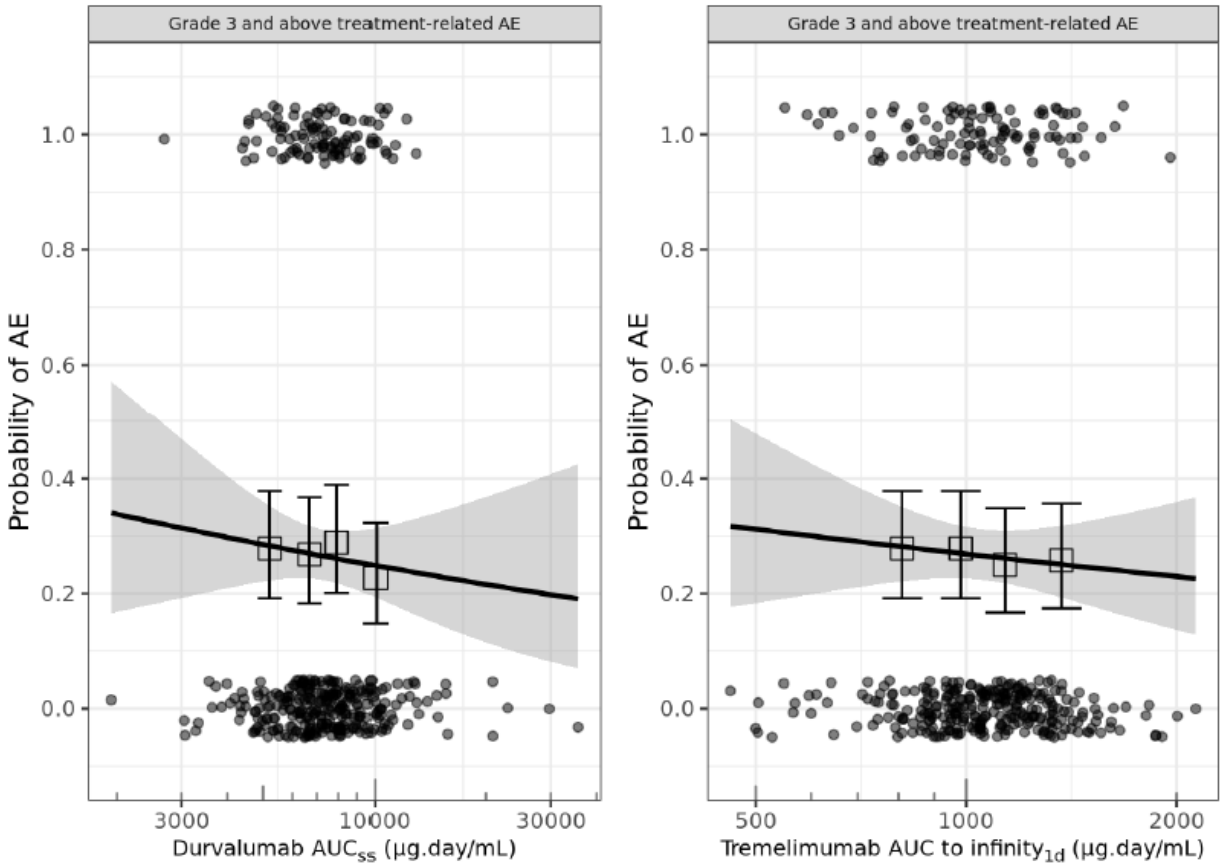
**Figure 30. PFS Kaplan-Meier Plots for Tremelimumab Exposure Metrics-AUC by Quartiles at Dose 1**




*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Figure19.*

Figure 31. Relationship Between the Probability of Having Grade 3 and Above Treatment-Related AESIs and $AUC_{dose\ 1}$ for Durvalumab and Tremelimumab (upper panel), AUC at Steady-State for Durvalumab and AUC0-infinity for Tremelimumab (lower panel)






*Source: Applicant's Population PK and Exposure-Response Report (MS-2021-02), Figure24 and Appendix 8.1.3.*

The FDA's Assessment:
In general, the Applicant's ER analysis for durvalumab and tremelimumab is considered acceptable as supportive analyses. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

### 19.4.2.5.ER Review Issues

*None*

### 19.4.2.6.Overall benefit-risk evaluation based on ER analyses

The Applicant's Position:
See Section 6 for details on overall benefit-risk evaluation based on ER analyses.

The FDA's Assessment:
FDA agrees with Applicant's position. Overall, no dose adjustment for durvalumab and tremelimumab is

needed based on PopPK covariates analyses and exposure-response for efficacy and safety analyses.

### 19.4.2.1.Reviewer's Independent Analysis

The FDA's assessment

**Bioanalytical Methods**

The Office of Clinical Pharmacology review team has assessed the acceptability of the following bioanalytical methods used in the pivotal study (HIMALAYA), 20 supportive durvalumab studies, and 17 supportive tremelimumab studies.

Summaries of method performance are provided in Table 57,Table 58Table 59 based on the information submitted in the BLA 761289.

