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RESEARCH**

APPLICATION NUMBER:

761038Orig1s000

MULTI-DISCIPLINE REVIEW
Summary / Clinical / Non-Clinical

BLA Multi-disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761038
Priority or Standard	Priority
Submit Date(s)	February 24, 2016
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Division/Office	DOP2/OHOP
Review Completion Date	
Established Name	Olaratumab
(Proposed) Trade Name	LARTRUVO
Pharmacologic Class	Platelet-derived growth factor receptor alpha (PDGFR- α) blocking antibody
Code name	IMC-3G3, LY3012207
Applicant	Eli Lilly and Company
Formulation(s)	Injection
Dosing Regimen	15 mg/kg on days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity
Applicant Proposed Indication(s)/Population(s)	Indicated in combination with doxorubicin, for the treatment of advanced soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery.
Recommendation on Regulatory Action	Accelerated approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated in combination with doxorubicin, for the treatment of adult patients with STS with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.

Table of Contents

Reviewers of Multi-Disciplinary Review and Evaluation	9
Additional Reviewers of Application.....	9
Glossary.....	11
1 Executive Summary	13
1.1 Product Introduction.....	13
1.2 Conclusions on the Substantial Evidence of Effectiveness	13
1.3 Benefit-Risk Assessment	14
2 Therapeutic Context.....	20
2.1 Analysis of Condition.....	20
2.2 Analysis of Current Treatment Options	20
3 Regulatory Background	22
3.1 U.S. Regulatory Actions and Marketing History.....	22
3.2 Summary of Presubmission/Submission Regulatory Activity	22
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	26
4.1 Office of Scientific Investigations (OSI)	26
4.2 Product Quality	26
4.3 Clinical Microbiology	26
4.4 Devices and Companion Diagnostic Issues	27
5 Nonclinical Pharmacology/Toxicology.....	28
5.1 Executive Summary	28
5.2 Referenced NDAs, BLAs, DMFs.....	30
5.3 Pharmacology.....	31
5.4 ADME/PK	41
5.5 Toxicology.....	43
5.5.1 General Toxicology.....	43
5.5.2 Genetic Toxicology.....	45
5.5.3 Carcinogenicity.....	45
5.5.4 Reproductive and Developmental Toxicology	45

5.5.5	Other Toxicology Studies	50
6	Clinical Pharmacology.....	52
6.1	Executive Summary	52
6.2	Summary of Clinical Pharmacology Assessment.....	53
6.2.1	Pharmacology and Clinical Pharmacokinetics	53
6.2.2	General Dosing and Therapeutic Individualization.....	54
6.3	Comprehensive Clinical Pharmacology Review	54
6.3.1	General Pharmacology and Pharmacokinetic Characteristics.....	54
6.3.2	Clinical Pharmacology Questions.....	56
7	Statistical and Clinical and Evaluation	69
7.1	Sources of Clinical Data and Review Strategy	69
7.1.1	Clinical trials included in the BLA submission	69
7.1.2	Table of Clinical Studies	70
7.1.3	Review Strategy	74
7.2	Review of Relevant Individual Trials Used to Support Efficacy.....	75
7.2.1	Trial JGDG (Protocol version 6).....	75
7.2.2	Study Results.....	87
7.3	Review of Safety	109
7.3.1	Safety Review Approach	109
7.3.2	Review of the Safety Database	110
7.3.3	Adequacy of Applicant’s Clinical Safety Assessments	112
7.3.4	Safety Results.....	114
7.3.5	Analysis of Submission-Specific Safety Issues.....	139
7.3.6	Safety Analyses by Demographic Subgroups.....	151
7.3.7	Specific Safety Studies/Clinical Trials.....	153
7.3.8	Additional Safety Explorations.....	153
7.3.9	Safety in the Postmarket Setting	154
7.3.10	Integrated Assessment of Safety.....	154
	SUMMARY AND CONCLUSIONS	156
7.4	Statistical Issues	156
7.5	Conclusions and Recommendations	156

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

8	Advisory Committee Meeting and Other External Consultations.....	159
9	Pediatrics	160
10	Labeling Recommendations	161
10.1	Prescribing Information.....	161
10.2	Patient Labeling	170
11	Risk Evaluation and Mitigation Strategies (REMS)	171
12	Postmarketing Requirements and Commitments.....	172
13	Appendices	173
13.1	Preferred Terms.....	173
13.2	References	174
13.3	Financial Disclosure	177
13.4	Nonclinical Pharmacology/Toxicology.....	177
13.5	OCP Appendices (Technical documents supporting OCP recommendations)	178
14	Division Director (DHOT)	185
15	Division Director (OCP)	186
16	Division Director (OB)	187
17	Division Director (Clinical)	188
18	Office Director (or designated signatory authority).....	189

Table of Tables

Table 1: FDA-Approved and Commonly Used Therapies for the Treatment of Patients with Advanced Soft Tissue Sarcoma	20
Table 2: Olaratumab Concentrations Determined Using the Original and Modified ELISA Methods.....	55
Table 3: Single Dose and Multiple Dose PK Parameters of Olaratumab in Combination with Doxorubicin in Cancer Patients (Cycle 1).....	56
Table 4: Steady-State PK Parameters of Olaratumab in Combination with Doxorubicin in Cancer Patients (Cycle 3)	56
Table 5: Immunogenicity Results for Olaratumab-Treated Patients.....	61
Table 6: Relationship between Immunogenicity and IRRs	64
Table 7: IHC PDGFR α Status by Histology; Trial JGDG Population assessed by Assay 2 (N=111). 65	
Table 8: Progression Free Survival and Overall Survival by IHC PDGFR α Status and Treatment Arms; Trial JGDG Population Assessed by Assay 2 (N=111)	66
Table 9: Comparative Analysis of Doxorubicin PK Parameters on Day 1 (Without Olaratumab) and Day 10 (With Olaratumab).....	67
Table 10: Clinical Trials Included in the BLA	70
Table 11 PFS Definition and Censoring Rules	86
Table 12: Demographics and Baseline Disease Characteristics.....	89
Table 13: Stratification Factors per IVRS, CRF, and Independent Review	90
Table 14: Detailed Histology by Independent Review of Pathology Forms	92
Table 15: Previous Anticancer Therapy	93
Table 16: Prior Chemotherapy in $\geq 3\%$ of Patients in Either Arm	94
Table 17: Analysis populations, Trial JGDG.....	94
Table 18: Reason for Screen failures in the Phase 2 Portion.....	95
Table 19: Inclusion/Exclusion Criteria Not Met by Patients Enrolled, Not Randomized.....	96
Table 20: Summary of Patient Disposition by Treatment Discontinuation	97
Table 21: Major Protocol Deviations	98
Table 22: Post-study Therapy in $\geq 3\%$ of Patients in Either Arm	99
Table 23: PFS Analyses, Per INV assessment	101
Table 24: PFS Analyses, Per BICR assessment	102
Table 25: Discordance in determination of PFS events or time of censoring between INV and BICR	104
Table 26: OS Analyses	104
Table 27: OS Sensitivity Analyses.....	105
Table 28: ORR Results Based on the INV Measurements.....	106
Table 29: ORR Results Based on the BICR Measurements	107
Table 30: OS Subgroup Analyses.....	107
Table 31: Exposure to Olaratumab, Trial JGDG	110
Table 32: Exposure to Doxorubicin, Trial JGDG	111
Table 33 Summary of Deaths, Trial JGDG	114

Table 34 Treatment-Emergent Adverse Events with an Outcome of Death by System Organ Class and Preferred Terms, Trial JGDG	115
Table 35 Probable cause of Death Occurring within 30 Days of Last Dose of Study Drug, Trial JGDG.....	115
Table 36 Serious Adverse Events by Preferred Term, Trial JGDG.....	119
Table 37 Adverse Events Leading to Discontinuation of Study Therapy, Trial JGDG	121
Table 38 Summary of Olaratumab and Doxorubicin Dose and Administration Modifications, Trial JGDG.....	124
Table 39 Summary of Adverse Events Leading to Olaratumab Dose Reductions, Trial JGDG ...	125
Table 40 Summary of Adverse Events Leading to Doxorubicin Dose Reductions, Trial JGDG ...	125
Table 41 Summary of Adverse Events Leading to Olaratumab Dose Delays, Trial JGDG	126
Table 42 Summary of Adverse Events Leading to Doxorubicin Dose Delays, Trial JGDG.....	126
Table 43 Summary of Overall TEAEs and Consolidated TEAE Categories (Grade 3 and Grade ≥4, Including AESIs), Trial JGDG	127
Table 44 Summary of Overall TEAEs and Consolidated TEAE Categories (Any Grade, Including AESIs), Trial JGDG	129
Table 45 Adverse Events by Narrow Scope MedDRA SMQ, Trial JGDG	132
Table 46 Most Common Treatment Emergent Adverse Events by MedDRA System Organ Class, Trial JGDG.....	134
Table 47 Most Common Treatment Emergent Adverse Events by MedDRA High-Level Group Term, Trial JGDG	135
Table 48 Most Common Treatment Emergent Adverse Events by MedDRA High-Level Term, Trial JGDG.....	136
Table 49 Common Laboratory Test Result Abnormalities ¹ , Trial JGDG.....	137
Table 50 Adverse Events of Special Interest, Infusion-Related Reaction, Trial JGDG	140
Table 51 Infusion-Related Reactions Interventions, Trial JGDG	140
Table 52 Infusion-related reactions (IRR) and Rate of IRR Recurrence in Olaratumab-treated Patients, Trial JGDG.....	141
Table 53 Premedication Administered to Patients who Experienced an IRR.....	142
Table 54 Infusion-Related Reactions, ISS ¹	143
Table 55 Adverse Events of Special Interest, Cardiac Dysfunction, Trial JGDG	144
Table 56 Summary of Abnormal LVEF Results, Trial JGDG	145
Table 57 Summary of Treatment-Emergent Musculoskeletal Pain (Consolidated Term), Trial JGDG.....	147
Table 58 Musculoskeletal Pain (Consolidated Term), ISS Database.....	149
Table 59 Treatment-Emergent Severe Infections and Neutropenic Infection, Trial JGDG	150
Table 60 Neutropenia by Laboratory Testing, ISS Database	151
Table 61 Comparison of Treatment-Emergent Adverse Events by Age, Trial JGDG	152
Table 62 Comparison of Treatment-Emergent Adverse Events by Gender, Trial JGDG.....	152
Table 63 Comparison of Treatment-Emergent Adverse Events by Race, Trial JGDG	153
Table 64 High-level summary of Adverse Events, Trial JGDG.....	154
Table 65 Preferred Terms for Infusion-Related Reaction, Trial JGDG	173
Table 66 Preferred Terms Cardiac Dysfunction, Trial JGDG	173

Table 67: Demographics at Study Entry for Patients Included in the Pharmacokinetic Analysis	178
Table 68: Pharmacokinetic Parameters in the Base Population Model	179
Table 69: Bootstrap Parameter Estimates for the Final Population Model	180
Table 70: Parameter Estimates for the Overall Survival Model	182
Table 71: Parameter Estimates for the Progression Free Survival Model.....	183

Table of Figures

Figure 1: Effect of Olaratumab alone and in combination with Doxorubicin on In Vitro PDGFR- α Signaling in Human Stromal Cells	32
Figure 2: Effect of Olaratumab on PDGF-induced WS-1 Fibroblast Proliferation	32
Figure 3: Effect of Olaratumab on AKT and MAPK Phosphorylation in Sarcoma Cell Lines	33
Figure 4: Effect of Olaratumab on Proliferation and Anchorage-Independent Growth of Sarcoma Cells	34
Figure 5: Effect of Olaratumab on In Vitro CDC Activity	35
Figure 6: PDGF and PDGFR Expression in Human Cancer Cell Lines	35
Figure 7: Effect of Olaratumab on Human SKLMS-1 Xenografts in Nude Mice	37
Figure 8: Effect of Olaratumab on Phosphorylated PDGFR- α in Tumor Lysates 168 hours post-dose from Mice Bearing U-118MG Xenografts	38
Figure 9: Effect of Olaratumab on Phosphorylated AKT and MAPK in Mice Bearing U-118MG Xenografts	39
Figure 10: Effect of Olaratumab in Combination with Doxorubicin on Tumor Volume and Body Weight in SKLMS-1 Xenografts in Nude Mice	40
Figure 11: Effect of IMC-1E10 on Tumor Volume and Body Weight in A549 NSCLC Xenografts in Nude Mice	41
Figure 12: Predicted Effect of Olaratumab on the Hazard Ratio for Overall Survival	58
Figure 13: Relationship between Olaratumab Clearance and Covariates of Interest	59
Figure 14: Olaratumab Concentration-Time Profiles for Patients with Positive Vs. Negative Treatment-Emergent Anti-Olaratumab Antibodies in Trial JGDG	62
Figure 15: No Evident Relationship between Olaratumab Clearance and Treatment-Emergent Anti-Drug Antibody	63
Figure 16 Study Schema	76
Figure 17: K-M Curves for PFS per INV Assessment	102
Figure 18: K-M Curves for PFS per BICR Assessment	103
Figure 19: K-M Curves for OS	105
Figure 20: Goodness-of-fit Plot for the Olaratumab Final Model	180
Figure 21: Visual Predictive Check of the Final Olaratumab Population Pharmacokinetic Model	181
Figure 22: Observed vs. Predicted Overall Survival in Study JGDG	182
Figure 23: Observed vs. Predicted Progression-free Survival in Study JGDG	183

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Leah Her, M.S., P.M.P.
Nonclinical Reviewer	Emily F. Wearne, Ph.D.
Nonclinical Team Leader	Whitney S. Helms, Ph.D.
Office of Clinical Pharmacology Reviewer(s)	Ruby Leong, Pharm.D./Fang Li, Ph.D. (pharmacometrics)/ Rosane Charlab Orbach, Ph.D. (genomics)
Office of Clinical Pharmacology Team Leader(s)	Hong Zhao, Ph.D./Jingyu (Jerry) Yu, Ph.D./Michael Pacanowski, Pharm.D., M.P.H.
Associate Director for Labeling	Jennie Chang, Pharm.D.
Clinical Reviewer	Meredith K. Chuk, M.D. (efficacy) Leslie Doros, M.D. (safety)
Clinical Team Leader	Marc R. Theoret, M.D.
Statistical Reviewer	Huanyu (Jade) Chen, Ph.D.
Statistical Team Leader	Kun He, Ph.D.
Cross-Disciplinary Team Leader	Marc R. Theoret, M.D.
Division Director (DHOT)	John Leighton, Ph.D.
Division Director (OCP)	Nam Atiqur Rahman, Ph.D.
Division Director (OB)	Rajeshwari Sridhara, Ph.D.
Division Director (OHOP)	Patricia Keegan, M.D.
Office Director (or designated signatory authority)	Richard Pazdur, M.D.

Additional Reviewers of Application

OPQ	Chikaka Torigoe, Ph.D./Rashmi Rawat, Ph.D. (Team Leader)
Microbiology	Monica (Markovski) Commerford, Ph.D. (Drug Substance)/ Patricia Hughes (Team Leader) Natalia Pripuzova, Ph.D. (Drug Product)/Colleen Thomas, Ph.D. (Team Leader)
Facilities	Ruth Moore, Ph.D./Zhihao Qiu, Ph.D. (Team Leader)
OPDP	Nazia Fatima, Pharm.D., M.B.A., R.A.C./Jessica Cleck Derenick, Ph.D. (Team Leader)
OSI	Lauren Iacono-Connor, Ph.D./Susan Thompson, M.D. (Team Leader)
OSE/DMEPA	Sarah Thomas, Pharm.D./Chi-Ming Tu, Pharm.D. (Team Leader)
OSE/DRISK	Mei-Yean Chen, Pharm.D./Naomi Redd, Pharm.D. (Team Leader)
DPMH	Leyla Sahin, M.D./Tamara Johnson, M.D., M.S. (Team Leader)

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

OPQ Labeling	Jibril Abdus-Samad, Pharm.D.

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DMPH= Division of Pediatric and Maternal Health

Glossary

ADCC	antibody-dependent cellular cytotoxicity
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BICR	blinded independent central review
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDC	complement-dependent cytotoxicity
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CI	confidence interval
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
DHOT	Division of Hematology Oncology Toxicology
DoR	duration of response
DVT	deep vein thrombosis
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	good clinical practice
HR	hazard ratio
ICH	International Conference on Harmonization
IHC	immunohistochemistry
IND	Investigational New Drug
INV	investigator
I.P.	intraperitoneal
ISR	incurred sample reanalysis
ISS	integrated summary of safety
ITT	intent to treat
I.V.	intravenous
IVRS	interactive voice response system

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

KM	Kaplan-Meier
LVEF	left ventricular ejection fraction
MAED	MedDRA-based Adverse Event Diagnostics tool
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MUGA	multigated acquisition
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NME	new molecular entity
OBf	O'Brien-Fleming
OPQ	Office of Pharmaceutical Quality
OR	odds ratio
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PE	pulmonary embolism
PK	pharmacokinetics
PFS	progression-free survival
PMR	postmarketing requirement
PTT	partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	Risk Evaluation and Mitigation Strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SMQ	standardized MedDRA queries
SOC	System Organ Class
SPR	surface plasmon resonance
STS	soft tissue sarcoma
TEAE	treatment emergent adverse event
ULN	upper limit of normal

1 Executive Summary Product Introduction

Eli Lilly and Company (Lilly) submitted BLA 761038 for olaratumab (Lartruvo), a new molecular entity (NME), for use in combination with doxorubicin for the treatment of advanced soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery. Olaratumab is a human IgG1 monoclonal antibody that blocks platelet-derived growth factor receptor (PDGFR) alpha, a type III receptor tyrosine kinase expressed on cells of mesenchymal origin that is activated by the ligands platelet-derived growth factor (PDGF)-AA, -AB, -BB, and -CC. The dosing regimen of olaratumab is 15 mg/kg on days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The application for olaratumab meets the statutory standards for marketing approval under 21 CFR 601, subpart E, with consideration of the principles described in 21 CFR 312, subpart E, for the following indication:

in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.

The primary trial supporting approval, Trial JGDG, is a multicenter, open-label, randomized (1:1), active-controlled trial comparing olaratumab plus doxorubicin to single-agent doxorubicin chemotherapy in patients with advanced STS who have not previously received an anthracycline. Trial JGDG met its primary endpoint based on the pre-specified, adjusted significance level of 0.1999 (two-sided). Progression-free survival (PFS) as assessed by the investigator was improved with an increase in median PFS from 4.1 months (95% CI: 2.8, 5.4) in the single-agent doxorubicin arm (n=67 patients) to 6.6 months (95% CI: 4.1, 8.3) in the olaratumab plus doxorubicin arm (n=66 patients) with a stratified HR of 0.67 (95% CI: 0.44, 1.02; two-sided p-value of 0.06). While designed as an activity-estimating trial with a PFS primary endpoint, Trial JGDG demonstrated a clinically meaningful and statistically significant improvement in overall survival with addition of olaratumab treatment to standard doxorubicin chemotherapy; the median OS was 26.5 months on the olaratumab plus doxorubicin arm (95% confidence interval [CI]: 20.9, 31.7 months) compared to 14.7 months on the single-agent doxorubicin arm (95% CI: 9.2, 17.1 months) with an unstratified hazard ratio (HR) of 0.52 (95% CI: 0.34, 0.79; p-value <0.05). Based on the statistical and clinical considerations of this application, there is greater uncertainty surrounding the magnitude of treatment effects of olaratumab in soft tissue sarcoma, and the treatment effects of olaratumab in any one histologic subtype of STS are uncertain (refer to Sections 7.2, 7.4, and 7.5 of the review). Consistent with the principles described in 21 CFR 312.80, greater uncertainty of the treatment effects is acceptable for drugs intended to treat serious and life-threatening illnesses. A confirmatory trial has completely enrolled and is ongoing to verify and describe the clinical benefit of olaratumab in the indicated population.

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Olaratumab is recommended for approval under the accelerated approval regulations and is indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.

Soft tissue sarcoma comprises a heterogeneous group of rare cancers arising predominantly in mesenchymally-derived tissues with 12,310 new cases and 4,990 deaths estimated to occur in the U.S. in 2016. Patients who do not have curative options with surgery or radiation have an extremely poor prognosis with an estimated median survival time of approximately 1 year. Doxorubicin is the only FDA-approved drug for first-line therapy of STS and demonstrates objective response rates between 10 to 25%. While the chemosensitivity among different histologic subtypes of STS varies widely, doxorubicin is a standard systemic treatment option for many patients with STS and advanced disease. Standard chemotherapeutics when added to doxorubicin have not demonstrated an improvement in overall survival.

The safety and efficacy of olaratumab was evaluated in the activity-estimating portion (Phase 2) of Trial JGDG, a multicenter, open-label trial that randomized (1:1) patients with advanced STS who had not previously received an anthracycline to receive doxorubicin with or without olaratumab. Randomization stratification factors through a dynamic minimization method were PDGFR- α expression (positive vs. negative), number of previous lines of treatment (0 vs. 1 or more), histologic subtype of STS (leiomyosarcoma vs. synovial sarcoma vs. all others), and Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs. 2). All patients received doxorubicin 75 mg/m² intravenously on Day 1 of each 21-day cycle for a maximum of eight cycles and were permitted to receive dexrazoxane prior to doxorubicin in cycles five to eight. Olaratumab was administered at a dose of 15 mg/kg as an intravenous infusion on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity. Patients on the single-agent doxorubicin arm with disease progression were offered single-agent olaratumab. The primary endpoint of Trial JGDG was PFS as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1. For the Phase 2 portion, assuming a hazard ratio of 0.67 with a median PFS of 2 months in the control arm and 3 months in the experimental arm, a total of 130 patients with 110 events for the final analysis were needed to provide 80% power at a two-sided alpha level of 20%. Overall survival (OS), a secondary endpoint, was to be tested at a two-sided alpha level of 5%. There was no pre-specified plan for controlling type I error in testing of the secondary efficacy endpoints.

Trial JGDG met its primary endpoint based on the pre-specified, adjusted significance level of 0.1999 (two-sided). The median PFS as assessed by the investigator was improved from 4.1 months (95% CI: 2.8, 5.4) in the single-agent doxorubicin arm (n=67 patients) to 6.6 months (95% CI: 4.1, 8.3) in the olaratumab plus doxorubicin arm (n=66 patients) with a stratified HR of 0.67 (95% CI: 0.44, 1.02; two-sided p-value of 0.06). Results of the analyses of PFS as assessed by blinded independent central review (BICR) were consistent with the investigator-assessed PFS results. Patients randomized to receive olaratumab plus doxorubicin demonstrated significantly improved OS compared to those randomized to receive single-agent doxorubicin with a median OS of 26.5 months (95% CI: 20.9, 31.7) vs. 14.7 months (95% CI: 9.2, 17.1), respectively, and an unstratified HR of 0.52 (95% CI: 0.34, 0.79; p-value <0.05). Confirmed objective response rates as assessed by BICR were low in both arms: 18.2% (95% CI: 9.8, 29.6) in the olaratumab plus doxorubicin arm and 7.5% (95% CI: 2.5, 16.6) in the single-agent doxorubicin arm.

The primary safety risks of olaratumab were evaluated in safety analyses of 485 patients with solid tumors who received olaratumab either as a single agent or in combination with chemotherapy. The major safety concern with olaratumab is the risk of serious infusion-related reactions (IRR). In Trial JGDG, the incidence of IRR was 12.6% (any grade), including 3.1% Grade 3 or 4 IRR, in the olaratumab plus doxorubicin arm, and 3.1% (any grade) with no Grade 3 or 4 IRR in the single-agent doxorubicin arm. One fatal IRR occurred in a patient who received single-agent olaratumab after disease progression on single-agent doxorubicin. While the majority of patients will receive corticosteroid as premedication on days when doxorubicin is also administered, the efficacy of a specific premedication regimen as primary or secondary prevention of IRR with olaratumab is unclear. In addition to the risk of IRR, the risk of certain severe adverse reactions associated with doxorubicin may be potentiated with administration of olaratumab. Most notably, the overall incidence of Grade 3 to 4 neutropenia was increased in the olaratumab plus doxorubicin arm (47%) vs. the single-agent doxorubicin group (37%). However, the risk of febrile neutropenia was similar in both treatment arms.

The risk-benefit assessment of olaratumab is favorable, when added to doxorubicin, for the treatment of patients with STS not amenable to curative treatment with radiotherapy or surgery and histologic subtypes for which doxorubicin treatment is appropriate. This patient population, with serious and life-threatening, rare cancers, has a high unmet medical need. In this population with few effective therapies, patients randomized to the olaratumab plus doxorubicin arm in Trial JGDG demonstrated a statistically significant and clinically meaningful improvement in overall survival compared with patients randomized to the single-agent doxorubicin arm, an improvement in median OS of 11.6 months with a 48% reduction (95% CI: 21%, 66%) in hazard of death. The major safety risks of olaratumab are toxicities that oncologists frequently manage, and are acceptable for a population with a serious and life-threatening condition in the context of the efficacy. While the heterogeneity with multiple histologic subtypes of STS in Trial JGDG is typical of clinical trials not limited by STS histologic subtype, treatment effects of olaratumab for any one histologic

subtype of STS are uncertain based on this heterogeneous population (with >25 different histologic subtypes) and small sample size. In addition, there is greater uncertainty regarding the treatment effects of olaratumab in STS based on the design and conduct of Trial JGDG as an activity-estimating trial with the attendant statistical and clinical limitations (refer to Sections 7.2, 7.4, and 7.5). Greater uncertainty of the treatment effects of olaratumab, in the context of the known safety profile, is acceptable based on the nature of incurable STS as a serious and life-threatening disease with limited treatment options. As a condition of the accelerated approval, the applicant must verify and describe the clinical benefit of olaratumab. A multicenter, double-blind, randomized controlled trial has completely enrolled and is ongoing to confirm the clinical benefit of olaratumab in combination with doxorubicin in patients with metastatic STS that is not amenable to curative treatment with surgery or radiation. FDA approval of olaratumab will represent a new therapeutic option with a novel mechanism of action for treatment of the indicated population.

BLA 761038 Multi-disciplinary Review and Evaluation
 LARTRUVO (Olaratumab)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• STS are a rare and heterogeneous group of solid tumors that include over 50 different histologic subtypes and represent 1% of all adult cancers. There is heterogeneity in the prognosis and chemosensitivity of different histologic subtypes. • While local control with primarily surgery and/or radiation is the mainstay for localized disease, 40 to 50% of patients with high-risk features will eventually develop metastatic disease. • Metastatic STS is a life-threatening condition with a median survival of approximately 11 to 15 months.	Advanced STS is generally incurable and represents a population with a high unmet medical need.
Current Treatment Options	• Doxorubicin is the only FDA-approved drug for first-line treatment of metastatic STS. In trials conducted in patients with STS, objective response rates with doxorubicin treatment range between 10 to 25%. • Non-FDA approved chemotherapeutics may be used as single agents, in combination with doxorubicin, or in combination with non-anthracycline chemotherapeutics. • Use of combination chemotherapy has not demonstrated improvement in overall survival in patients with STS.	Increases in objective response rates and progression-free survival have been demonstrated with combination chemotherapy. First-line treatments for advanced STS that demonstrate a clinically important improvement in survival would address a high unmet medical need.
Benefit	• Trial JGDG is an open-label, multicenter, randomized (1:1), active-controlled trial comparing the treatment effect of olaratumab plus doxorubicin to single-agent doxorubicin in 133 patients with advanced STS who have not previously received an anthracycline. The trial met its primary endpoint of an increase in investigator-assessed progression-free survival per RECIST v1.1 in the olaratumab plus doxorubicin arm based on the pre-specified statistical analysis plan. The median PFS was 6.6 months on the olaratumab plus doxorubicin arm and 4.1 months on the single-agent doxorubicin arm (HR of 0.67 [95% CI: 0.44, 1.02]; p=0.06).	Trial JGDG demonstrated a statistically significant and clinically meaningful improvement in overall survival with the addition of treatment with olaratumab to doxorubicin chemotherapy. Treatment effects of olaratumab for any one histologic subtype of STS are uncertain based on the small sample size and heterogeneity of the study population. In addition, there is greater uncertainty regarding the treatment effects of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Trial JGDG demonstrated a statistically significant increase in overall survival; the median OS was 26.5 months in the olaratumab plus doxorubicin arm vs. 14.7 months in the single-agent doxorubicin arm (unstratified HR of 0.52 [95% CI: 0.34, 0.79]; p-value <0.05). • Treatment effects of olaratumab for any one histologic STS subtype are uncertain based on the heterogeneity of the STS population enrolled in Trial JGDG (> 25 histologic subtypes of STS) and its design as an activity-estimating trial with a relatively small sample size. • There is greater uncertainty regarding the treatment effects of olaratumab in STS based on the design, conduct, and results of Trial JGDG as an activity-estimating trial, including: ○ Greater type I error for the evaluation of the primary endpoint ○ Lack of pre-specified statistical criteria surrounding analysis of secondary endpoints ○ Incomplete information on known prognostic factors ○ Level of discordance between IVRS and CRFs in documentation of stratification factors and reliance on these for stratified analyses ○ Discrepancy in the magnitude of the absolute and relative effect size of olaratumab on PFS and OS	olaratumab in STS based on the clinical and statistical limitations of the trial. Greater uncertainty of the treatment effects of olaratumab, in the context of the known safety profile, is acceptable based on the nature of incurable STS as a serious and life-threatening disease with limited treatment options in accordance with the principles described in 21 CFR 312, subpart E.
Risk	• The major safety concerns with olaratumab are the increased risks of serious infusion-related reactions (2.3% of olaratumab-treated patients with Grade ≥3 infusion-related reactions including one fatality) and of severe neutropenia (Grade 3 or 4 neutropenia 47% in the olaratumab plus doxorubicin arm vs. 37% in the single-agent doxorubicin arm).	The overall safety profile of olaratumab is acceptable for a monoclonal antibody intended for treatment of a serious or life-threatening condition. Infusion-related reactions are a common safety concern of monoclonal antibodies. In general, other risks

BLA 761038 Multi-disciplinary Review and Evaluation
 LARTRUVO (Olaratumab)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• While the majority of patients will receive corticosteroid premedications on days when doxorubicin is also administered, efficacy of a specific premedication regimen as primary or secondary prevention of infusion-related reactions with olaratumab is unclear. • Musculoskeletal pain events were increased in olaratumab-treated patients (64%) compared to the single-agent doxorubicin group (25%). • Potentiation by olaratumab of adverse reactions of doxorubicin is confounded based on the increased cumulative doxorubicin dose received by olaratumab-treated patients.	of olaratumab appear consistent with the known risks of doxorubicin albeit certain potentially serious risks may be potentiated, including Grade 3-4 neutropenia.
<u>Risk Management</u>	• Olaratumab is intended to be prescribed by oncologists and administered intravenously by trained nursing staff. • Oncologists are well versed in the identification and management of the toxicities associated with monoclonal antibodies and with cytotoxic chemotherapy.	A Risk Evaluation and Mitigation Strategy (REMS) is not needed to ensure the risks of olaratumab outweigh its risks.

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Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

Soft tissue sarcomas (STS) are a rare and very heterogeneous group of solid tumors that include over 50 different histologies and represent 1% of all adult cancers. The most common STS histologies are undifferentiated pleomorphic sarcoma, gastrointestinal stromal tumor (GIST), liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor. It is estimated that there will be 12,310 new cases and 4,990 deaths from all STS in the U.S. in 2016 (ACS 2016). Local control with primarily surgery and/or radiation is the mainstay for localized disease; however, 40 to 50% of patients with high-risk features (including large and intermediate or high-grade tumors) will eventually develop metastatic disease. Patients with metastatic disease are generally considered incurable with a median survival of approximately 11 to 15 months.

2.2 Analysis of Current Treatment Options

Doxorubicin is the only FDA-approved drug for first-line therapy of STS and, alone or in combination with ifosfamide, is the standard systemic treatment option for many patients with advanced disease. However, the chemosensitivity varies widely among different STS histologies, and as more is learned about the biologic differences of these tumors, the treatment of advanced STS is becoming increasingly driven by histology and molecular alterations. Table 1 lists the FDA-approved and commonly used therapies for advanced STS (non-GIST).

Table 1: FDA-Approved and Commonly Used Therapies for the Treatment of Patients with Advanced Soft Tissue Sarcoma

Drug	FDA-approved for treatment of STS	Evidence of Activity
Doxorubicin ^a	Yes	- Activity against multiple subtypes of STS first described in 1970s - Response rates of 10-25% have been reported^b - Often administered in combination with ifosfamide with improved response rate and PFS, but no OS benefit^c
Pazopanib	Yes	- Approved in 2012 for patients with “advanced soft tissue sarcoma who have received prior chemotherapy” based upon an improvement in PFS compared to placebo - median PFS 4.6 months (m) vs. 1.6 m, HR (95% CI)= 0.35 (0.26, 0.48) - No difference in OS: median OS 12.6 m vs. 10.7 m, HR (95% CI)=0.87 (0.67, 1.12)

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Drug	FDA-approved for treatment of STS	Evidence of Activity
		Limitation of use for GIST and liposarcoma as efficacy has not been demonstrated
Trabectedin	Yes	- Approved October 2015 for patients with “unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen” based upon an improvement in median PFS compared to dacarbazine: - median PFS (95% CI) 4.2 m (3, 4.8) vs. 1.5 m (1.5, 2.6), HR (95% CI)=0.55 (0.44, 0.7). - No difference in OS: median OS (95% CI) 13.7 m (12.2, 16) vs. 13.1 m (9.1, 16.2), HR (95% CI)=0.93 (0.75, 1.15) - No difference in response rate: ORR (95% CI) 7% (4.3, 9.8) vs. 6% (2.8, 10.4)
Eribulin	Yes	- Approved January 2016 for patients with “unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen” based on an improvement in median OS compared to dacarbazine: - median OS (95% CI) 15.6 m (10.2, 18.6) vs. 8.4 m (5.2, 10.1), HR (95% CI)=0.51 (0.35, 0.75) - mPFS (95% CI) 2.9 m (2.6, 4.8) vs. 1.7 m (1.4,2.6), HR (95% CI)=0.52 (0.35, 0.78)
Ifosfamide	No	- Response rates of ≥ 25% have been reported in multiple trials - Typically administered in combination with doxorubicin - Combination chemotherapy for front-line treatment failed to improve overall survival^f - Active against multiple STS histologies, particularly synovial sarcoma
Dacarbazine	No	Response rates of ~18% have been reported in multiple histologies^d
Gemcitabine	No	- Higher response rates have been reported when administered in combination regimens - In a randomized phase 2 study comparing gemcitabine with gemcitabine and docetaxel, response rate (16% vs. 9%), PFS (6.2 vs. 3.0 months) and OS (17.9 vs. 11.5 months) were all superior in the combination arm^e

(Source: Pazopanib USPI, Trabectedin USPI, Eribulin USPI)

^a Other anthracyclines are also used in the treatment of STS but are not included in this table

^b Maki, Robert G. Role of chemotherapy in patients with soft tissue sarcomas. Expert Review of Anticancer Therapy, 2004. 4:2, 229-236.