**Table 57 Summary method performance of a bioanalytical method to measure tremelimumab in human serum**

| | |
|---|---|
| Bioanalytical method review summary | Validation of method was adequate for determination of MEDI-1123 in human serum. |
| **Bioanalytical method validation report name, amendments, and hyperlinks** | Validation of the Quantitative ELISA Assay for Measurement of MEDI-1123 Concentrations in Human Serum (Report AR4785).<br>Selectivity in human serum from patients with solid tumors from:<br>Validation of the Quantitative ELISA Assay for Measurement of MEDI-1123 Concentrations in Human Serum Amendment 4 (Report VR4785 Amendment 4).<br>Long-term stability data from:<br>Long Term Stability of MEDI-1123 Quality Control Samples in Human Serum Using an Enzyme Linked Immunosorbent Assay (ELISA) (Report AR4785 Addendum 2). |
| **Method description** | This method utilizes an indirect ELISA format to measure the concentrations of tremelimumab in human serum. Standards, controls, and test samples are incubated with recombinant CTLA-4 (human CD152 muIg) that has been immobilized on a microtiter plate. After incubation, unbound material is washed away and tremelimumab is detected using biotinylated mouse monoclonal antibody to human IgG2, followed by HRP-streptavidin conjugate, and tremelimumab is visualized with peroxidase substrate TMB. The color development was stopped, and the intensity of the color was measured at 450 nm with wavelength correction set to 650 nm. |
| **Materials used for calibration curve & concentration** | Tremelimumab in human serum at final concentrations (in 5% human serum) of 3.9, 7.8, 15.6, 31.3, 62.5, 125.0, 250.0, 500.0 ng/mL |
| **Validated assay range** | 156 ng/mL to 5000 ng/mL in 100% human serum |

| | |
|---|---|
| **Material used for QCs & concentration** | Tremelimumab in 100% human serum at concentrations of 156.0 (LLOQ-QC), 300.0 (LQC), 1000.0 (MQC), 4000.0 (HQC), and 5000.0 (ULOQ-QC) ng/mL |
| **Minimum required dilutions (MRDs)** | 1:20 |
| **Source & lot of reagents (LBA)** | Tremelimumab Lot:PS01<br>CD152-mulg (Coat) Lot: 202603<br>Biotinylated Mouse Monoclonal Antibody IgG2 Lot: 977038A<br>Streptavidin-HRP Conjugate Lot: 1094380<br>Pooled Human Serum Lot: BRH673682<br>Selectivity in human serum from patients with solid tumors from Report VR4785 Amendment 4:<br>Tremelimumab Lot:PS01<br>CD152-mulg (Coat) Lot: 243102<br>Biotinylated Mouse Monoclonal Ab IgG2 Lot: QK221423<br>Streptavidin-HRP Conjugate Lot: 1711869<br>Pooled Human Serum Lot: BRH1222126 |
| **Regression model & weighting** | Data were fit using a linear adjusted variance weighted five-parameter logistic function. |

| **Validation parameters** | **Method validation summary** | | **Acceptability** |
|---|---|---|---|
| **Standard calibration curve performance during accuracy & precision** | Number of standard calibrators from LLOQ to ULOQ | 6 | Yes |
| | Cumulative accuracy (%bias) from LLOQ to ULOQ [a] | -2.4 to 0.5% | Yes |
| | Cumulative precision (%CV) from LLOQ to ULOQ | ≤ 4.9% | Yes |
| **QCs performance during accuracy & precision** | Cumulative accuracy (%bias) in 5 QCs<br>QCs:156.0 (LLOQ-QC), 300.0 (LQC), 1000.0 (MQC), 4000.0 (HQC), and 5000.0 (ULOQ-QC) ng/mL | −8.7 to −2.3% | Yes |
| | Inter-batch %CV<br>QCs:156.0 (LLOQ-QC), 300.0 (LQC), 1000.0 (MQC), 4000.0 (HQC), and 5000.0 (ULOQ-QC) ng/mL | ≤ 19.4% | Yes |
| | Total Error (TE)<br>QCs:156.0 (LLOQ-QC), 300.0 (LQC), 1000.0 (MQC), 4000.0 (HQC), and 5000.0 (ULOQ-QC) ng/mL | ≤ 21.7% | Yes |

| | | |
|---|---|---|
| **Selectivity & matrix effect** | Normal serum<br>Ten individual human serum samples of mixed gender were analyzed in an assay together with 3 replicate spikes of the pool matrix. The individual samples and the pool spikes were tested both unspiked and spiked with 0.20 µg/mL (10 ng/mL in 5% human serum) tremelimumab. 100% of the unspiked serum samples and the unspiked matrix returned values below the LLOQ and 100% of the spiked serum samples measured between -13.8% and 13.8% of the mean value of the spiked pool matrix.<br><br>Human serum from patients with solid tumors<br>Selectivity in disease state matrix was evaluated using 18 serum samples from human individuals with solid tumors: Three different lots of breast, lung, bladder, ovarian, head/neck, and gastric cancer sera were used. The individual serum samples were tested both unspiked and spiked with tremelimumab at a concentration (200 ng/mL) between LLOQ and the LQC levels. For controls, pooled normal human serum was tested both unspiked (3 duplicate determinations) and spiked (3 separate aliquots each tested in duplicate), using the same spike solution used for the samples.<br>Specificity (unspiked samples) and selectivity (spiked samples) of tremelimumab measurement in samples from patients with solid tumors met the acceptance criteria in 100% of the lots tested. | Yes |
| **Interference & specificity** | Specificity of tremelimumab measurement was tested in the presence of several co-drugs (including durvalumab) in prepared QCs. The assay was found to be specific to the measurement of tremelimumab. | Yes |
| **Hemolysis effect** | Not applicable | Yes |
| **Lipemic effect** | Not applicable | Yes |
| **Dilution linearity & hook effect** | Dilution linearity tested and passed at 10 µg/mL (dilution factor = 200), 100 µg/mL (dilution factor = 2000), and 1000 µg/mL (dilution factor = 2000) | Yes |
| **Bench-top/process stability** | 24 hours in human serum at room temperature | Yes |
| **Freeze-Thaw stability** | 5 cycles in human serum at -70°C | Yes |

| | | |
|---|---|---|
| **Long-term storage** | Tremelimumab is stable in human serum for 733 days at -70°C ± 10°C<br><br>Tremelimumab is stable in human serum for 121 days at -20°C ± 5°C | Yes |
| **Parallelism** | Not applicable | Yes |
| **Carry over** | Not applicable | Yes |
| **Method performance in study D419CC00002 (HIMALAYA)** | | |
| **Assay passing rate** | • 78 out of 95 (82%) | Yes |
| **Standard curve performance** | • Cumulative bias range: -2.8 to 2.1% (from LLOQ to ULOQ)<br>• Cumulative precision: ≤ 11.7% CV (from LLOQ to ULOQ) | Yes |
| **QC performance** | • Cumulative bias range: -9.2 to -1.0%<br>• Cumulative precision: ≤ 17.5% CV<br>• TE: ≤ 26.7% [c] | Yes |
| **Method reproducibility** | Incurred sample reanalysis was not performed for this study | Yes |
| **Study sample analysis/ stability** | All standards, QCs, and study samples were analyzed within the established stability of 733 days at -70°C ± 10°C. | Yes |
| **Method performance in study D419MC00004 (POSEIDON)** | | |
| **Assay passing rate** | 40 out of 50 (80%) | Yes |
| **Standard curve performance** | • Cumulative bias range: -1.4 to 0.9% (from LLOQ to ULOQ)<br>• Cumulative precision: ≤ 8.7% CV (from LLOQ to ULOQ) | Yes |
| **QC performance** | • Cumulative bias range: -12.6 to -4.4%<br>• Cumulative precision: ≤ 12.7% CV<br>• TE: ≤ 25.3% [a] | Yes |

| | | |
|---|---|---|
| **Method reproducibility** | Incurred sample reanalysis was not performed for this study | Yes |
| **Study sample analysis/ stability** | All standards, QCs, and study samples were analyzed within the established stability of 733 days at -70°C ± 10°C | Yes |
| **Method performance in study D4190C00006 (Study 06)** | | |
| **Assay passing rate** | 95 out of 103 (92%) | Yes |
| **Standard curve performance** | • Cumulative bias range: -3.4 to 0.6% (from LLOQ to ULOQ) [a]<br>• Cumulative precision: ≤ 6.1% CV (from LLOQ to ULOQ) | Yes |
| **QC performance** | • Cumulative bias range: -7.0 to -2.7% [b]<br>• Cumulative precision: ≤ 6.1% CV<br>• TE: ≤ 14.9% [c] | Yes |
| **Method reproducibility** | Incurred sample reanalysis was not performed for this study | Yes |
| **Study sample analysis/ stability** | All standards, QCs, and study samples (except for 4 samples) were analyzed within the established stability of 733 days at -70°C ± 10°C. The 4 samples that exceeded the long-term stability were reported as Non-Reportable Result. | Yes |
| **Method performance in study D4190C00022 (Study 22)** | | |
| **Assay passing rate** | 53 out of 64 (83%) | Yes |
| **Standard curve performance** | • Cumulative bias range: -0.1 to 0.3% (from LLOQ to ULOQ) [a]<br>• Cumulative precision: ≤ 8.7% CV (from LLOQ to ULOQ) | Yes |
| **QC performance** | • Cumulative bias range: -7.0 to -3.0% [b, d]<br>• Cumulative precision: ≤ 14.4% CV [d] | Yes |
| **Method reproducibility** | Incurred sample reanalysis was not performed for this study | Yes |

| | | |
|---|---|---|
| **Study sample analysis/ stability** | All standards, QCs, and study samples were analyzed within the established stability of 733 days at -70°C ± 10°C | Yes |

Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ calculated using the equation of (Observed Concentration – Nominal Concentration)/Nominal Concentration* 100%.
b Cumulative accuracy (%bias) in QCs calculated using the equation of (Observed Concentration – Nominal Concentration)/Nominal Concentration* 100%.
c Total error (TE) calculated using the equation of %TE= %CV + |%RE|.

**Table 58 Summary method one performance of a bioanalytical method to measure durvalumab in human serum**



| | | | |
|---|---|---|---|
| **Bioanalytical method validation report name, amendments, and hyperlinks** | Validation Report for the Quantitative Determination of MEDI4736 in Human Serum Using an Electrochemiluminescent (ECL) Assay (Report AR4646).<br>Tremelimumab interference data from:<br>AR4646 Addendum 1: Tremelimumab Drug Interference Study in the Quantitative Determination of MEDI4736 in Human Serum Using an Electrochemiluminescent (ECL) Assay (Report AR4646 Addendum 1).<br>Long-term stability data from:<br>AR4646 Addendum 5: Long-Term Stability (LTS) Studies for the Quantitative Determination of MEDI4736 in Human Serum Using an | | |
| **Method description** | The method utilizes an ECL assay format to measure the concentration of durvalumab in human serum. Standards, controls, and test samples are incubated with durvalumab anti-Idiotype Antibody (clone AB0470011) Biotin which has been immobilized on an MSD Streptavidin Coated Standard MA2400 96-Well Plate. After incubation, unbound material is washed away and durvalumab is detected with anti-TM (clone A8) Sulfotag, visualized with | | |
| **Materials used for calibration curve & concentration** | Durvalumab in human serum at final concentrations (incorporating dilutions) of 1.25, 2.50, 5.00, 10.0, 20.0, 40.0, 80.0, 160, and 320 ng/mL. | | |
| **Validated assay range** | 50.0 to 3200 ng/mL in undiluted human serum | | |
| **Material used for QCs & concentration** | Durvalumab in human serum at 2.50, 5.00, 20.0, 100, and 160 ng/mL | | |
| **Minimum required dilutions (MRDs)** | 1:20 | | |
| **Source & lot of reagents (LBA)** | Not specified | | |
| **Regression model & weighting** | 5-parameter logistic curve with adjusted variance weighting | | |
| **Validation parameters** | **Method validation summary** | | **Accetapability** |
| | Number of standard calibrators from LLOQ to ULOQ | 7 | **Yes** |