^c Judson, I., et al., Doxorubicin alone vs. intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. The Lancet Oncology, 2014. 15(4): 415-423.

^d Buesa, JM et al., High-dose DTIC in advanced soft-tissue sarcomas in the adult. A phase II study of the E.O.R.T.C. Soft Tissue and Bone Sarcoma Group. Annals of Oncology, 1991. 2(4):307-9.

^e Maki, R.G., et al., Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002. Journal of Clinical Oncology, 2007. 25(19): p. 2755-2763.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Olaratumab is an NME and is not currently marketed in the U.S.

3.2 Summary of Presubmission/Submission Regulatory Activity

The following summarizes the important clinical presubmission regulatory activity for olaratumab:

- March 17, 2014: IND 121500 opened with ongoing Trial JGDG [REDACTED] (b) (4) [REDACTED] for the development program of STS
- March 21, 2014: Teleconference to discuss preliminary request for breakthrough designation based upon an interim analysis from Trial JGDG. FDA recommended waiting until the results of the final PFS analysis are available to support the request for breakthrough designation. FDA stated if interim results were to be provided, adequate information to assess the robustness of the preliminary clinical data with regard to the treatment effects of olaratumab on PFS and OS should be provided including the statistical analysis plan for the trial to provide details of the pre-specified analyses of the primary endpoint, including censoring rules for PFS as well as the plan for Type I error adjustment for interim analyses, sensitivity analyses for PFS based on histological subtype of sarcoma, and analyses to assess for investigator bias in an open-label trial with a primary endpoint of investigator-assessed PFS.
- August 21, 2014: Fast Track status granted for olaratumab, in combination with doxorubicin, for the treatment of patients with advanced STS not amenable to treatment with radiotherapy or surgery to demonstrate improved PFS and OS.
- August 21, 2014: FDA Advice letter; FDA stated that:
 - If Eli Lilly seeks approval based on the final analysis of progression-free survival (PFS) and objective response rate (ORR) in an open-label trial, FDA strongly recommends that the analysis of tumor-response based endpoints use disease status as determined by an independent radiologic review committee blinded to treatment assignment.
 - If the minimization technique was used in the randomization, a re-randomization test (not a stratified log-rank test) on the intent-to-treat (ITT) population should be the primary analysis.
- October 9, 2014: Orphan Drug Designation granted for treatment of STS
- February 20, 2015: Breakthrough Therapy Designation granted for olaratumab, in combination with doxorubicin, for the treatment of patients with advanced or metastatic STSs that are not amenable to curative treatment with radiotherapy or surgery. The preliminary clinical data FDA used to support this designation was from the final PFS results as determined by the investigator and interim OS results in the ITT population from Trial JGDG. The median PFS was 6.6 months (95% CI: 4.1, 8.3) in the

olaratumab plus doxorubicin arm compared with 4.1 months (95% CI: 2.8, 5.4) in the doxorubicin arm (hazard ratio [HR] = 0.67; 95% confidence interval [CI]: 0.44, 1.02; p=0.06). The median OS was 25 months (95% CI: 20.9, 30.9) in the olaratumab plus doxorubicin arm compared with 14.7 months (95% CI: 9.2, 18) in the doxorubicin arm (hazard ratio [HR] = 0.44; 95% confidence interval [CI]: 0.28, 0.70; p=0.0004).

- March 4, 2015: end-of-phase 2 (EOP2) meeting to discuss acceptability of the randomized portion of Study I5B-IE-JGDG for regulatory approval and to discuss and confirm the acceptability of Study I5B-MC-JGDJ to serve as a confirmatory trial and support labeling claims
 - FDA stated that interpretation of the results from Trial JGDG are limited by the trial's design (open-label) and lack of pre-specified statistical criteria around important efficacy endpoints. In addition, for a single trial intended to support approval, the observed effect should be statistically robust, be internally consistent across relevant subgroups and individual study sites, and the trial must be considered adequate and well-controlled (e.g., a limited number of minor protocol deviations, limited missing data).
 - FDA requested that Lilly provide information to FDA regarding the conduct of clinical trial JGDG demonstrating that it was well-conducted, a discussion of the potential sources of bias and Lilly's plan to address them, and justification for why the totality of the results would be considered statistically robust. Potential sources of bias in the design, conduct, analysis, and interpretation of the results of Trial JGDG need to be identified and adequately addressed within a proposed BLA submission. Potential sources of bias may include:
 - Unknown type I error and type II error considerations for secondary efficacy variables because the pre-specified hypothesis is limited to progression-free survival
 - Effect of multiple comparisons on the estimate of the size and determination of a treatment effect, e.g., multiple comparisons between treatment arms, multiple efficacy variables, and multiple analyses of the data
 - Insufficient description of the process and procedures for examining data, including informal and formal analyses
 - Measures taken to minimize bias in the conduct of the trial and assessment of the efficacy parameters
 - Heterogeneous trial population with potential imbalance in important prognostic factors
 - FDA expressed concerns that the effects on PFS in the overall population in Trial JGDG are driven by the results in the stratified subgroup of patients with leiomyosarcoma. FDA requested that Lilly consider hierarchical testing in the proposed confirmatory trial, JGDJ, testing in the LMS subgroup first followed by the ITT (intent-to-treat) population.
- June 18, 2015: Type B Multidisciplinary meeting: FDA advised that Lilly describe the proposed plans in the pre-BLA meeting package to include the following information as

part of the efficacy and safety analyses in the clinical study report (CSR) for Study JGDG in the initial BLA submission:

- Analyses to assess for imbalances of the cumulative doxorubicin dose received by patients between arms
- Analysis of dexrazoxane use by patients in each arm
- Copy of the charter for independent radiology review
- Tumor response analysis datasets that include data adequate to allow analysis of PFS and ORR for the independent radiology review and the investigator
- Analysis of the differences in responses (PFS and ORR) between investigator and the independent radiology review
- August 18, and October 16, 2015: Type B Administrative and PreBLA multidisciplinary meetings: agreement on select content and format of the BLA submission. FDA stated/requested:
 - There are substantial differences in the results based on the stratified analysis per interactive voice response system (IVRS) and CRFs. All differences between the IVRS stratification variables and CRFs for each patient should be provided in the BLA, together with Lilly's determination of which variable was incorrect and the basis for this conclusion.
 - There is uncertainty regarding the magnitude of the treatment effect on overall survival. Therefore, approval may be granted under provisions of 21 CFR 601.41 subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit.
 - Efficacy claims (either in labeling or promotional material) for overall response rate, response duration, and progression-free survival must be based on tumor status according to blinded independent central review. In addition, claims for overall response rate and response duration should be limited to responses with a confirmed duration by radiographic imaging obtained at least 4 weeks after initial determination of tumor response.
 - Provide a strategy for the completion of trial JGDJ, in the event that this is considered necessary to confirm the clinical benefit of olaratumab in combination with doxorubicin, if olaratumab is licensed prior to full enrollment of trial JGDJ.

The following summarizes the important clinical post submission regulatory activity for olaratumab:

- April 27, 2016 and teleconference April 29, 2016: FDA requested that Eli Lilly conduct an interim OS analysis in the intent-to-treat population in the confirmatory Trial JGDJ at approximately 30% of planned total OS events for the final OS analysis to provide a more accurate estimation of the magnitude of the treatment effect on OS. FDA stated that the protocol and statistical analysis plan should be formally amended to include the plan for this additional interim analysis of OS, which should assess both futility and efficacy. FDA noted that Eli Lilly may choose an alpha spending function other than O'Brien-Fleming (OBF), such as the Pocock method or other method for this specific

interim analysis.

- June 1, 2016: Midcycle meeting:
 - FDA stated that there are concerns regarding the robustness of the progression-free survival (PFS) results in addition to the small effect size in PFS relative to the observed effect size in overall survival. FDA analyses are still ongoing.
 - FDA clarified that the April 27, 2016, request for an earlier interim analysis of Trial JGDJ is to provide additional information regarding the treatment effect of olaratumab in order to benefit patients and the decision whether or not to continue the ongoing trial would be up to Eli Lilly. FDA also clarified that it would be possible to conduct and submit these results in a manner that would ensure Eli Lilly remains blinded to the results.
- June 22, 2016, Response to April 27, 2016, Information Request:

(b) (4)



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 Products 2 (DOP2) consulted the Office of Scientific Investigation (OSI) to perform an audit of three clinical trial sites (Site #1 Dr. Tap, Site #12 Dr. VanTine, and Site #15 Dr. Kim) the Applicant site, and (b) (4) the contract radiology site to identify any issues that could affect the quality and interpretation of the data submitted with this application regarding clinical Trial JGDG. The Division, in consultation with OSI, selected clinical sites for inspection based on enrollment characteristics, patterns of protocol violations reported for the sites, patterns of efficacy reporting, and patterns of serious adverse event (SAE) reporting.

OSI inspections revealed the following:

- Site #1: Conducted by EMA; FDA will use findings of EMA inspection in support of BLA 761038. EMA found no significant concerns. Data appear reliable.
- Site #12: no issues; the final classification for this inspection is No Action Indicated (NAI)
- Site #15: minor issues, data appear reliable; the preliminary classification for this inspection is Voluntary Action Indicated (VAI)
- Applicant site: no issues; the preliminary classification for this inspection is No Action Indicated (NAI)
- (b) (4) (contract radiology site): no issues; the preliminary classification for this inspection is No Action Indicated (NAI)

4.2 Product Quality

Please see FDA CMC review by Chikako Torigoe and Rashmi Rawat for further details. Per the CMC reviewer, there are no identified CMC deficiencies. The intended commercial drug substance will be manufactured using (b) (4) which was also used for manufacturing drug substance used in Trial JGDG. Commercial drug product will be manufactured at Eli Lilly and Company, which is a change from the (b) (4) manufacturing site for drug product used in Trial JGDG.

4.3 Clinical Microbiology

Please see FDA product quality microbiology reviews by Monica Markovski (drug substance reviewer) and Natalia Pripuzova (drug product reviewer) for further details. Per the reviewers, there are no currently identified microbiology issues. The allowed storage time of olaratumab drug product after dilution was decreased to 4 hours at (b) (4) degrees Celsius (b) (4) proposed by the Applicant, and the endotoxin release specification was tightened to NMT (b) (4) EU/mg at the request of FDA.

4.4 Devices and Companion Diagnostic Issues

There is no device or companion diagnostic test for review in support of this BLA.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

Olaratumab is a human IgG1 monoclonal antibody that targets platelet-derived growth factor receptor alpha (PDGFR- α), a type III receptor tyrosine kinase expressed on cells of mesenchymal origin that is activated by the ligands PDGF-AA, -AB, -BB, and -CC. PDGFR- α signaling is involved in cell growth, chemotaxis, mesenchymal stem cell differentiation, and wound healing. PDGFR- α is also expressed in various tumor types, including sarcomas, and plays an important role in transformation, cancer cell proliferation, recruitment of tumor stroma, and metastasis.

In in vitro studies, olaratumab bound to human and cynomolgus monkey PDGFR- α with similar affinity, but did not bind appreciably to mouse or rabbit PDGFR- α , supporting the use of cynomolgus monkeys as the single pharmacologically relevant species for toxicity assessment. Olaratumab binds specifically to PDGFR- α and did not bind human PDGFR- β . Olaratumab inhibited PDGF-AA and -BB ligand binding to PDGFR- α as well as PDGF-AA, -BB, and -CC-mediated PDGFR- α phosphorylation and downstream signaling in human stromal and tumor cell lines. Despite binding to human Fc γ R1IIa in vitro, as expected for an IgG1 antibody, olaratumab induced only minimal in vitro antibody-dependent cellular cytotoxicity (ADCC) activity compared to the positive control rituximab. Similarly, although olaratumab exhibited in vitro binding to human C1q, it did not induce in vitro complement-dependent cytotoxicity (CDC) activity against PDGFR- α -expressing cells. Thus, induction of ADCC and CDC activity do not appear to play significant roles in the in vivo activity of olaratumab.

Pre-treatment with olaratumab inhibited PDGF-induced in vitro proliferation of numerous human cancer cell lines, including leiomyosarcoma and osteosarcoma cell lines, with IC₅₀ values ranging from 1 to 5 nM. Olaratumab also decreased the anchorage-independent growth of leiomyosarcoma cells. In keeping with these findings, olaratumab exhibited in vivo anti-tumor activity in nude mice bearing human sarcoma xenografts. In mice, anti-tumor activity against leiomyosarcoma xenografts occurred at steady-state olaratumab plasma trough concentrations in the range of 155 to 210 μ g/mL, which is below the mean of 296 μ g/ml achieved in patients administered olaratumab at the recommended dose of 15 mg/kg. Further, treatment with olaratumab in combination with doxorubicin improved anti-tumor activity in mice bearing leiomyosarcoma and osteosarcoma xenografts compared to either drug alone without inducing a substantial increase in toxicity based on mortality and body weight, potentially due to increased apoptosis.

Olaratumab was evaluated in GLP-compliant repeat-dose toxicology studies in cynomolgus monkeys of up to 39 weeks in duration. There were no mortalities following intravenous (I.V.) administration of the antibody at dose levels up to 75 mg/kg once weekly for up to 39 weeks. This dose resulted in exposures approximately 9.5- and 6-fold higher based on AUC_{0-t} and AUC₀₋₁₆₈, respectively, than the steady-state AUC_{tau} seen on Day 8 at the recommended human dose

of 15 mg/kg, though anti-drug antibody (ADA) responses seen in at least 22% of monkeys resulted in variable exposure in all toxicology studies. Potential target organs of olaratumab-related toxicity in the 39-week toxicology study were the skin (alopecia), liver, lung, and pancreas. One female monkey exhibited a substantial increase in alanine aminotransferase (ALT) following 39 weeks of olaratumab at the 75 mg/kg dose level compared to baseline and controls, which correlated histologically with minimal individual cell necrosis and moderate lymphocyte/macrophage infiltration in the liver. Significant hepatic toxicity has not been observed in the clinic with olaratumab (refer to Section 7.4). Weekly I.V. infusion of olaratumab for 39 weeks induced an increase in the incidence and/or severity of lymphocyte infiltration in numerous tissues, which often persisted or developed during the 8-week recovery period. Some histologic findings were observed at the 75 mg/kg dose level in the 39-week study following 8 weeks of recovery but not after the terminal sacrifice, suggesting potential delayed toxicity. These histologic findings included moderate atrophy and chronic inflammation in the pancreas, minimal to slight pleural fibrosis and subpleural lymphoid aggregate in the lung, slight interstitial fibrosis in the kidney, and minimal perivascular neutrophil infiltration in the heart. Olaratumab concentrations were ≤ 1479 ng/mL in three out of six monkeys at the end of the recovery period; however, not all recovery cohort monkeys exhibiting histologic findings had detectable drug at the end of the recovery period. Based on clinical trials done to support the approval of olaratumab in the proposed patient population, the only clear toxicity associated with olaratumab alone was the potential for infusion reactions. Increases in toxicities observed with combination of olaratumab and doxorubicin compared to doxorubicin alone included musculoskeletal pain and gastrointestinal tract toxicity (refer to Section 7.4). Expression of PDGFR- α has been identified as a marker of some subsets of mesenchymal stem cells capable of differentiation into osteoblastic, adipogenic, chondrogenic, and hematopoietic lineages (Pinho, Lacombe, et al. 2013) and of embryonic stem cells capable of myogenic differentiation (Hwang, Suk, et al. 2013). Reports have also demonstrated increased PDGFR- α expression following cardiac injury and a role for the signaling pathway in repair processes following vascular injury (Zhao, Zhao, et al. 2011 and Chong, Reinecke, et al. 2013). Together, these studies suggest a potential mechanistic basis for the apparent increase in doxorubicin-mediated toxicity recorded when used in combination with olaratumab.

Fertility/early embryonic development studies were not conducted with olaratumab and are not required to support a marketing application for a drug intended for the treatment of patients with advanced cancer. Data from the literature suggest that loss of PDGF-A/PDGFR- α signaling may adversely affect male fertility. Tissue cross-reactivity analysis demonstrated that rabbit anti-PDGFR- α stained various cell types in the human testis and ovary, but there were no adverse histologic findings in these reproductive organs in toxicology studies.

Reproductive and developmental toxicology studies were not conducted with olaratumab. Rather, consistent with the alternative approach to providing information on the potential for reproductive toxicity described in ICH S6(R1), the Applicant provided a scientific literature review and assessment of the potential reproductive toxicity of olaratumab in conjunction with an embryo-fetal development study in mice using a chimeric surrogate antibody, IMC-1E10.