| | | | |
|---|---|---|---|
| **Standard calibration curve performance during accuracy & precision** | Cumulative accuracy (%bias) from LLOQ to ULOQ | -2.8 to 2.4% | Yes |
| | Cumulative precision (%CV) from LLOQ to ULOQ | ≤10.4% | Yes |
| **QCs performance during accuracy & precision** | Cumulative accuracy (%bias) in 5 QCs<br>QCs: 2.50 (LLOQ-QC), 5.00 (LQC), 20.0 (MQC), 100 (HQC), and 160 (ULOQ-QC) ng/mL | 0.5 to 12.1% | Yes |
| | Inter-batch %CV<br>QCs: 2.50 (LLOQ-QC), 5.00 (LQC), 20.0 (MQC), 100 (HQC), and 160 (ULOQ-QC) ng/mL | ≤ 3.2% | Yes |
| | Total Error (TE)<br>QCs: 2.50 (LLOQ-QC), 5.00 (LQC), 20.0 (MQC), 100 (HQC), and 160 (ULOQ-QC) ng/mL | ≤ 15.3% | Yes |
| **Selectivity & matrix effect** | 9/10 normal human serum samples had concentrations below the LLOQ, 12/12 human serum samples from cancer patients had concentrations below the LLOQ.<br>Following spiking of normal human serum and serum from cancer patients:<br>Acceptable recovery (100 ± 25% for the Low QC) was obtained in 90% (9/10) of the normal human serum individuals evaluated for the low spike. Acceptable recovery (1 00 ± 20% recovery for High QC) was obtained in 100% (10/10) of the normal human serum individuals evaluated for the high spike.<br>Acceptable recovery (100 ± 25% for the Low QC) was obtained in 100% (12/12) of the cancer individual human | | Yes |
| **Interference & specificity** | Interference with tremelimumab tested. There was no evidence of interference in the presence of up to 20 µg/mL tremelimumab in 5% human serum (equivalent to 400 µg/mL in undiluted matrix) | | Yes |
| **Hemolysis effect** | Not applicable | | Yes |
| **Lipemic effect** | Not applicable | | Yes |

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| **Dilution linearity & hook effect** | To assess the dilutional linearity of durvalumab in human serum, the durvalumab stock standard was spiked into normal human serum pool at a concentration of 160,000 ng/mL followed by the minimum required dilution in assay buffer to 8,000 ng/mL. The 8,000 ng/mL linearity sample was then serially diluted in matrix diluent (5% human serum in assay buffer) down to 0.63 ng/mL in duplicate. Final concentrations to be plated were 8,000 ng/mL, 1000 ng/mL, 120.00 ng/mL, 60.00 ng/mL, 30.00 ng/mL, 10.00 ng/mL, 2.50 ng/mL, and 0.63 ng/mL. A linear response was observed for the dilutions with expected nominal concentrations within the range of quantitation. No hook effect was observed as both 8000 and 1000 ng/mL samples recovered above the limit of quantitation. | Yes |
| **Bench-top/process stability** | 24 hours in human serum at room temperature | Yes |
| **Freeze-Thaw stability** | 5 cycles at -70°C ± 10°C | Yes |
| **Long-term storage** | Durvalumab in human serum is stable for up to 732 days when stored at -70°C ± 10°C and for 735 days when stored at -20°C ± 5°C. | Yes |
| **Parallelism** | Not assessed | Yes |
| **Carry over** | Not assessed | Yes |
| **Method performance in study D419MC00004 (POSEIDON)** | | |
| **Assay passing rate** | 76 out of 98 (78%) | Yes |
| **Standard curve performance** | • Cumulative bias range: -1.0 to 7.2% (from LLOQ to ULOQ) [a]<br>• Cumulative precision: ≤ 19.0% CV (from LLOQ to ULOQ) | Yes |
| **QC performance** | • Cumulative bias range: -4.9 to 2.6% [b]<br>• Cumulative precision: ≤ 17.2% CV<br>• TE: ≤ 19.8% [c] | Yes |

| | | |
|---|---|---|
| **Method reproducibility** | Incurred sample reanalysis was not performed for this study | Yes |
| **Study sample analysis/ stability** | All standards, QCs, and study samples were analyzed within the established stability of 885 days at 70°C ± 10°C. | Yes |
| **Method performance in study D4190C00006 (Study 06)** | | |
| **Assay passing rate** | 98 out of 117 (84%) | Yes |
| **Standard curve performance** | • Cumulative bias range: -4.6 to 6.3% (from LLOQ to ULOQ) [a] – runs regressed using ALIS LIMS<br>• Cumulative precision: ≤ 6.0% CV (from LLOQ to ULOQ) – runs regressed using ALIS LIMS<br>• Cumulative bias range: -2.7 to 2.5% (from LLOQ to ULOQ) [a] – runs regressed using WATSON LIMS<br>• Cumulative precision: ≤ 11.2% CV (from LLOQ to ULOQ) – runs regressed using WATSON LIMS | Yes |
| **QC performance** | • Cumulative bias range: -3.6 to -0.4% [b] – runs regressed using ALIS LIMS<br>• Cumulative precision: ≤ 9.9% CV – runs regressed using ALIS LIMS<br>• TE: ≤ 13.5% [c] – runs regressed using ALIS LIMS<br>• Cumulative bias range: -13.2 to -6.7% – runs regressed using WATSON LIMS<br>• Cumulative precision: ≤ 2.3% CV – runs regressed using WATSON LIMS | Yes |
| **Method reproducibility** | Incurred sample reanalysis was not performed for this study | Yes |
| **Study sample analysis/ stability** | All standards, QCs, and study samples (except for 13 samples) were analyzed within the established stability of 885 days at 70°C ± 10°C. The 13 samples that exceeded the long-term stability were reported as Non-Reportable Result. | Yes |