Data from PDGFR- α knockout mice demonstrated that PDGFR- α is critical for normal embryonic survival, development, and organogenesis, and suggested that inhibition of the PDGFR- α signaling pathway with olaratumab may be embryonic lethal and teratogenic. Data from literature reports demonstrated a critical role for PDGFR- α signaling in the proper development of the vertebral arch, skeleton, lung, intestine, heart, brain, skin, eye, testis, kidney, palate, and teeth.

IMC-1E10 is comprised of the same human IgG1 backbone as olaratumab and a Fab domain demonstrated to bind mouse PDGFR- α with relatively similar affinity as olaratumab has for human PDGFR- α . IMC-1E10 inhibited PDGF-AA binding to mouse PDGFR- α and subsequent PDGFR- α signaling in mouse fibroblasts, suggesting IMC-1E10 exhibits similar in vitro binding and functional activity as olaratumab. Intravenous administration of IMC-1E10 once every 3 days to pregnant mice during the period of organogenesis [gestation days (GD) 6 to 15] did not result in maternal toxicity at the 50 and 150 mg/kg dose levels. Administration of 5 mg/kg IMC-1E10 did, however, result in 15 maternal mortalities attributed to an immune reaction to the chimeric antibody. A potential explanation for the absence of maternal mortality at the mid and high dose levels may be induction of tolerance to high doses of antibody, which has been previously seen in mice. Caesarean findings (GD 18) at the 5 mg/kg dose level included 14 aborted fetuses in one mouse and 10 late resorptions in another dam that had no clinical signs of hypersensitivity. Embryo-lethality was not observed at the mid and high doses. IMC-1E10 was teratogenic at maternal IMC-1E10 exposures below the human exposure to olaratumab at the recommended dose of 15 mg/kg. There was a dose-related increase in abnormal eyelid development in mice dosed with ≥ 50 mg/kg IMC-1E10 compared to controls. Administration of IMC-1E10 resulted in skeletal malformations at the mid dose level and detached rib and malrotated limb at the high dose level. Further, there was a dose-related increase in additional ossification sites in the frontal/parietal skull in fetuses from mice dosed with all dose levels of IMC-1E10 compared to controls. Based on literature reports describing the role of PDGFR- α in embryonic development and organogenesis as well as the embryo-fetal developmental toxicity study conducted with IMC-1E10, a warning for embryofetal toxicity is recommended for LARTRUVO. Based on a half-life of olaratumab of approximately 11 days, it is advised that females of reproductive potential use effective contraception during treatment with olaratumab and for at least 3 months following cessation of therapy. IMC-1E10 crossed the placental barrier in pregnant mice, but transfer to milk was not evaluated. The Applicant did not evaluate transfer of olaratumab to the fetus or milk. As a result, prescribers should advise women not to breastfeed during treatment with LARTRUVO and for 3 months following the last dose.

5.2 Referenced NDAs, BLAs, DMFs

None

5.3 Pharmacology

Primary pharmacology

A. In Vitro Studies

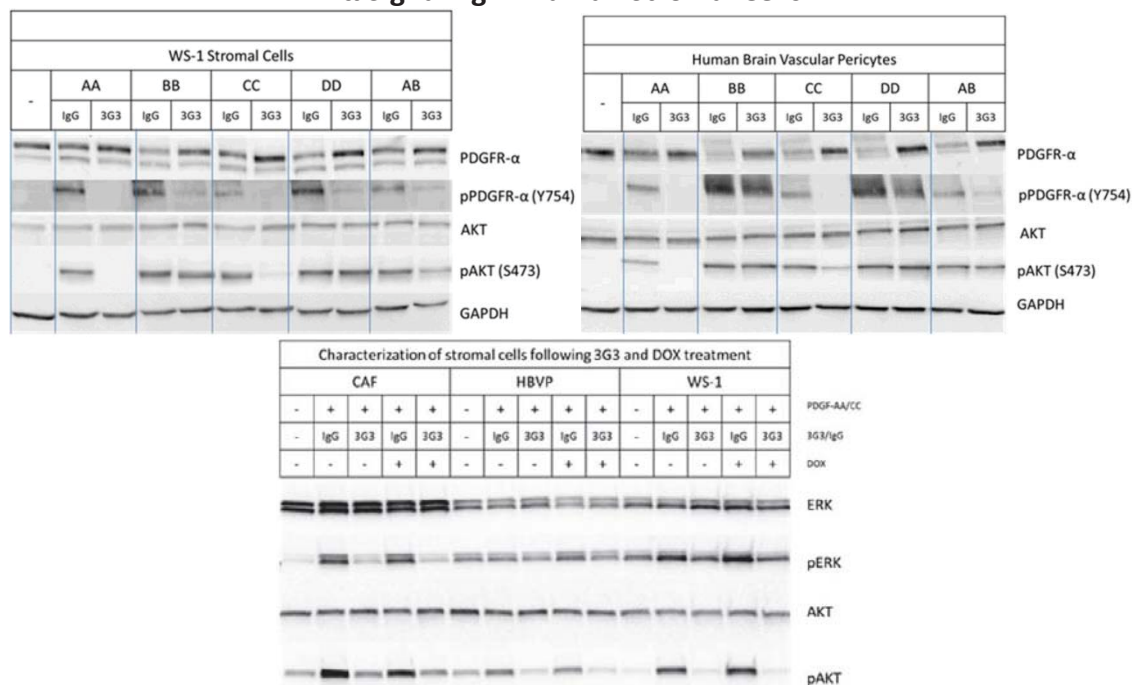
The Applicant determined the binding affinities of olaratumab for human, cynomolgus monkey, and rabbit PDGFR- α using surface plasmon resonance (SPR; Study # 3G3-2B). Olaratumab (IMC-3G3; 30 nM) exhibited relatively similar binding affinity for Fc-tagged human ($K_D=0.33$ nM) and cynomolgus monkey ($K_D=0.6$ nM) PDGFR- α . Olaratumab bound to rabbit PDGFR- α with a K_D value of 40.7 nM. The Applicant also assessed the binding affinities of olaratumab for the human, cynomolgus monkey, and rabbit PDGFR- α extracellular domains (ECDs) using enzyme-linked immunosorbent assay (ELISA). Olaratumab exhibited dose-dependent binding to human and cynomolgus monkey PDGFR- α -ECD with EC_{50} values of 0.026 nM and 0.067 nM, respectively, but did not bind rabbit PDGFR- α -ECD or human PDGFR β . Olaratumab binding to rodent PDGFR- α was not assessed in this study, but immunoprecipitation analysis performed in Study # IMC-33G3-01 demonstrated that olaratumab did not bind mouse PDGFR- α . Based on sequence alignment, mouse PDGFR- α ECD exhibited 85% amino acid identity to human PDGFR- α . Olaratumab also blocked PDGF-AA-induced phosphorylation of PDGFR- α and AKT in cynomolgus monkey skin fibroblasts, indicating that olaratumab is pharmacologically active in cynomolgus monkey cells. These data support the use of cynomolgus monkeys as a pharmacologically relevant species for toxicity assessment.

In vitro pharmacology studies (Study # IMC-33G3-01) demonstrated that olaratumab inhibited PDGFR- α ligand binding. In a solid-phase assay, olaratumab was pre-incubated with well-coated PDGFR- α -ECD for 30 min, followed by addition of ^{125} I-PDGF-AA for 2 hours. Binding was measured using a gamma counter. In a cell-based assay, porcine aortic endothelial cells expressing human PDGFR- α (PAE R α cells) were incubated with olaratumab and ^{125} I-PDGF-AA for 2 hours. The cells were then washed, extracted, and counted. Olaratumab inhibited ^{125} I-PDGF-AA binding to immobilized PDGFR- α -ECD and PAE R α cells with IC_{50} values of 0.24 nM and 0.58 nM, respectively. Olaratumab also blocked ^{125} I-PDGF-BB binding to immobilized PDGFR- α -ECD with an IC_{50} value of 0.43 nM.

The Applicant investigated the effects of olaratumab on in vitro PDGFR- α signaling in primary human stromal cell lines including WS-1 human skin fibroblasts, lung cancer-associated fibroblasts (CAF), and human brain vascular pericytes (HBVP) (Study # CCGS312). Serum-starved WS-1 and HBVP cells were pre-treated with 1 μ M human IgG control or olaratumab for 15 min, followed by stimulation with the PDGFR ligands PDGF-AA, -AB, -BB, -CC, or -DD at 5 nM for 15 min. As shown in Figure 1, western blot analysis demonstrated that pre-treatment with olaratumab inhibited PDGFR- α phosphorylation at Y754 induced by PDGF-AA, -BB, -CC, -DD, and -AB in WS-1 cells and PDGF-AA, -CC, and -AB in HBVP cells. Further, olaratumab-induced inhibition of PDGFR- α activation resulted in a decrease in downstream AKT phosphorylation induced by PDGF-AA, -CC, and to a lesser extent, -AB in WS-1 cells and PDGF-AA and -CC in HBVP cells. Notably, incubation with doxorubicin did not appreciably affect the ability of

olaratumab to inhibit PDGFR- α pathway activation induced by a PDGF-AA and -CC cocktail in WS-1, HBVP, or CAF cells.

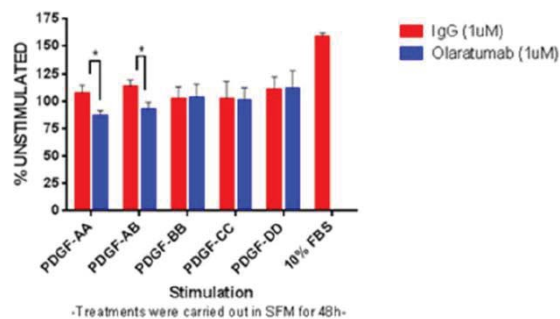
Figure 1: Effect of Olaratumab alone and in combination with Doxorubicin on In Vitro PDGFR- α Signaling in Human Stromal Cells



(Applicant Figure reproduced from Study # CCGS312)
3G3: olaratumab; Dox: doxorubicin

As assessed using the CellTiter-Glo[®] Luminescent assay, pre-treatment with 1 μ M olaratumab slightly but significantly inhibited PDGF-AA- and PDGF-AB-induced WS-1 proliferation by $\sim$ 20% ($p < 0.01$), but did not affect proliferation induced by PDGF-BB, -CC, or -DD.

Figure 2: Effect of Olaratumab on PDGF-induced WS-1 Fibroblast Proliferation



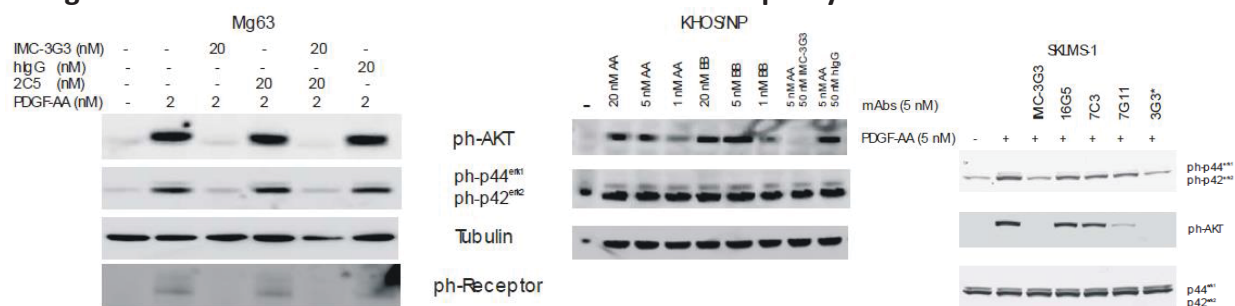
(Applicant Figure reproduced from Study # CCGS312)

As shown in Study # IMC-33G3-01, olaratumab also inhibited PDGFR- α activation and downstream signaling in porcine aortic endothelial cells expressing human PDGFR- α (PAE R α)

cells). Western blot analysis demonstrated that pre-treatment with 10 nM olaratumab for 30 min inhibited PDGF-CC-induced phosphorylation of PDGFR- α and PDGF-BB-induced phosphorylation of PDGFR- α , MAPK, and AKT. Further, pre-treatment with olaratumab inhibited PDGF-AA-induced phosphorylation of PDGFR- α in a dose-dependent manner with an IC₅₀ value of 0.25 nM. In keeping with this, pre-treatment with olaratumab inhibited PDGF-AA- and PDGF-BB- induced proliferation of PAE R α cells with IC₅₀ values of 8.27 nM and 1.25 nM, respectively.

Flow cytometry and/or immunoprecipitation analysis demonstrated PDGFR- α expression in numerous tumor cell lines including examples derived from leiomyosarcoma (SKLMS-1), osteosarcoma (KHOS/NP, MNNG/HOS, and MG-63), glioblastoma (U118), lung cancer (Calu-6), and small-cell lung cancer (NCI-H146). Western blot analysis demonstrated that pre-treatment with olaratumab inhibited PDGF-AA-induced phosphorylation of AKT and MAPK in MG63 and SKLMS-1 human sarcoma cells (see Figure 3) as well as in Hs578T breast cancer cells, C272/hTert/E7 ovarian cancer cells, and U118 cells. Olaratumab also inhibited PDGF-AA-induced AKT phosphorylation in KHOS/NP sarcoma cells, but did not affect downstream AKT or MAPK activation in Calu6, MNNG/HOS, or NCI-H146 cells. Although treatment with PDGF-AA resulted in PDGFR- α downregulation as expected, treatment with olaratumab did not downmodulate PDGFR- α expression in MG63 cells.

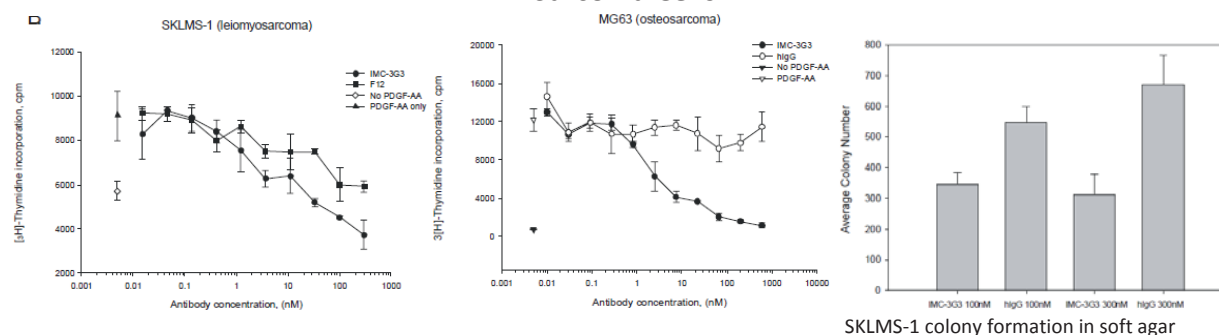
Figure 3: Effect of Olaratumab on AKT and MAPK Phosphorylation in Sarcoma Cell Lines



(Applicant Figure reproduced from Study # IMC-3G3-01)
IMC-3G3: olaratumab

As assessed by thymidine incorporation, olaratumab-induced inhibition of downstream PDGFR- α signaling led to dose-dependent inhibition of PDGF-AA-induced proliferation of SKLMS-1, MG63, U118, C272/hTert/E7, and Hs578T cells, with IC₅₀ values ranging from 1-5 nM. Further, as measured by colony formation in soft agar, treatment with 100 nM olaratumab for 14 days decreased anchorage-independent growth of SKLMS-1 leiomyosarcoma cells by 37% compared to the human IgG negative control.

Figure 4: Effect of Olaratumab on Proliferation and Anchorage-Independent Growth of Sarcoma Cells



(Applicant Figure reproduced from Study # CCGS312)
3G3: olaratumab

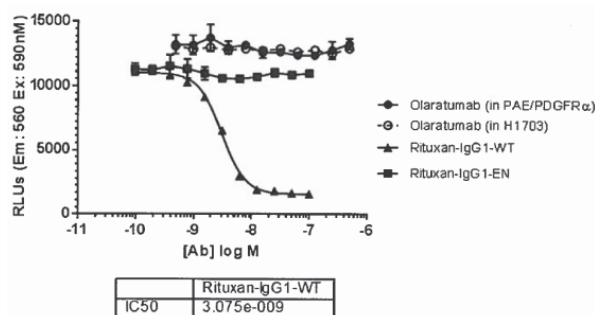
The Applicant investigated the in vitro olaratumab sensitivity of a genetically and histologically diverse set of 310 human cancer cell lines (Study # IMC-3G3). Cell lines were incubated with 100 $\mu\text{g}/\text{mL}$ olaratumab in triplicate for two doubling times, and cell viability was measured using CellTiter-Glo[®] (Promega). Overall, olaratumab inhibited in vitro proliferation of five cancer cell lines by >20%: H1703 (lung), HSC-4 (upper aerodigestive tract), A204 (rhabdoid), HuO9 (osteosarcoma), and SK-MES-1 (lung). Olaratumab did not inhibit proliferation of the SKLMS-1 cell line under the conditions of this assay. The Applicant also evaluated the expression of ~17,000 genes for association with olaratumab sensitivity. Notably, there was a statistically significant association between olaratumab sensitivity and expression of *PDGFRA* and the PDGFR- α ligand *PDGFC* ($p < 0.001$).

As expected for an IgG1 antibody, SPR analysis demonstrated that olaratumab bound human recombinant Fc γ R11a (Study # SDR14080-00). As a result, the Applicant assessed the ability of olaratumab to induce in vitro ADCC against PDGFR- α -expressing cells using reporter gene assays and peripheral blood mononuclear cell (PBMC) assays. In the reporter gene ADCC assay, Jurkat cells co-transfected with Fc γ R11a-171vv and luciferase (i.e. Jurkat-vv-NFAT-Luc cells) were used as effector cells. Following assay optimization, olaratumab induced minimal in vitro ADCC activity against target cell lines expressing high levels of PDGFR- α (NCI-H1703 and PAE R α cells) using effector:target (E:T) ratios of 5 and 1, respectively, although a positive control was not included for comparison. In contrast, olaratumab did not induce ADCC activity against cell lines exhibiting low levels of PDGFR- α . In another reporter gene assay comparing olaratumab to the positive control (anti-CD20 antibody rituximab; Rituxan[®]), incubation with olaratumab for 5 hours at an E:T ratio of 5:1 induced minimal ADCC activity against NCI-H1703 cells (2 to 3-fold increase at 150 nM) compared to that induced by rituximab against Wil2S cells (20-fold increase at 1.85 nM). Further, olaratumab did not induce ADCC activity using human PBMCs stimulated overnight with IL-2 as effector cells.

The Applicant also assessed the ability of olaratumab to bind C1q and mediate CDC (Study # PS-EF-3G3-01). As determined by ELISA, olaratumab and the positive control Rituxan-IgG1-WT

bound to human C1q with EC₅₀ values of 12 nM and 33 nM, respectively. As expected, the negative control rituxan-IgG1-EN did not induce CDC activity, but rituximab (Rituxan-IgG1-WT) induced in vitro CDC activity against Wil2-S cells with an EC₅₀ value of 3.1 nM. In contrast, olaratumab did not induce in vitro CDC activity against PAE/PDGFR-α or H1703 cells (see Figure 5). Thus, there is a relatively low potential for olaratumab to induce ADCC and CDC activity in vivo.

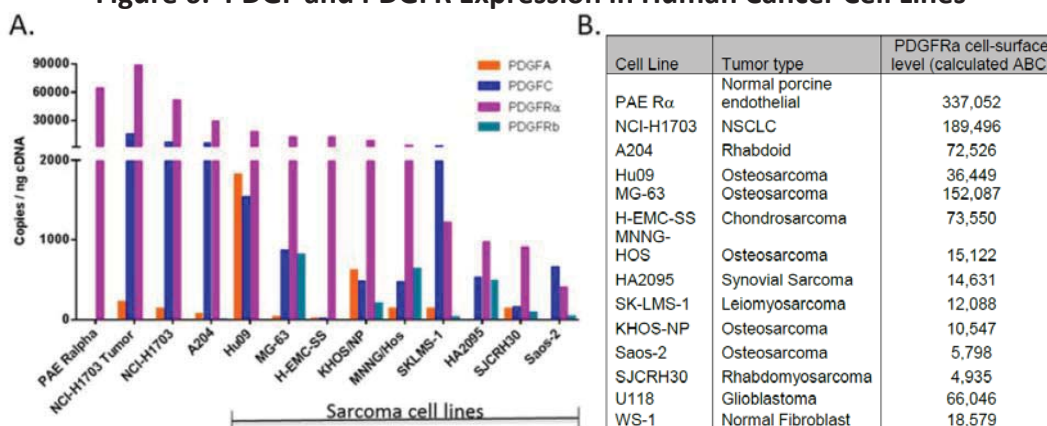
Figure 5: Effect of Olaratumab on In Vitro CDC Activity



(Applicant Figure reproduced from Study # PS-EF-3G3-01)

The Applicant characterized the expression of PDGFR-α and its ligands in human cancer cell lines (Study # CCL-GG3-02). Quantitative real-time PCR was performed on human cancer cell lines to quantify PDGFA, PDGFC, PDGFR-α, and PDGFRβ mRNA expression. Cell-surface levels of PDGFR-α were also measured using quantitative flow cytometric analysis. PDGF and PDGFR expression levels in human cancer cell lines including sarcomas are shown in Figure 6.

Figure 6: PDGF and PDGFR Expression in Human Cancer Cell Lines



(Applicant Figure 6A reproduced from Pharmacology Written Summary; Applicant Figure 6B reproduced from Study # CCL-GG3-02)
A: mRNA expression; B: PDGFR-α cell-surface expression

Further, gene expression outlier analysis using data from The Cancer Genome Atlas and microarray dataset GSE21124 from the GEO website demonstrated high prevalence of PDGFR-α mRNA expression in soft tissue sarcoma (STS; 37% prevalence) and pancreatic cancer (41% prevalence) compared to normal tissue (Study # BIX-PDGFR-1). PDGF-C was also

overexpressed in sarcomas (20% prevalence). PDGFR- α and PDGF-C overexpression varied among STS subtypes, with the highest prevalence in dedifferentiated liposarcoma. PDGFR- α demethylation was consistent with increased PDGFR- α mRNA expression, suggesting that PDGFR- α hypomethylation likely contributes to PDGFR- α overexpression in STS. PDGFR- α copy number gain may also play a role.

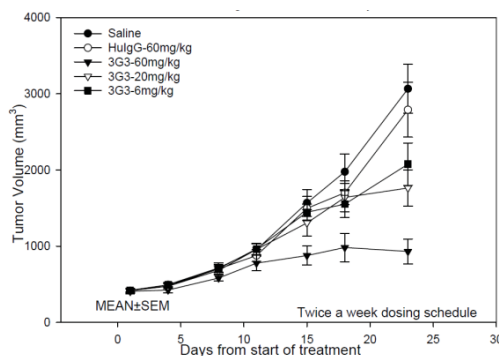
Since olaratumab does not bind mouse PDGFR- α , the Applicant developed a chimeric surrogate antibody of olaratumab (IMC-1E10), which contains the same human IgG1 backbone as olaratumab (Study # I-1E10-01). As determined by ELISA, IMC-1E10 exhibited dose-dependent binding to immobilized mouse PDGFR- α extracellular domain with an EC₅₀ value of 0.091 nM. SPR analysis demonstrated that IMC-1E10 bound Fc-tagged mouse PDGFR- α with a K_D value of 0.62 nM. Thus, the binding affinity of IMC-1E10 for mouse PDGFR- α was relatively similar to that of olaratumab for human (K_D = 0.33 nM) and cynomolgus monkey (K_D = 0.6 nM) PDGFR- α , as determined by SPR in Study #3G3-2B. IMC-1E10 did not bind rat or rabbit PDGFR- α ; binding to human PDGFR- α was not tested. Notably, human and mouse PDGF-AA bound mouse PDGFR- α with relatively similar affinity. IMC-1E10 inhibited human PDGF-AA binding to mouse PDGFR- α with an IC₅₀ of 2.5 nM, whereas olaratumab was unable to prevent binding. The Applicant also investigated the effect of IMC-1E10 on ligand-induced mitogenesis and downstream PDGFR- α signaling. As assessed by thymidine incorporation, pre-treatment with IMC-1E10 for 30 min inhibited PDGF-AA-induced DNA synthesis in NIH-3T3 mouse fibroblasts. Western blot analysis demonstrated that IMC-1E10 inhibited PDGF-AA-induced phosphorylation of mouse PDGFR- α , but not PDGF-BB-induced phosphorylation of mouse PDGFR β , indicating specificity for PDGFR- α . The lack of IMC-1E10 binding to mouse PDGFR β was confirmed in a solid phase binding assay. Further, IMC-1E10, but not olaratumab, inhibited PDGF-AA-induced phosphorylation of MAPK in NIH-3T3 cells. Thus, based on the assays conducted, the chimeric surrogate antibody IMC-1E10 exhibited similar in vitro binding and functional activity against mouse PDGFR- α as olaratumab did against the human protein.

B. In Vivo Studies

The Applicant investigated the in vivo anti-tumor activity of olaratumab in several xenograft models in nude mice, including human sarcoma cell lines. In Study # 3015-04, 12 female nude mice/group were subcutaneously implanted with 5×10^6 SKLMS-1 leiomyosarcoma cells. When the mean tumor size was ~ 400 - 450 mm³, mice were administered intraperitoneal (i.p.) loading doses (21.4, 71.4, and 214 mg/kg) of olaratumab followed by twice weekly i.p. administration of 6, 20, and 60 mg/kg olaratumab, respectively. Whereas treatment with saline or human IgG did not significantly affect xenograft growth, twice weekly i.p. administration of 6, 20, and 60 mg/kg olaratumab resulted in statistically significant inhibition of SKLMS-1 xenograft growth compared to controls (T/C% values of 66%, 57%, and 31%, respectively; Figure 7). Treatment with olaratumab did not significantly affect mean body weight. The steady-state plasma trough (C_{min}) olaratumab concentrations following i.p. administration of 6, 20, and 60 mg/kg olaratumab were 175, 155, and 210 μ g/mL, respectively, indicating that steady-state olaratumab plasma trough concentrations in the range of 155-210 μ g/mL resulted in anti-tumor activity. Immunohistochemical (IHC) analysis demonstrated that tumors harvested from mice

dosed with 60 mg/kg olaratumab generally exhibited decreased severity and incidence of intratumoral hemorrhage, increased lymphocytes within the tumor core and periphery, decreased individual cell and regional necrosis, and decreased cellularity compared to controls.

Figure 7: Effect of Olaratumab on Human SKLMS-1 Xenografts in Nude Mice



(Applicant Figure reproduced from Study # 3015-04)

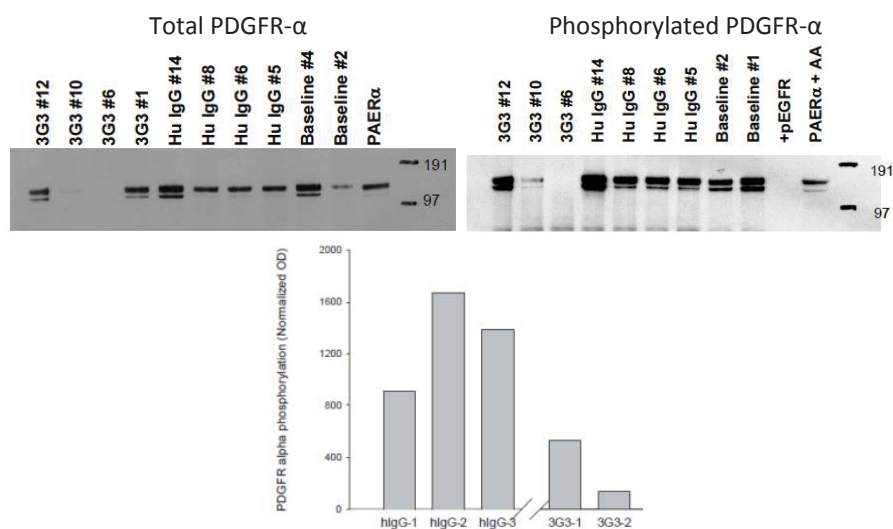
3G3: olaratumab; 6 mg/kg: P = 0.02 vs. saline; 20 mg/kg: P = 0.003 vs. saline; 60 mg/kg: P < 0.0001 vs. saline

Olaratumab also exhibited *in vivo* anti-tumor activity against subcutaneously implanted U-118MG human glioblastoma xenografts. As a result, the Applicant went on to examine the *in vivo* PDGFR- α signaling effects of olaratumab or human IgG in female nude mice bearing U-118MG glioblastoma xenografts following an *i.p.* loading dose of 214 mg/kg on Day 1 and a second *i.p.* dose of 60 mg/kg on Day 4 (Study # 3132-04). Dosing was initiated when the mean tumor size was ~ 400 mm³, and tumors were harvested pre-treatment (4 mice; referred to as baseline animals) and 4 (4 mice/group), 72 (4 mice/group), and 168 (5 or 6 mice/group) hours after the first dose on Day 1. The mean tumor volumes on Day 8 in mice dosed with IgG and olaratumab were 608.45 mm³ and 539.02 mm³, respectively. Of note, in Study # 3016-04 (not reviewed in detail), *i.p.* administration of a 214 mg/kg loading dose of olaratumab followed by 60 mg/kg twice weekly resulted in a statistically significant inhibition of U-118MG xenograft growth compared to controls in female nude mice with a T/C value of 35%. IHC analysis demonstrated that treatment with olaratumab did not significantly affect ApopTag (TUNEL; detects fragmented DNA of apoptotic cells), caspase-3, phosphorylated histone-3, or Meca-32 staining compared to human IgG. There was a statistically significant decrease in phosphorylated MAPK at 72 and 168 hours post-dose in mice dosed with olaratumab compared to IgG, but not phosphorylated AKT. IHC analysis also demonstrated a statistically significant decrease in the percentage of Ki67-positive cells at 4, 72, and 168 hours after administration of olaratumab compared to IgG, demonstrating decreased proliferation in olaratumab-treated tumors.

Although olaratumab induced internalization of PDGFR- α from the cell surface of prostate cancer cells (Doloff, Russell, et al. 2007), *in vitro* treatment with olaratumab did not reduce total PDGFR- α levels in sarcoma cell lines. Thus, to further investigate olaratumab effects on PDGFR- α expression, the cell lysates from the same U-118MG tumors used for IHC were immunoprecipitated with olaratumab and then immunoblotted with anti-PDGFR- α or anti-

phosphotyrosine antibodies. As shown in Figure 8, total PDGFR- α levels varied in the tumor samples. There was a decrease in phosphorylated PDGFR- α at 168 hours post-dose in two out of the three olaratumab-treated tumors compared to IgG and baseline; however, total PDGFR- α expression was also decreased in these tumor samples, suggesting either downmodulation of PDGFR- α or incomplete immunoprecipitation of the receptor. Tubulin and EGFR levels were not substantially affected in these tumor sample cell lysates. Quantification of phosphorylated PDGFR- α normalized to total PDGFR- α is shown at the bottom of Figure 8. Only three tumors treated with human IgG and two tumors treated with olaratumab were included in this analysis (tumor numbers were not specified); the third olaratumab-treated tumor was excluded because the extracted material was less than the 4 mg required for immunoprecipitating the receptor. Although few samples were included, the performed quantification suggests that olaratumab tends to reduce PDGFR- α phosphorylation in vivo.

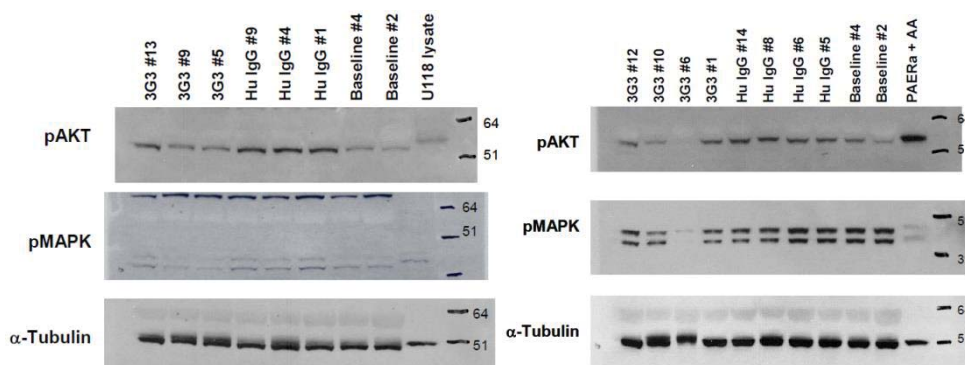
Figure 8: Effect of Olaratumab on Phosphorylated PDGFR- α in Tumor Lysates 168 hours post-dose from Mice Bearing U-118MG Xenografts



(Top Applicant Figures reproduced from Study # 3132-04. Bottom Applicant Figure normalized to total PDGFR- α reproduced from Study # IMC-3G3-01). 3G3: olaratumab

As measured by western blotting, two out of the three olaratumab-treated tumor samples exhibited a decrease in phosphorylated AKT and MAPK at 72 hours post-dose compared to IgG but not baseline. Total MAPK and AKT levels were not assessed, but α -tubulin was used as a loading control. One out of the four olaratumab-treated tumor samples exhibited a clear decrease in phosphorylated AKT and MAPK at 168 hours post-dose compared to samples from IgG-treated and untreated mice.