**Table 59 Summary method 2 performance of a bioanalytical method to measure durvalumab in human serum**

| | |
|---|---|
| **Bioanalytical method validation report name, amendments, and hyperlinks** | Original validation:<br>Validation Report for the Determination of MEDI4736 in Human Serum by Quantitative ECLA.<br>Long-term stability from:<br>Addendum II to the Report Entitled "Validation Report for the Determination of MEDI4736 in Human Serum by Quantitative Electrochemiluminescent Assay (ECLA), (b) (4) Job Number: 183708"<br>Additional precision and accuracy tables from:<br>Addendum III to the Report Entitled "Validation Report for the Determination of MEDI4736 in Human Serum by Quantitative |
| **Method description** | This ECL immunoassay method utilized MSD technology designed to quantify durvalumab in human serum. Streptavidin Gold Multi Array 96-well MSD Plates were blocked with Block/Diluent Buffer for at approximately 1 hour at ambient temperature with non-vigorous shaking. After washing the plates, the working capture solution was added and incubated for 30 minutes ± 5 minutes with non-vigorous shaking at ambient temperature. Plates were washed and standards, controls, and samples were added to the wells. Plates were<br>incubated for 1 hour ± 10 minutes with non-vigorous shaking at ambient temperature. After a washing step, the working SulfoTag conjugate solution was added for 1 hour ± 10 minutes with non-vigorous shaking at ambient temperature. The plate was washed and a TPA-containing read buffer was added to the plate. The plate was read immediately. In the presence of TPA, ruthenium produces a chemiluminescent signal that is triggered when voltage is applied. Durvalumab concentrations were determined on a standard curve obtained by plotting RLUs versus concentration using a 4-parameter logistic curve-fitting program with $1/y^2$ weighting. The calibration |
| **Materials used for calibration curve &** | Durvalumab in 100% human serum at 25.0, 50.0, 75.0, 100, 150, 200, 300, 400, 600, 800, 1300, 1600, and 2200 ng/mL |
| **Validated assay range** | 50.0 ng/mL to 1600 ng/mL in 100% human serum |
| **Material used for QCs & concentration** | Durvalumab in 100% human serum at concentrations of 50.0 (LLOQ-QC), 100 (LQC), 400 (MQC), 1200 (HQC), and 1600 (ULOQ-QC) ng/mL |
| **Minimum required dilutions (MRDs)** | 1:20 |

| | | | |
|---|---|---|---|
| **Source & lot of reagents (LBA)** | Durvalumab (from MedImmune) Lot: WRS4736-1 AB<br>0470011-Biotin (labeled at (b) (4)) Lot: 16B014BI<br>Anti TM, clone A8-STAG (labeled at (b) (4)) Lot: 16B016RU | | |
| **Regression model & weighting** | Durvalumab concentrations are determined on a standard curve obtained by plotting RLUs versus concentration using a 4-parameter logistic curve-fitting program with $1/Y^2$ weighting | | |
| **Validation parameters** | **Method validation summary** | | **Accetapability** |
| **Standard calibration curve performance during accuracy & precision** | Number of standard calibrators from LLOQ to | 11 | Yes |
| | Cumulative accuracy (%bias) from LLOQ to ULOQ | -3.80 to | |
| | Cumulative precision (%CV) from LLOQ to ULOQ | ≤ 5.69% | |
| **QCs performance during accuracy & precision** | Cumulative accuracy (%bias) in 5 QCs<br>QCs: 50.0 (LLOQ-QC), 100 (LQC), 400 (MQC), 1200 (HQC), and 1600 (ULOQ-QC) ng/mL<br>Quick Plex<br>Secor Imager | -4.50 to 17.8% | Yes |
| | Inter-batch %CV<br>QCs: 50.0 (LLOQ-QC), 100 (LQC), 400 (MQC), 1200 (HQC), and 1600 (ULOQ-QC) ng/mL<br>Quick Plex<br>Sector Imager | ≤ 10.6% | |
| | Total Error (TE)<br>QCs: 50.0 (LLOQ-QC), 100 (LQC), 400 (MQC), 1200 (HQC), and 1600 (ULOQ-QC) ng/mL<br>Quick Plex<br>Sector Imager | ≤ 29.4% | Yes |