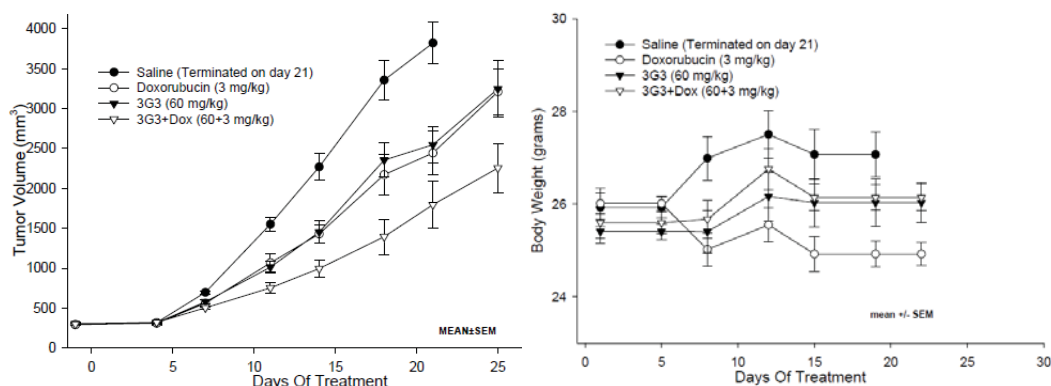
Figure 9: Effect of Olaratumab on Phosphorylated AKT and MAPK in Mice Bearing U-118MG Xenografts



(Applicant Figure reproduced from Study # 3132-04)
Left: 72 hours; Right: 168 hours

In support of the proposed indication, the Applicant investigated the anti-tumor activity of i.p. olaratumab in combination with i.p. doxorubicin in 12 female nude mice/group bearing human SKLMS-1 leiomyosarcoma xenografts (Study # 3276-05). Following subcutaneous implantation of 5×10^6 SKLMS-1 cells/mouse, dosing was initiated when the mean tumor size was $\sim 300 \text{ mm}^3$. Mice were administered the maximum tolerated i.p. dose of doxorubicin, 3 mg/kg twice weekly, alone or in combination with an i.p. loading dose of 214 mg/kg olaratumab followed by 60 mg/kg olaratumab administered i.p. twice weekly. As shown in Figure 10, twice weekly i.p. administration of olaratumab and doxorubicin as single-agents significantly inhibited xenograft growth compared to saline to a similar extent (T/C 64%; $p \leq 0.001$). Combined treatment with olaratumab and doxorubicin significantly improved anti-tumor activity (T/C 46%) compared to saline ($p < 0.0001$), olaratumab alone ($p = 0.03$), and doxorubicin alone ($p = 0.05$). There were no mortalities. Treatment with doxorubicin resulted in $\sim 8\%$ body weight loss compared to baseline, as well as a statistically significant 14% decrease in mean body weight on Day 19 compared to saline ($p = 0.0008$). In contrast, treatment with olaratumab alone ($p = 0.5$) or in combination with doxorubicin ($p = 0.43$) did not significantly affect mean body weight compared to saline. Overall, combined treatment with olaratumab and doxorubicin improved anti-tumor activity compared to either agent alone without inducing a substantial increase in toxicity based on limited safety endpoints including mortality and body weight. Similar results were seen with human KHOS/NP osteosarcoma xenografts (Study # 3521-05).

Figure 10: Effect of Olaratumab in Combination with Doxorubicin on Tumor Volume and Body Weight in SKLMS-1 Xenografts in Nude Mice



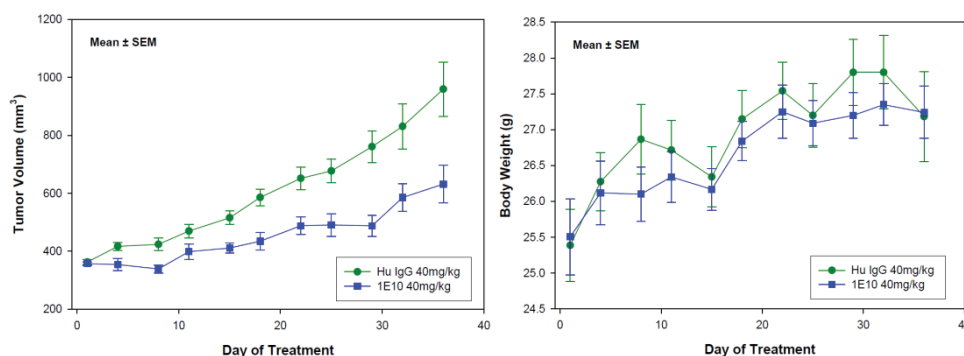
(Applicant Figure reproduced from Study # 3276-05)

The Applicant next investigated the mechanism of action for the increased in vivo anti-tumor activity of olaratumab in combination with doxorubicin (Study # 3347-05). Twelve female nude mice/group were subcutaneously implanted with SKLMS-1 cells and treated intraperitoneally with saline, 214/60 mg/kg olaratumab, 3 mg/kg doxorubicin, or olaratumab plus doxorubicin as described in Study # 3276-05. Tumors were harvested 3 and 7 days after the start of treatment (after two doses). IHC analysis demonstrated that treatment with olaratumab, doxorubicin, and olaratumab plus doxorubicin resulted in a statistically significant increase in ApopTag (TUNEL) staining on Day 3 compared to saline; combined treatment with olaratumab and doxorubicin was also statistically significant compared to olaratumab alone. Combined treatment with olaratumab and doxorubicin, but not either agent alone, significantly increased ApopTag staining on Day 7 compared to saline, olaratumab, and doxorubicin, indicating a more sustained effect on apoptosis, though there was no significant difference in cleaved caspase-3 staining between treatment groups. Treatment with olaratumab, doxorubicin, and olaratumab plus doxorubicin also resulted in a statistically significant decrease in phosphorylated Histone-3 (ph-H3) staining (marker for cells actively undergoing mitosis) on Day 3 compared to saline; combined treatment with olaratumab and doxorubicin was also statistically significant compared to doxorubicin alone. The majority of the effect on Day 3 appeared to be due to decreased ph-H3 staining in the tumor periphery rather than the tumor core. Combined treatment with olaratumab and doxorubicin, but not either agent alone, significantly decreased ph-H3 staining on Day 7 compared to saline, olaratumab, and doxorubicin, indicating a more sustained effect on tumor cell mitosis. In contrast, IHC analysis demonstrated that combined treatment with olaratumab and doxorubicin did not significantly affect expression of the proliferation marker Ki67, although there was a trend towards increased Ki67 staining on Day 7 in tumors treated with the combination compared to saline. Further, as measured by western blotting and/or IHC, the anti-tumor efficacy of olaratumab in combination with doxorubicin in SKLMS-1 xenografts is not due to significantly reduced AKT or MAPK phosphorylation.

The Applicant also investigated the in vivo anti-tumor activity of the chimeric surrogate antibody IMC-1E10 in 12 female nude mice/group bearing human A549 non-small cell lung

cancer (NSCLC) xenografts (Study # 4749-10). A549 cells express high PDGF-AA and PDGF-CC levels and have a high stromal content when grown in vivo. As shown in Figure 11, i.p. administration of 40 mg/kg IMC-1E10 three times per week significantly ($p=0.01$) inhibited xenograft growth compared to IgG, with a T/C value of 67% on Day 36. Treatment with IMC-1E10 did not significantly affect mean body weight compared to IgG. Since A549 is a human cell line, these data suggest that IMC-1E10 is targeting stromal fibroblasts in this mouse model.

Figure 11: Effect of IMC-1E10 on Tumor Volume and Body Weight in A549 NSCLC Xenografts in Nude Mice



(Applicant Figure reproduced from Study # 4749-10)

5.4 ADME/PK

Absorption studies conducted with olaratumab were not relevant and were not reviewed. Distribution, metabolism, and excretion studies were not conducted with olaratumab because it is a monoclonal antibody.

Type of study	Major findings
Absorption Pharmacokinetics of Monoclonal Antibody LSN3338786 Following a Single Intravenous Dose of 5 or 150 mg/kg LSN3338786 to Female Mice, Study # 8315117	<u>CD-1 Mice</u> $T_{1/2}$: 65-71 hrs AUC_{0-288} (5 mg/kg; LD): 1480 $\mu\text{g}\cdot\text{hr}/\text{mL}$ AUC_{0-360} (150 mg/kg; HD): 116000 $\mu\text{g}\cdot\text{hr}/\text{mL}$ C_{max} ($\mu\text{g}/\text{mL}$): 103 (LD) and 3040 (HD) $Clearance$ ($\text{mL}/\text{hr}/\text{kg}$): 3.35 (LD) and 1.25 (HD)
TK data from general toxicology studies 5-week toxicology study in monkeys, Study # 7573-104	<u>5-week Monkey</u> $T_{1/2}$: Day 1, 1.6-6.5 days; Day 29, 1.6-8.6 days in normal clearance (NC) monkeys and 0.1-0.5 days in rapid clearance monkeys. <i>Dose proportionality</i> : C_{max} generally increased dose proportionally in males and less than dose proportionally in females on Day 1. $AUC_{0-\infty}$ generally increased greater than dose proportionally on Days 1 and 29. <i>Accumulation</i> : Yes, based on $AUC_{0-\infty}$ at 5 mg/kg (~5-fold) and 50 mg/kg (~2-fold) on Day 29 compared to Day 1 in NC monkeys. <i>Gender differences</i> : C_{max} and AUC were ~2-fold higher in HD males compared to HD females.

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Type of study	Major findings
39-week toxicology study in monkeys, Study # 8201-235	Clearance: There was a dose-dependent decrease in mean clearance on Day 1. Four, 4, and 1 monkeys dosed with 5, 16, and 50 mg/kg olaratumab, respectively, exhibited rapid clearance after the fourth dose of olaratumab, suggestive of an immune response. These monkeys exhibited decreased olaratumab concentrations, half-lives, and AUC; TK data was provided separately for NC and rapid clearance animals on Day 29. ADA: Detected in 5 monkeys dosed at the low (5 mg/kg) dose level. Results were generally indeterminate at the HD due to high olaratumab concentrations. Only three of the LD rapid clearance monkeys exhibited anti-olaratumab antibodies; however, an overall immune response was observed in 6/6, 4/6, and 1/10 monkeys dosed with 5, 16, and 50 mg/kg olaratumab, respectively. <u>39-week Monkey</u> $T_{1/2}$: ≤ 3.2 days C_{max} (Day 267; M/F; mean; $\mu\text{g/mL}$): 7.5 mg/kg: 294 / 284 24 mg/kg: 994 / 1179 75 mg/kg: 3073 / 3654 AUC_{0-t} (Day 267; M/F; mean; $\mu\text{g}\cdot\text{hr/mL}$): 7.5 mg/kg: 20277 / 30322 24 mg/kg: 121854 / 153489 75 mg/kg: 446491 / 448122 AUC_{0-168} (Day 267; M/F; mean; $\mu\text{g}\cdot\text{hr/mL}$): 7.5 mg/kg: 19909 / 21870 24 mg/kg: 82951 / 105681 75 mg/kg: 270348 / 299605 Dose proportionality: Generally greater than dose proportionally Accumulation: There was ≤ 4-fold accumulation based on AUC_{0-t} on Day 267 compared to Day 1. Gender differences: None ADA: Detected in 5, 2, and 1 monkeys dosed with 7.5, 24, and 75 mg/kg olaratumab, respectively (22% of olaratumab-treated monkeys); resulted in substantially lower olaratumab concentrations. ADA production may have been masked at the mid and high dose levels by high olaratumab concentrations. ADA production generally correlated with rapid clearance. Volume of distribution: Less than total body water, suggesting limited distribution into tissues
TK data from reproductive toxicology studies An Embryo-Fetal Developmental Toxicity and Toxicokinetics Study in Mice Given LSN3338786 by Intravenous Injections	<u>Maternal</u> $T_{1/2}$: GD 6, ≤ 54.4 hrs; GD 15, ≤ 12.1 hrs C_{max} (GD 15; mean $\pm$ SD; $\mu\text{g/mL}$): 5 mg/kg: 45.8 ± 8.41 50 mg/kg: 913 ± 183 150 mg/kg: 3620 ± 595 AUC_{0-72hr} (GD 15; mean $\pm$ SEM; $\mu\text{g}\cdot\text{hr/mL}$):

Type of study	Major findings
During Gestation Days 6 through 15, Study #8332306	5 mg/kg: 560 ± 98.4 50 mg/kg: 10600 ± 592 150 mg/kg: 29600 ± 1470 <i>Dose proportionality:</i> Increased greater than dose proportionally between 5 and 50 mg/kg. <i>Accumulation:</i> None <i>Clearance:</i> Increased with repeat dosing and was higher in mice than in monkeys. <u>Fetal:Maternal Ratios</u> Minimally detected in the fetus on GD 10 and GD 12 GD 18: 5 mg/kg, 29.6; 50 mg/kg: 38.6 ± 25.4; 150 mg/kg, 16.3 ± 4.45

NC: Monkeys with normal clearance; LD: low dose; HD: high dose; SD: standard deviation; SEM: standard error of mean;
 Fetal:Maternal ratios = fetal tissue homogenates:maternal serum concentrations on GD 10 and GD 12, and fetal serum concentrations:maternal serum concentrations on GD 18

5.5 Toxicology

5.5.1 General Toxicology

Study title/ number: 39-Week Intravenous Chronic Toxicity and Toxicokinetic Study with IMC-3G3 in Cynomolgus Monkeys with a 8-Week Recovery Period/ 8201-235

Key Study Findings

- There were no mortalities.
- Potential target organs were the skin (alopecia), liver (increased ALT and individual cell necrosis), lung (pleural fibrosis), and pancreas (atrophy and chronic inflammation).

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 7.5, 24, and 75 mg/kg once weekly
 Route of administration: I.V. infusion over approximately 20 minutes
 Formulation/Vehicle: 10 mM histidine, 100 mM glycine, 50 mM sodium chloride, 75 mM mannitol, and 0.02% Tween 20, pH 5.5
 Species/Strain: *Macaca fascicularis* (cynomolgus monkey)
 Number/Sex/Group: 3/sex/group; 3/sex/group for a 8-week recovery period
 Age: 2 years, 6 months old to 6 years, 7 months old
 Satellite groups/ unique design: None/ immunogenicity and immunophenotyping
 Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical signs	MD: Red feces Alopecia at all dose levels but generally not dose-related
Body weights	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Hematology	MD: -7% MCHC on Day 120 HD: -4% MCHC on Day 120
Clinical chemistry	One HD female (#I65162) exhibited 444% and ~574% increases in ALT on Day 274 compared to baseline and controls, respectively
Urinalysis	One HD female (#I65161) exhibited 1049% and 1379% increases in urine volume on Day 120 compared to baseline and controls, respectively
Gross pathology	LD: Large thyroid in 1 male (#I65124), discolored colon in 1 male (#I65126) MD: Thickened colon in 1 female (#I65155), discolored mesenteric lymph node in 1 female (#I65155)
Organ weights	Dose-dependent increase in mean heart weight relative to body weight up to 22% at HD. Decrease in mean ovarian weight (absolute and relative to body and brain weight) in MD and HD females up to ~60% at MD. Decrease in mean seminal vesicle, prostate, and testis weight (absolute and relative to body and brain weight) at all dose levels, which likely reflected delayed organ maturity.
Histopathology Adequate battery: Yes	LD: Minimal adrenal medulla mineralization, slight kidney arteritis, minimal hypoplastic tubules in the testis MD: Minimal inflammation/crypt abscess in stomach, minimal to slight mixed infiltrate and congestion in colon, minimal depletion of zymogen granules in pancreas, cyst in thymus, minimal lymphocyte/macrophage infiltrate in brain HD: Minimal individual cell necrosis in liver, kidney arteritis, depletion in mandibular salivary gland, lymphocyte infiltrate in seminal vesicle/prostate, and hypoplastic tubules in testis, minimal to slight lymphocyte infiltrate in heart*, minimal lymphocyte/macrophage infiltrate in brain and minimal lymphocyte/macrophage infiltrate at infusion site
Reversibility	Findings trended towards recovery, except for the following gross pathology and histologic findings, some of which developed during the recovery period: Minimal lymphocyte infiltrate in the kidney (HD), prostate (LD-HD), and heart (LD-HD) Increase in the severity of chronic inflammation up to moderate in the pancreas at the HD LD: Small thyroid, moderate adrenal medulla mineralization, minimal tongue inflammation MD: Lung adhesion, discolored lung, lung pigment HD: Lung adhesion, minimal to slight pleural fibrosis in lung, minimal subpleural lymphoid aggregate in lung, lung pigment, slight interstitial fibrosis in kidney, moderate atrophy in pancreas accompanied by moderate chronic inflammation in one female (#I65163), minimal perivascular neutrophil infiltrate in heart, parasitic cyst in brain

LD: low dose; MD: mid dose; HD: high dose.

-: indicates reduction in parameters compared to control; +: indicates increase in parameters compared to control

*minimal findings also seen in all other groups, including control

General toxicology; additional studies

A Five-Week (4-dose) Toxicity, Toxicokinetic, and Immunogenicity Study of IMC-3G3 Administered Intravenously to Cynomolgus Monkeys with a Recovery Period / 7573-104

Olaratumab was administered intravenously once weekly at dose levels of 5, 16, or 50 mg/kg for 5 weeks (4 doses) to cynomolgus monkeys. There were no mortalities or clear target organs of toxicity. An increase in mean ALT (67% compared to controls) occurred in male monkeys at the 50 mg/kg dose level, which did not correlate with any histologic findings. At doses $\geq$ 16 mg/kg monkeys showed decreases (15 to 21%) in mean potassium. A dose-dependent increase in mean glucose occurred in female monkeys dosed with $\geq$ 5 mg/kg olaratumab compared to controls. These clinical chemistry findings trended towards recovery. There were no significant gross pathology or histologic findings.

A 13-Week Toxicity, Toxicokinetic and Immunogenicity Study of IMC-3G3 Administered Intravenously Weekly to Cynomolgus Monkeys with an 8-Week Recovery Period / 7573-105

Olaratumab was administered intravenously once weekly at dose levels of 7.5, 24, or 75 mg/kg for 13 weeks to cynomolgus monkeys. This study was not reviewed in detail because it examined the same dose levels of olaratumab that were evaluated in the 39-week study in monkeys. There were no mortalities or unexpected findings.

5.5.2 Genetic Toxicology

Not conducted per ICH S6.

5.5.3 Carcinogenicity

Not conducted per ICH S6, ICH S1, and ICH S9.

5.5.4 Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Fertility and early embryonic development studies were not conducted with olaratumab and are not required for pharmaceuticals intended to treat advanced cancer, but the Applicant did submit literature suggesting that loss of PDGF-A/PDGFR- α signaling may adversely affect male fertility. PDGF-A-deficient male mice exhibit progressive reduction in testicular size, Leydig cell loss, and spermatogenic arrest (Gnessi, Basciani, et al. 2000). Hoch and Soriano (2003) demonstrated that PDGFR- α is required for the differentiation of fetal and adult Leydig cells while Brennan et al. presented data showing that PDGFR- α -null embryos exhibit reduced XY gonad proliferation, mesonephric cell migration, and fetal Leydig cell differentiation (Brennan, Tilmann, et al. 2003). In addition, a tissue cross-reactivity study (# IM1236) demonstrated that rabbit anti-PDGFR- α stained the human testis (Leydig cells, Sertoli cells, spermatogenic precursors, and mature spermatids) and ovary (granulosa and thecal cells), though there were

no adverse histological findings in these reproductive organs in monkey general toxicology studies at olaratumab dose levels up to 75 mg/kg.

Embryo-Fetal Development

Literature Assessment

Embryo-fetal development studies were not conducted with olaratumab. Rather, the Applicant provided a scientific literature review and assessment of the reproductive toxicity potential of olaratumab, and conducted an embryo-fetal development study in mice using the murine surrogate antibody IMC-1E10. FDA advised the Applicant during the End-of-Phase 2 meeting in March 2015 that their initial scientific assessment of PDGFR- α was insufficient on its own to support an assessment of the reproductive risk associated with olaratumab, and that if data building a bridge between mouse knockout data and the use of olaratumab was not available, then an embryofetal development study or extended pre- and post-natal development (EPPND) study would be warranted to support a BLA. Following the Applicant's subsequent proposal to also conduct an embryo-fetal development study in mice with IMC-1E10, FDA agreed in June 2015 that this dual approach appeared reasonable.

A tissue cross-reactivity study (# IM1236) demonstrated that rabbit anti-human PDGFR- α stained the subtrophoblast stromal cells, amniotic epithelium, trophoblasts, endothelium, intravascular and interstitial lymphocytes, and Hofbauer cells of the human placenta. PDGFR has been detected on embryonic cells, and experiments using cultured blastocysts from mice demonstrated that PDGF neutralizing antibodies abrogated the normal increase in mouse trophoblast outgrowth surface area in vitro (Haimovici and Anderson 1993). These data suggest that PDGFR signaling is involved in blastomere and early embryonic development, which may impair implantation or lead to early death. Further, *Xenopus* embryos injected with dominant negative PDGFR- α mRNA exhibited aberrant gastrulation (Andrae, Gallini, et al. 2008).

PDGF-A and PDGFR- α are expressed at high levels during early embryogenesis and in the developing embryo/fetus, respectively (Soriano 1997), and animal studies have shown that PDGFR- α expression is important for normal embryonic survival and development. The absence of PDGFR- α has been investigated in various mouse knockout models, including mutant *Patch* (Ph) mice. The *Patch* mutation arose spontaneously and leads to coat color abnormalities and increased width of the prefrontal bone in heterozygous (Ph/+) mice; Ph/+ mice otherwise appear normal (Bowen-Pope, Van Koppen, et al. 1991). The gene encoding PDGFR- α is deleted in *Patch* homozygous (Ph/Ph) mutant mice (Stephenson, Mercola, et al. 1991), whereas Ph/+ mice express half of the wild-type level of PDGFR- α transcripts (Bowen-Pope, Van Koppen, et al. 1991). Although it is unknown whether other genes are also deleted in this mouse model, Stephenson et al. showed that the deletion associated with the *Patch* mutation does not extend into the coding sequences of the adjacent *Kit* gene. Further, since PDGFR- α expression generally correlates with the defects observed in these mice, PDGFR- α deletion is generally considered to be the primary cause of many of the observed abnormalities in Ph/Ph mice (Schatteman, Morrison-Graham, et al. 1992). PDGFR- α is expressed in mesenchymal

populations during embryonic development. Lack of PDGFR- α expression retards the proliferation of mesenchymal cells in Ph/Ph embryos, leading to poorly developed mesodermal derivatives by Day 6.5 to 9.5 of embryonic development (E6.5 to E9.5; Bowen-Pope, Van Koppen, et al. 1991). Ph/Ph homozygous mutants on a C57BL6/J background generally die by E10.5 and exhibit numerous defects including reduced growth, deficiencies in mesoderm structures, dilation of the pericardium, subepidermal blebs, a wavy neural tube, defects of neural crest origin, and defects in the yolk sac (Orr-Urtreger, Bedford, et al. 1992). About a third of Ph/Ph homozygotes backcrossed to a CBA or Balb/C background survive until E16 to E17, however, and exhibit spina bifida and a cleft face. Surviving Ph/Ph embryos generally exhibit defects in connective tissue arising from the mesoderm by E13.5, resulting in depletion of most connective tissue by E18. Ph/Ph embryos also exhibit distortion of the lens and cornea and malformation of the esophagus and trachea (Schatteman, Morrison-Graham, et al. 1992).

Soriano (1997) generated C57BL6/J mice carrying a targeted PDGFR- α null mutation. Data from this mouse model demonstrated that PDGFR- α is required for neural crest cell development and normal patterning of somites. Most homozygous embryos died by E16, but survivors exhibited extensive bleeding in the head and along the enlarged vertebral column. Homozygous mutant embryos also exhibited incomplete cephalic closure, increased apoptosis on pathways followed by migrating neural crest cells, alterations in vertebrae, ribs, and sternum, fusions of cervical vertebrae and ribs, and defects in the skull. Unlike the Ph/+ mice, mice heterozygous for the PDGFR- α null mutation did not exhibit a pigmentation defect (Soriano 1997). Deletion of PDGFR- α in both mouse models resulted in cleft face and spina bifida, possibly due to defects in migration of cranial neural crest cells, vertebral neural arch formation, and migration of somite derivatives. Inhibition of PDGFR signaling in *Xenopus* embryos also resulted in spina bifida, and cleft palates have been observed in other PDGFR- α -null mouse models (Andrae, Gallini, et al. 2008).

Other studies have further elucidated the role of PDGFR- α signaling in the development of murine organs and tissues. PDGFR- α knockout mice exhibited severe mesenchymal hypoplasia in the embryonic kidney (Xuri, Pontén, et al. 2000) as well as diaphragm malformations (Bleyl, Moshrefi, et al. 2007). PDGFR- α expression is also involved in the development of skin, hair follicles, teeth, lungs, and intestine. The skin of Ph/Ph mice is generally devoid of a dermal layer (Schatteman, Morrison-Graham, et al. 1992), and PDGFR- α -null mice exhibit severe dermal mesenchymal hypoplasia and skin blistering (Andrae, Gallini, et al. 2008). Further, surviving PDGF-A-null mice develop lung emphysema secondary to failure of alveolar septation (Boström, Willetts, et al. 1996). To investigate the role of PDGFR in cardiovascular development, French et al. used Cre/*loxP* technology to generate embryos lacking PDGFR- α and/or PDGFR- β in cardiomyocytes and vascular smooth muscle cells. Deletion of PDGFR- α or PDGFR- β did not result in overt vascular effects, but deletion of both receptors led to disruption in yolk sac blood vessel development (French, Creemers, et al. 2008). Further, Ph/Ph mice exhibit decreased smooth muscle cells, thin myocardium, reduced heart size, malformed valves, defective interventricular and interatrial septa (Schatteman, Motley, et al. 1995), and severe heart defects including failure of the heart to separate. Ph/Ph embryos also exhibit a poorly

developed choroid plexus, which results in the inability to produce enough cerebrospinal fluid to maintain adequate intraventricular pressure in embryos that survive to E18 (Bowen-Pope, Van Koppen, et al. 1991).

In summary, data from PDGFR- α knockout mice has demonstrated that PDGFR- α is critical for normal embryonic survival and development. PDGFR- α is required for the development of a subset of non-neuronal neural crest cell derivatives in the cardiac and cranial regions. PDGFR- α signaling plays an important role in the proper development of the vertebral arch, skeleton, lung, intestine, heart, brain, skin, eye, testis, kidney, palate, and teeth, suggesting that inhibition of this signaling pathway with olaratumab may adversely affect human embryo-fetal survival. Further, data from PDGFR- α knockout mice indicate an association between PDGFR- α deficiency and malformations. In addition, in humans, PDGFR- α mutations and promoter haplotypes have been associated with cleft palate (Rattanasopha, Tongkobpetch, et al. 2012) and spina bifida (Joosten, Toepoel, et al. 2001), suggesting that findings in animal models may be translatable to humans. To establish a link between inhibition with olaratumab and the findings seen in PDGFR- α knockout models, the Applicant conducted an embryo-fetal development study in mice using the murine surrogate antibody IMC-1E10 (reviewed below).

Study title/ number: An Embryo-Fetal Developmental Toxicity and Toxicokinetics Study in Mice Given LSN3338786 by Intravenous Injections During Gestation Days 6 through 15 / 8332306

Key Study Findings

- Increased post-implantation loss occurred at a dose of 5 mg/kg.
- IMC-1E10 crossed the placental barrier in pregnant mice.
- IMC-1E10 was teratogenic at dose levels $\geq$ 50 mg/kg.
- IMC-1E10 resulted in a dose-related increase in partially open eye malformations and additional ossification sites in the frontal/parietal skull compared to controls.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Dose and frequency of dosing: 5, 50, and 150 mg/kg administered on gestation day (GD) 6, 9, 12, and 15. 150 mg/kg is the maximum feasible dose (MFD).

Route of administration: I.V. injection

Formulation/Vehicle: Phosphate-buffered saline (PBS)

Species/Strain: Crl:CD-1 mice

Number/Sex/Group: 30 mated females/group

Satellite groups: TK: Blood was collected from up to 6 pregnant females/group/time point on GD 6, 12, 15, and 18. Fetal homogenates and blood were collected on GD 12 and GD 18, respectively. 6

additional HD TK females were dosed on GD 6 and GD 10 only; maternal blood and fetal homogenates were collected on GD 10.

Study design:

- Females were mated with male mice; Day 0 of gestation (GD 0) was the day of mating confirmation (sperm or sperm plug).
- Cesarean section was performed on GD 18: gross observations, live/dead fetuses, early/late resorptions, abnormalities, number of corpora lutea
- Fetal examinations: gender, body weights, external abnormalities; half of the fetuses from each litter were processed for visceral examination

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings																																																																						
Mortality	15 LD mice (7 main and 8 TK) following dosing on Days 12 or 15. Exhibited hypoactivity, twitching, sternal recumbency, squinting or discolored dark red eyes, labored respiration, discolored skin, blue hind legs, rough hair coat, and/or general debilitation potentially associated with an immune reaction to IMC-1E10.																																																																						
Clinical signs	See clinical signs listed above for preterm decedents. Fourteen additional LD mice exhibited at least one of these clinical signs but survived to scheduled euthanasia. Clinical signs at MD and HD were unremarkable.																																																																						
Body weights	Unremarkable																																																																						
Necropsy findings Cesarean section data	<table border="1"> <thead> <tr> <th>Dose (mg/kg)</th> <th>0</th> <th>5</th> <th>50</th> <th>150</th> </tr> </thead> <tbody> <tr> <td># Mated females</td> <td>30</td> <td>30</td> <td>30</td> <td>30</td> </tr> <tr> <td># Pregnant (%)</td> <td>25 (83)</td> <td>16 (53)*</td> <td>21 (72)</td> <td>22 (73)</td> </tr> <tr> <td># Dams with live fetuses</td> <td>25</td> <td>15</td> <td>21</td> <td>22</td> </tr> <tr> <td>Mean # corpora lutea</td> <td>14.1</td> <td>14.2</td> <td>14.3</td> <td>15.5</td> </tr> <tr> <td>Mean % pre-implantation loss</td> <td>7.8</td> <td>4.5</td> <td>7</td> <td>6.5</td> </tr> <tr> <td>Mean postimplantation loss</td> <td>0.7</td> <td>2.6</td> <td>0.8</td> <td>0.7</td> </tr> <tr> <td>Mean postimplantation loss (%)</td> <td>4.7</td> <td>19.5</td> <td>5.7</td> <td>5.2</td> </tr> <tr> <td>Mean # late resorptions</td> <td>0</td> <td>1.1</td> <td>0.4</td> <td>0</td> </tr> <tr> <td>Mean # total resorptions</td> <td>0.6</td> <td>1.6</td> <td>0.8</td> <td>0.7</td> </tr> <tr> <td>Mean # dead fetuses</td> <td>0</td> <td>0.9</td> <td>0</td> <td>0</td> </tr> <tr> <td>Mean # live fetuses</td> <td>12.4</td> <td>11</td> <td>12.6</td> <td>13.8</td> </tr> <tr> <td>Mean fetal body weight (g)</td> <td>1.41</td> <td>1.43</td> <td>1.38</td> <td>1.39</td> </tr> <tr> <td>Mean fetal sex ratio (% males)</td> <td>51.8</td> <td>52.2</td> <td>53.4</td> <td>52.3</td> </tr> </tbody> </table> (Reviewer generated table based on cesarean section data from Study # 8332306) *Excludes animals found dead/euthanized early due to hypersensitivity reactions LD: animal #A02159 (10 late resorptions) and #A02187 (14 aborted fetuses on GD 18, considered an early delivery)	Dose (mg/kg)	0	5	50	150	# Mated females	30	30	30	30	# Pregnant (%)	25 (83)	16 (53)*	21 (72)	22 (73)	# Dams with live fetuses	25	15	21	22	Mean # corpora lutea	14.1	14.2	14.3	15.5	Mean % pre-implantation loss	7.8	4.5	7	6.5	Mean postimplantation loss	0.7	2.6	0.8	0.7	Mean postimplantation loss (%)	4.7	19.5	5.7	5.2	Mean # late resorptions	0	1.1	0.4	0	Mean # total resorptions	0.6	1.6	0.8	0.7	Mean # dead fetuses	0	0.9	0	0	Mean # live fetuses	12.4	11	12.6	13.8	Mean fetal body weight (g)	1.41	1.43	1.38	1.39	Mean fetal sex ratio (% males)	51.8	52.2	53.4	52.3
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Parameters		Major findings			
		Dose (mg/kg)	0	5	50
Necropsy findings Offspring	# Fetuses examined (litters)	312 (25)	176 (15)	264 (21)	303 (22)
	External malformations: # of fetuses affected (litters); presented as %				
	Open eye	0.29 (4)	0 (0)	1.12 (5)	2.02 (14)
	Partially open eye	0 (0)	0 (0)	1.17 (14)	2.27 (18*)
	Exencephaly	0.31 (4)	0 (0)	0.66 (10)	0 (0)
	Limb malrotated	0 (0)	0.48 (7)	0 (0)	0.24 (5)
	Tail bent	0 (0)	0 (0)	0.32 (5)	0 (0)
	# Fetuses examined (litters)	157 (25)	87 (14)	131 (21)	151 (22)
	Visceral variations: # of fetuses affected (litters); presented as %				
	Carotid/innominate arteries-common origin	0 (0)	5.48 (14)	0 (0)	2.81 (9)
	# Fetuses examined (litters)	155 (25)	90 (15)	133 (21)	152 (22)
	Skeletal variations: # of fetuses affected (litters); presented as %				
	Calcaneum-unossified	4.7 (20)	0 (0)	6.08 (14)	0.51 (5)
	Rib				
	Detached	0 (0)	0 (0)	0 (0)	2.05 (9)
	Nodulated	0 (0)	0 (0)	0.95 (5)	0 (0)
	Skull				
	Frontal/parietal: additional ossification site	8.51 (28)	17.17 (40)	29.93 (62*)	29.83 (68**)
	Hyoid: additional ossification site	0 (0)	0 (0)	1.9 (5)	0 (0)
	Hyoid: bipartite ossification	0 (0)	0 (0)	0.95 (5)	0 (0)
	Hyoid: unossified	0 (0)	0.95 (7)	0 (0)	0 (0)
	Skeletal malformation: # of fetuses affected (litters); presented as %				
	Rib: interrupted	0 (0)	1.33 (7)	0 (0)	0.65 (5)
	Skull				
	Frontal: misshapen	0.57 (4)	0 (0)	1.28 (10)	0 (0)
	Interparietal: absent	0.57 (4)	0 (0)	1.28 (10)	0 (0)
	Parietal: absent	0 (0)	0 (0)	0.68 (5)	0 (0)
	Presphenoid: absent	0 (0)	0 (0)	0.68 (5)	0 (0)
	Squamosal: misshapen	0 (0)	0 (0)	1.28 (10)	0 (0)
	Supraoccipital: absent	0 (0)	0 (0)	0.68 (5)	0 (0)

(Reviewer generated table based on fetal examination data from Study # 8332306)
*, P ≤ 0.05 vs. controls; **, P ≤ 0.01 vs. controls

LD: low dose; MD: mid dose; HD: high dose; historical control range of anomalies for the test facility were not provided

Prenatal and Postnatal Development

Not conducted and not required to support the approval of a pharmaceutical intended for the treatment of patients with advanced cancer.