| | | |
|---|---|---|
| **Selectivity & matrix effect** | To assess possible matrix effects, 20 individual lots of blank diseased state (cancer) human serum were spiked with durvalumab (prepared in 100% human serum and diluted to the minimum dilution) at a concentration of 80.0 ng/mL (in 100% human serum). Matrix effects samples were analyzed in replicates of one (2 wells) on Plates 14-16. A blank of each individual lot was also analyzed in replicates of one. All 20 individual lots met the following criteria: the observed mean concentration of the QC sample must have been within ± 25.0% of the nominal value with precision ≤ 25.0%. Matrix effects were acceptable as at least 80% of the lots tested met the above criteria. The blank lots met the following acceptance criteria: the observed mean concentration of the blank matrix must have been < LLOQ in at least 80% of the lots tested. | |
| **Interference & specificity** | Not assessed | Yes |
| **Hemolysis effect** | Not applicable | Yes |
| **Lipemic effect** | Not applicable | Yes |
| **Dilution linearity & hook effect** | The maximum validated dilution integrity is 1:10,000 (overall dilution of 1:200,000) as the QC samples met the following criteria: the observed concentrations of at least two thirds of the within-range QC samples should not have deviated by more than ± 20.0% of the nominal value with precision ≤ 20.0%. | Yes |
| **Bench-top/process stability** | 24 hours in human serum at ambient temperature<br>72 hours in human serum at 2°C to 8°C<br><br>Processed sample stability: Durvalumab is stable in 1:20 diluted human serum for at least 27.5 hours at 2°C to 8°C | Yes |
| **Freeze-Thaw stability** | 6 cycles in 100% human serum at -80°C/ambient temperature | Yes |
| **Long-term storage** | Durvalumab is stable in human serum for 721 days at -80°C and at -20°C | Yes |
| **Parallelism** | Not assessed | Yes |

| | | |
|---|---|---|
| **Carry over** | Not assessed | Yes |
| **Method performance in study D419CC00002 (HIMALAYA)** | | |
| **Assay passing rate** | 94%, including incurred sample reanalysis | Yes |
| Standard curve performance | • Cumulative bias range: -5.93 to 6.03%<br>• Cumulative precision: ≤ 3.87% CV | Yes |
| QC performance | Cumulative bias range: 2.49 to 11.47%<br>Cumulative precision: ≤ 8.21% CV<br>• TE: ≤ 19.68% a | Yes |
| Method reproducibility | Incurred sample reanalysis was performed in 6.57% (215) of study samples and 96.7 % of samples met the pre-specified criteria. | Yes |
| Study sample analysis/ stability | All standards, QCs, and remaining study samples were analyzed within the established stability of 885 days at 70°C ± 10°C. | Yes |

[a] Total error (TE) calculated using the equation of %TE= %CV + |%RE|.

| | | |
|---|---|---|
| **Method performance in study D419MC00004 (POSEIDON)** | | |
| **Assay passing rate** | 76 out of 98 (78%) | Yes |
| **Standard curve performance** | • Cumulative bias range: -1.0 to 7.2% (from LLOQ to ULOQ) [a]<br>• Cumulative precision: ≤ 19.0% CV (from LLOQ to ULOQ) | Yes |
| **QC performance** | • Cumulative bias range: -4.9 to 2.6% [b]<br>• Cumulative precision: ≤ 17.2% CV<br>• TE: ≤ 19.8% [c] | Yes |
| **Method reproducibility** | Incurred sample reanalysis was not performed for this study | Yes |

| | | |
|---|---|---|
| **Study sample analysis/ stability** | All standards, QCs, and study samples were analyzed within the established stability of 885 days at 70°C ± 10°C. | Yes |
| **Method performance in study D4190C00006 (Study 06)** | | |
| **Assay passing rate** | 98 out of 117 (84%) | Yes |
| **Standard curve performance** | • Cumulative bias range: -4.6 to 6.3% (from LLOQ to ULOQ) [a] – runs regressed using ALIS LIMS<br>• Cumulative precision: ≤ 6.0% CV (from LLOQ to ULOQ) – runs regressed using ALIS LIMS<br>• Cumulative bias range: -2.7 to 2.5% (from LLOQ to ULOQ) [a] – runs regressed using WATSON LIMS<br>• Cumulative precision: ≤ 11.2% CV (from LLOQ to ULOQ) – runs regressed using WATSON LIMS | Yes |
| **QC performance** | • Cumulative bias range: -3.6 to -0.4% [b] – runs regressed using ALIS LIMS<br>• Cumulative precision: ≤ 9.9% CV – runs regressed using ALIS LIMS<br>• TE: ≤ 13.5% [c] – runs regressed using ALIS LIMS<br>• Cumulative bias range: -13.2 to -6.7% – runs regressed using WATSON LIMS<br>• Cumulative precision: ≤ 2.3% CV – runs regressed using WATSON LIMS | Yes |
| **Method reproducibility** | Incurred sample reanalysis was not performed for this study | Yes |
| **Study sample analysis/ stability** | All standards, QCs, and study samples (except for 13 samples) were analyzed within the established stability of 885 days at 70°C ± 10°C. The 13 samples that exceeded the long-term stability were reported as Non-Reportable Result. | Yes |
| **Method performance in study D4190C00010 (Study 10)** | | |
| **Assay passing rate** | 61 out of 72 (85%) | Yes |
| **Standard curve performance** | • Cumulative bias range: -5.7 to 7.3% (from LLOQ to ULOQ) [a] – runs regressed using ALIS LIMS<br>• Cumulative precision: ≤ 4.6% CV (from LLOQ to ULOQ) – runs regressed using ALIS LIMS<br>• Cumulative bias range: -6.4 to 11.6% (from LLOQ to ULOQ) [a] – runs regressed using WATSON LIMS<br>• Cumulative precision: ≤ 12.6% CV (from LLOQ to ULOQ) – runs regressed using WATSON LIMS | Yes |

| | | |
|---|---|---|
| **QC performance** | Cumulative bias range: -6.0 to -1.3% [b] – runs regressed using ALIS LIMS<br>Cumulative precision: ≤ 11.0% CV – runs regressed using ALIS LIMS<br>TE: ≤ 17.0% [c] – runs regressed using ALIS LIMS<br>Cumulative bias range: -5.8 to 12.9% [b] – runs regressed using WATSON LIMS<br>Cumulative precision: ≤ 4.9% CV – runs regressed using | Yes |
| **Method reproducibility** | Incurred sample reanalysis was not performed for this study | Yes |
| **Study sample analysis/ stability** | All standards, QCs, and study samples (except for 2 samples) were analyzed within the established stability of 885 days at 70°C ± 10°C. The 2 samples that exceeded the long-term stability were reported as Non-Reportable Result. | Yes |
| **Method performance in study D419MC00004 (POSEIDON)** | | |
| **Assay passing rate** | 76 out of 98 (78%) | Yes |
| **Standard curve performance** | • Cumulative bias range: -1.0 to 7.2% (from LLOQ to ULOQ) [a]<br>• Cumulative precision: ≤ 19.0% CV (from LLOQ to ULOQ) | Yes |
| **QC performance** | • Cumulative bias range: -4.9 to 2.6% [b]<br>• Cumulative precision: ≤ 17.2% CV<br>• TE: ≤ 19.8% [c] | Yes |
| **Method reproducibility** | Incurred sample reanalysis was not performed for this study | Yes |
| **Study sample analysis/ stability** | All standards, QCs, and study samples were analyzed within the established stability of 885 days at 70°C ± 10°C. | Yes |
| **Method performance in study D4190C00006 (Study 06)** | | |
| **Assay passing rate** | 98 out of 117 (84%) | Yes |

| | | |
|---|---|---|
| **Standard curve performance** | • Cumulative bias range: -4.6 to 6.3% (from LLOQ to ULOQ) [a] – runs regressed using ALIS LIMS<br>• Cumulative precision: ≤ 6.0% CV (from LLOQ to ULOQ) – runs regressed using ALIS LIMS<br>• Cumulative bias range: -2.7 to 2.5% (from LLOQ to ULOQ) [a] – runs regressed using WATSON LIMS<br>• Cumulative precision: ≤ 11.2% CV (from LLOQ to ULOQ) – runs regressed using WATSON LIMS | Yes |
| **QC performance** | • Cumulative bias range: -3.6 to -0.4% [b] – runs regressed using ALIS LIMS<br>• Cumulative precision: ≤ 9.9% CV – runs regressed using ALIS LIMS<br>• TE: ≤ 13.5% [c] – runs regressed using ALIS LIMS<br>• Cumulative bias range: -13.2 to -6.7% – runs regressed using WATSON LIMS<br>• Cumulative precision: ≤ 2.3% CV – runs regressed using WATSON LIMS | Yes |
| **Method reproducibility** | Incurred sample reanalysis was not performed for this study | Yes |
| **Study sample analysis/ stability** | All standards, QCs, and study samples (except for 13 samples) were analyzed within the established stability of 885 days at 70°C ± 10°C. The 13 samples that exceeded the long-term stability were reported as Non-Reportable Result. | Yes |
| **Method performance in study D4190C00010 (Study 10)** | | |
| **Assay passing rate** | 61 out of 72 (85%) | Yes |
| **Standard curve performance** | • Cumulative bias range: -5.7 to 7.3% (from LLOQ to ULOQ) [a] – runs regressed using ALIS LIMS<br>• Cumulative precision: ≤ 4.6% CV (from LLOQ to ULOQ) – runs regressed using ALIS LIMS<br>• Cumulative bias range: -6.4 to 11.6% (from LLOQ to ULOQ) [a] – runs regressed using WATSON LIMS<br>• Cumulative precision: ≤ 12.6% CV (from LLOQ to ULOQ) – runs regressed using WATSON LIMS | Yes |

| | | |
|---|---|---|
| **QC performance** | Cumulative bias range: -6.0 to -1.3% [b] – runs regressed using ALIS LIMS<br>Cumulative precision: ≤ 11.0% CV – runs regressed using ALIS LIMS<br>TE: ≤ 17.0% [c] – runs regressed using ALIS LIMS<br>Cumulative bias range: -5.8 to 12.9% [b] – runs regressed using WATSON LIMS<br>Cumulative precision: ≤ 4.9% CV – runs regressed using | Yes |
| **Method reproducibility** | Incurred sample reanalysis was not performed for this study | Yes |
| **Study sample analysis/ stability** | All standards, QCs, and study samples (except for 2 samples) were analyzed within the established stability of 885 days at 70°C ± 10°C. The 2 samples that exceeded the long-term stability were reported as Non-Reportable Result. | Yes |

[a] Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ calculated from Table 3 and Table 4 of Report 6049, using the equation of (Observed Concentration – Nominal Concentration)/Nominal Concentration* 100%.
[b] Cumulative accuracy (%bias) in QCs calculated from Table 6 and Table 7 of Report 6049, using the equation of (Observed Concentration – Nominal Concentration)/Nominal Concentration* 100%.

## 19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
See each subsection within Section 8.2.

## Signatures

| DISCIPLINE | REVIEWER | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED |
|---|---|---|---|---|
| Clinical Reviewer | Timil Patel, M.D. | Division of Oncology 3 | Sections: 1.2, 1.3, 7, 8.2, 8.4, 9, 10, 11, 12 | **Select one:** ☒Authored ☐Approved |
| | **Signature:** Timil H. Patel -S Digitally signed by Timil H. Patel -S Date: 2022.09.26 20:40:01 -04'00' | | | |
| Clinical Team Leader | Jamie Brewer, M.D. | Division of Oncology 3 | Sections: All | **Select one:** ☒Authored ☒Approved |
| | **Signature:** Refer to final assessment aid electronic signature. | | | |
| Statistics Reviewer | Jiaxin Fan, Ph.D. | Division of Biometrics 5 | Sections: 1, 8.1, 8.3 | **Select one:** ☒Authored ☐Approved |
| | **Signature:** Jiaxin Fan -S (Affiliate) Digitally signed by Jiaxin Fan -S (Affiliate) Date: 2022.09.27 15:20:41 -04'00' | | | |
| Statistics Team Leader | Joyce Cheng, Ph.D. | Division of Biometrics 5 | Sections: 1, 8.1, 8.3 | **Select one:** ☒Authored ☒Approved |
| | **Signature:** Joyce Cheng -S Digitally signed by Joyce Cheng -S Date: 2022.09.26 14:27:28 -04'00' | | | |
| Supervisory Mathematical Statistician (OB) | Yuan-Li Shen, Dr.PH. | Division of Biometrics 5 | Sections: 1, 8.1, 8.3 | **Select one:** ☒Approved |
| | **Signature:** Yuan-li Shen -S Digitally signed by Yuan-li Shen -S Date: 2022.09.26 13:48:28 -04'00' | | | |
| Nonclinical Reviewer | Brian Christmas, Ph.D. | Division of Hematology, Oncology, Toxicology (DHOT) | Sections: 5 | **Select one:** ☒Authored ☐Approved |
| | **Signature:** Brian J. Christmas -S Digitally signed by Brian J. Christmas -S Date: 2022.09.27 16:00:30 -04'00' | | | |

| DISCIPLINE | REVIEWER | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED |
|---|---|---|---|---|
| Nonclinical Reviewer | Melissa Pegues, Ph.D. | Division of Hematology, Oncology, Toxicology (DHOT) | Sections: 5 | **Select one:** ☒Authored ☐Approved |
| | **Signature:** Melissa A. Pegues -S Digitally signed by Melissa A. Pegues -S Date: 2022.09.27 16:09:09 -04'00' | | | |
| Nonclinical Team Leader | Matthew Thompson, Ph.D., M.P.H. | Division of Hematology, Oncology, Toxicology (DHOT) | Sections: 5 | **Select one:** ☒Authored ☒Approved |
| | **Signature:** Matthew D. Thompson -S Digitally signed by Matthew D. Thompson -S Date: 2022.09.28 07:56:31 -04'00' | | | |
| Nonclinical Division Director | John Leighton, Ph.D., DABT | Division of Hematology, Oncology, Toxicology (DHOT) | Sections: 5 | **Select one:** ☒Authored ☒Approved |
| | **Signature:** John K. Leighton -S Digitally signed by John K. Leighton -S Date: 2022.09.26 13:53:10 -04'00' | | | |
| Clinical Pharmacology Reviewer | Yue Xiang, Ph.D. | Division of Cancer Pharmacology II | Sections: 6, 19.4 | **Select one:** ☒Authored ☐Approved |
| | **Signature:** Yue Xiang -S Digitally signed by Yue Xiang -S DN: c US o U S Government ou HHS ou FDA ou People cn Yue Xiang -S 0 9 2342 19200300 100 1 1 2002587662 Date: 2022 09 27 17:35:37 04 00 | | | |
| Clinical Pharmacology Team Leader | Hong Zhao, Ph.D. | Division of Cancer Pharmacology II | Sections: 6, 19.4 | **Select one:** ☒Authored ☒Approved |
| | **Signature:** Hong Zhao -S Digitally signed by Hong Zhao -S Date: 2022.09.26 15:28:47 -04'00' | | | |
| Pharmacometrics Reviewer | Yuzhuo Pan, Ph.D. | Division of Pharmacometrics | Sections: 6, 19.4 | **Select one:** ☒Authored ☐Approved |
| | **Signature:** Yuzhuo Pan -S Digitally signed by Yuzhuo Pan -S Date: 2022.09.27 20:00:20 -04'00' | | | |
| Pharmacometrics Team Leader | Jiang Liu, Ph.D. | Division of Pharmacometrics | Sections: 6, 19.4 | **Select one:** ☐Authored ☒Approved |
| | **Signature:** Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2022.09.27 17:44:23 -04'00' | | | |

| DISCIPLINE | REVIEWER | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED |
|---|---|---|---|---|
| Clinical Pharmacology Division Director | Nam Atiqur Rahman, Ph.D. | Division of Cancer Pharmacology II | Sections: 6; 19.4 | **Select one:** ☒Approved |
| | **Signature:** Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2022.09.26 12:54:47 -04'00' | | | |
| Associate Director for Labeling (ADL) | Doris Auth, PharmD | Office of Oncologic Diseases | Sections: 11, Prescribing Information, Patient Information | **Select one:** ☒Authored ☒Approved |
| | **Signature:** Doris Auth -S Digitally signed by Doris Auth -S Date: 2022.09.28 09:40:12 -04'00' | | | |
| Cross-Disciplinary Team Leader (CDTL) | Jamie Brewer, M.D. | Division of Oncology 3 | Sections: All | **Select one:** ☒Approved |
| | **Signature:** Refer to final assessment aid electronic signature. | | | |
| Deputy Division Director | 'Lola Fashoyin-Aje, M.D., M.P.H. | Division of Oncology 3 | Sections: All | **Select one:** ☒Approved |
| | **Signature:** Refer to final assessment aid electronic signature. | | | |

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**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.**

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/s/

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JAMIE R BREWER
10/21/2022 03:27:26 PM

STEVEN J LEMERY on behalf of IBILOLA A FASHOYIN-AJE
10/21/2022 03:32:09 PM

PAUL G KLUETZ
10/21/2022 03:38:14 PM