5.5.5 Other Toxicology Studies

Peripheral blood immunophenotyping was performed in the 39-week toxicology study in monkeys; findings were unremarkable.

Reactivity Study of Rabbit Anti-PDGFR α with Normal Human and Cynomolgus Monkey Tissues / IM1236

Because IHC staining of PDGFR- α -expressing elements could not be achieved with olaratumab, the Applicant conducted a GLP-compliant tissue cross-reactivity study with normal human (three donors/tissue) and cynomolgus monkey (two donors/tissue) tissues using a commercially available rabbit anti-PDGFR- α antibody (NeoMarkers). Anti-PDGFR- α staining was generally similar between human and cynomolgus monkey tissues. Rabbit anti-PDGFR- α stained the cytoplasm of human mesenchymal cells (smooth muscle cells, stromal cells, myofibroblasts, and adipocytes), glial cells in the brain, myenteric plexus, spinal cord, and pituitary, cerebral neurons, and the epithelium; the membrane and cytoplasm of platelets and endothelial cells in most tissues; the membrane and cytoplasmic granules of interstitial/intravascular lymphocytes in numerous tissues; the cytoplasmic granules of bone marrow-derived cells; and the membrane of mesangial cells in the kidney. Notably, rabbit anti-PDGFR- α also stained

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

numerous cell types in the human testis, prostate, ovary, fallopian tube, placenta, and uterus. Overall, the pattern of observed rabbit anti-PDGFR- α staining was generally consistent with the expected pattern of PDGFR- α expression.

X Emily Fox -S
Digitally signed by Emily Fox S
DN: c=US, o=US Government, ou=HHS
ou=FDA, ou=People, cn=Emily Fox, S
0923421920030010011-2001296929
Date: 2016.10.19.06:49:50 -0400

X Whitney S. Helms -S
Digitally signed by Whitney S Helms S
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ou=People, o=923421920030010011, 2000585776
cn=Whitney S Helms, S
Date: 2016.10.19.09:02:06 -0400

Primary Reviewer

Team Leader

6 Clinical Pharmacology

6.1 Executive Summary

The Applicant seeks approval of olaratumab in combination with doxorubicin for the treatment of patients with advanced soft tissue sarcoma (STS) not amenable to curative treatment with surgery or radiotherapy. The proposed olaratumab dosing regimen is 15 mg/kg administered by intravenous infusion over 60 minutes on days 1 and 8 of 21-day cycles until disease progression or unacceptable toxicity.

The Clinical Pharmacology Section of the BLA is supported by single and repeat dose pharmacokinetics (PK) studies of olaratumab as a single agent and in combination with doxorubicin in cancer patients and the following evaluations and analyses: potential pharmacokinetic drug-drug interaction (DDI) between olaratumab and doxorubicin, potential QT/QTc prolongation, and population pharmacokinetics (PopPK) and exposure-response (ER) relationships. The covariates that were found to have no clinically important influence on olaratumab PK include age (22 to 85 years old), sex (47% females), and race (86% Whites), mild to moderate renal impairment (calculated creatinine clearance (CLcr) 30-89 mL/min as estimated by the Cockcroft-Gault formula (C-G)), and mild (total bilirubin within upper limit of normal (ULN) and aspartate aminotransferase (AST) greater than ULN or total bilirubin greater than 1.0 and up to 1.5 times ULN and any AST) to moderate (total bilirubin greater than 1.5 and up to 3.0 times ULN and any AST) hepatic impairment. Exposure-response analysis for efficacy suggested that higher exposure to olaratumab may have increased survival benefit. Although a higher incidence of neutropenia and leukopenia after treatment with olaratumab plus doxorubicin as compared with doxorubicin alone was observed, higher olaratumab exposure was not associated with greater incidence of neutropenia and leukopenia in the exposure-safety analysis.

Recommendations

The proposed dosing regimen of 15 mg/kg administered by intravenous infusion over 60 minutes on days 1 and 8 of 21-day cycles has demonstrated clinical efficacy with a tolerable safety profile; therefore the proposed dosing regimen is acceptable. From a Clinical Pharmacology standpoint, the BLA is acceptable to support approval provided that the Applicant and the FDA reach an agreement regarding the labeling language.

The adequacy of the clinical pharmacology program in the overall drug development plan of olaratumab is summarized below:

- The Proposed dosing regimen of 15 mg/kg on days 1 and 8 in 21-day cycles for the general patient population is sufficiently supported.
- The effect of immunogenicity on PK, efficacy, and safety is sufficiently supported

- Labeling Recommendation: The effect of anti-olaratumab antibodies on efficacy, safety, and exposure could not be assessed due to (b) (4) the limited number of patients with treatment-emergent anti-olaratumab antibodies.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Disposition

Based on a population PK analysis, the PK of olaratumab at the doses of 15 mg/kg and 20 mg/kg was best described by a 2-compartment model with linear elimination. The estimated elimination half-life of olaratumab was approximately 11 days (range 6 to 24 days) with steady-state volume of distribution (CV%) of 7.7 L (16%) and clearance (CV%) of 0.56 L/day (33%).

Exposure-Response (ER) Relationships

ER for overall survival: Olaratumab exposure (C_{avg}) and other covariates of interest were evaluated in ER analysis for overall survival (OS). Covariates evaluated include PDGFR α (positive vs. negative by immunohistochemistry assessment), previous lines of treatment (0 vs 1 or more), histological tumor type, and ECOG Performance Status. The ER analysis suggested the higher exposures may result in a greater survival benefit. The distribution of influential covariates in high and low exposure groups is generally balanced. Further analyses did not identify additional covariates.

Population concentration-QTc analyses using time-matched ECG and PK data from 15 patients with STS showed no statistically significant relationship between olaratumab concentrations and Δ QTcF. No large changes (i.e., > 20 ms) in QTcF intervals were detected with olaratumab 15 mg/kg.

Immunogenicity

Of 370 patients, 13 patients (3.5%) were positive for treatment-emergent (TE) anti-drug antibodies (ADAs). Neutralizing antibodies were detected in these 13 patients who tested positive for TE-ADAs. The effect of ADAs on efficacy, safety, and exposure of olaratumab could not be assessed due to low incidence resulting in the limited number of patients with treatment-emergent anti-olaratumab antibodies.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen of olaratumab for the treatment of advanced STS is 15 mg/kg on days 1 and 8 of each 3-week cycle until disease progression or unacceptable toxicity, co-administered with doxorubicin on day 1 of each cycle in the first 8 cycles following the olaratumab infusion. The selected dose was based on results of nonclinical studies in animal tumor models, safety data obtained from Trial JGDC, ER analysis, and efficacy and safety data from Trial JGDG. Nonclinical studies in animal tumor models indicated that olaratumab plasma concentration in a range of 155 to 258 µg/mL were associated with antitumor activity. In Trial JGDG, a clinically meaningful improvement in OS of 11.8 months was observed with the proposed dosing regimen, in comparison to treatment with doxorubicin alone. The ER analysis suggested that higher olaratumab exposure may have increased survival. Treatment with olaratumab is associated with adverse events such as nausea, musculoskeletal pain, neutropenia, mucositis, vomiting, and diarrhea. Dose reduction to 12 mg/kg occurred in patients with severe adverse events.

Therapeutic Individualization

Factors including age, sex, race, renal function, and hepatic function were not found to have a clinically important effect on olaratumab PK. Dose adjustment is not necessary for these factors.

Outstanding Issues

None.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics Bioanalytical Method

Serum olaratumab concentrations were determined either by the original bioanalytical method (Method Validation Report VR1776) or the modified bioanalytical method (Method Validation Report 178103). Although both methods have been independently validated, cross-validation between the 2 methods showed a lack of comparability for 23 samples from Trial JGDE. The Applicant states that the original bioanalytical method had lack of specificity and selectivity assessment, unconventional determination of lower and upper limit of quantitation, and incurred sample reanalysis (ISR) was not conducted with the original bioanalytical method. In contrast, the modified bioanalytical method (178103) was fully validated according to industry and regulatory guidelines with ISR demonstrating internal reproducibility. Therefore, serum

concentration data from Trial JGDG, JGDB, JGDE, JGDI, and JGDH measured with the modified bioanalytical method will be the primary source for olaratumab PK characterization.

Table 2: Olaratumab Concentrations Determined Using the Original and Modified ELISA Methods

Sample #	Lilly Original Assay (µg/mL)	(b) (4) Modified Assay (µg/mL)	% Difference
1	923	434	72
2	203	111	59
3	981	519	62
4	1236	659	61
5	496	150	107
6	1159	645	57
7	652	409	46
8	558	390	35
9	174	81	73
10	887	520	52
11	117	59	65
12	738	464	46
13	547	166	107
14	195	105	60
15	766	445	53
16	346	254	31
17	710	321	75
18	206	144	36
19	552	283	64
20	316	97	106
21	888	489	58
22	731	392	60
23	866	439	65
%Difference calculated as ((original-modified)/mean (original, modified))*100			
Source: Olaratumab Cross Validation Report, Table 1, Page 9.			

Pharmacokinetics

PK parameters were determined by intensive PK samples collected from Trial JGDG and noncompartmental analysis. Sparse PK samples were collected from Trials JGDG, JGDB, JGDE, and JGDH and analyzed via popPK analyses.

PK parameters of olaratumab in combination with doxorubicin were determined using noncompartmental analysis and summarized in Table 3 and Table 4.

Table 3: Single Dose and Multiple Dose PK Parameters of Olaratumab in Combination with Doxorubicin in Cancer Patients (Cycle 1)

PK Parameter	Geometric Mean (CV%)	
	Day 1 (n=14)	Day 8 (n=7)
AUC _{0-168h} (µg·h/mL)	19800 (32.2)	39200 (29.0)
C _{max} (µg/mL)	276 (25.6) ^b	305 (12.4)
C _{min} (µg/mL)	56.2 (51.5)	44.7 (47.0)
CL (L/h)	0.062 (28.6)	0.033 (33.0)
V _{ss} (L)	8.15 (30.7)	7.03 (33.7)
t _{1/2} (day) ^a	4.0 (2.1-6.3)	6.7 (4.3-9.6)
^a Geometric mean (range) ^b n=13		

Source: Trial JGDG Final Study Report, Table JGDG.11.23., Page 139.

Table 4: Steady-State PK Parameters of Olaratumab in Combination with Doxorubicin in Cancer Patients (Cycle 3)

PK Parameter	Geometric Mean (CV%)	
	Day 1 (n=3)	Day 8 (n=4)
AUC _{0-168h} (µg·h/mL)	28200 (35.9)	47300 (35.0)
C _{max} (µg/mL)	286 (39.7)	296 (19.9)
C _{min} (µg/mL)	120 (21.0)	84.3 (47.2)
CL (L/h)	0.041 (39.7)	0.024 (25.8)
V _{ss} (L) ^a	7.4 ; 4.4	9.5 ; 6.6
t _{1/2} (day) ^a	5.7 ; 4.4	14.4 ; 6.7
^a Individual values, n=2		

Source: Trial JGDG Final Study Report, Table JGDG.11.24., Page 139.

Based on a popPK analysis, the estimated elimination half-life of olaratumab was approximately 11 days (range 6 to 24 days) with steady-state volume of distribution (CV%) of 7.7 L (16%) and clearance (CV%) of 0.56 L/day (33%).

6.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Support for evidence of effectiveness was obtained from Trial JGDG.

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

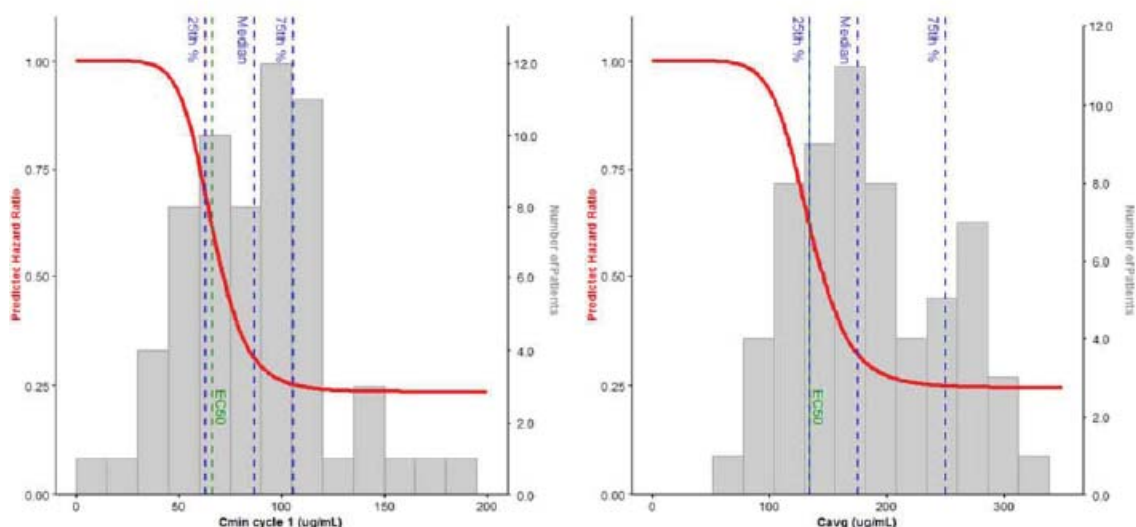
The proposed dosing regimen for olaratumab is 15 mg/kg administered on days 1 and 8 of a 21-day cycle in combination with 75 mg/m² doxorubicin. The selected dose was supported by results of nonclinical studies in animal tumor models, ER analyses, and efficacy and safety data from Trial JGDG. In vivo tumor growth inhibition was demonstrated in athymic mice bearing

PDGFR α -positive subcutaneous human tumor xenografts representing glioblastoma (U118 model), leiomyosarcoma (SKLMS-1 MODEL), RHABDOID (A204 model), and NSCLC (NCI-H1703 model). The nonclinical studies suggested that olaratumab serum concentrations in a range of 155 to 258 $\mu\text{g}/\text{mL}$ were associated with antitumor activity.

Safety data obtained from the olaratumab single agent Trial JGDC indicated that olaratumab was consistently well tolerated with no dose-limiting toxicities observed up to a dose of 20 mg/kg administered every 2 weeks. In addition, a PK model developed using the PK data obtained from Trial JGDC suggested that a dose of 15 mg/kg administered on days 1 and 8 of a 21-day cycle would yield steady-state trough serum concentrations exceeding the target minimum trough levels of olaratumab associated with antitumor activity observed in nonclinical tumor xenograft models. Based on these results, an olaratumab dose of 15 mg/kg administered on days 1 and 8 of a 21-day cycle was selected for Trial JGDG.

Trial JGDG demonstrated a statistically significant and clinically meaningful improvement in OS of 11.8 months with olaratumab plus doxorubicin treatment. ER modeling (survival model) performed using Trial JGDG OS data indicated an effective $\text{EC}_{\text{min}150}$ value of 66.1 $\mu\text{g}/\text{mL}$. The model also predicted an E_{max} of 0.75 (corresponding to a maximum improvement in the HR of 75%) achievable within the range of serum concentrations observed in the trial. Similar results were obtained from a similar model relating OS to C_{avg} ($\text{EC}_{\text{avg}50} = 134.4 \mu\text{g}/\text{mL}$, $E_{\text{max}} = 0.75$). Since the $\text{EC}_{\text{min}150}$ and $\text{EC}_{\text{avg}50}$ correspond, respectively, to the 25th percentiles of the $C_{\text{min}1}$ and C_{avg} distribution in Trial JGDG, these results indicate that the dose of 15 mg/kg olaratumab is predicted to provide the majority of patients with a survival benefit.

Figure 12: Predicted Effect of Olaratumab on the Hazard Ratio for Overall Survival



Abbreviations: C_{avg} = average concentration over patient's entire treatment; C_{min1} = trough serum concentration at the end of Cycle 1; EC_{avg50} = olaratumab C_{avg} yielding a 50% decrease in the baseline hazard; EC_{min150} = olaratumab C_{min1} yielding a 50% decrease in the baseline hazard; HR = hazard ratio.

Overall survival as predicted by C_{min1} -based model (left panel) and the C_{avg} -based model (right panel). The solid red lines describe the change in HR as a function of C_{min1} and C_{avg} ; the grey histograms describe the distribution of olaratumab C_{min1} and C_{avg} in the Study JGDG experimental arm together with their quartiles (dashed blue lines); the green dashed lines indicate EC_{min150} and EC_{avg50} .

Source: Figure 8.14 on page 59 of applicant's population PK report

In addition, the safety data from Trial JGDG demonstrated that olaratumab administered in combination with doxorubicin was generally tolerated.

Given the evident survival benefit and acceptable safety profile, the dose of 15 mg/kg olaratumab administered on days 1 and 8 of a 21-day cycle in combination with doxorubicin is deemed acceptable. The ER analysis suggests that higher exposure of olaratumab may be associated with increased survival. (b) (4)

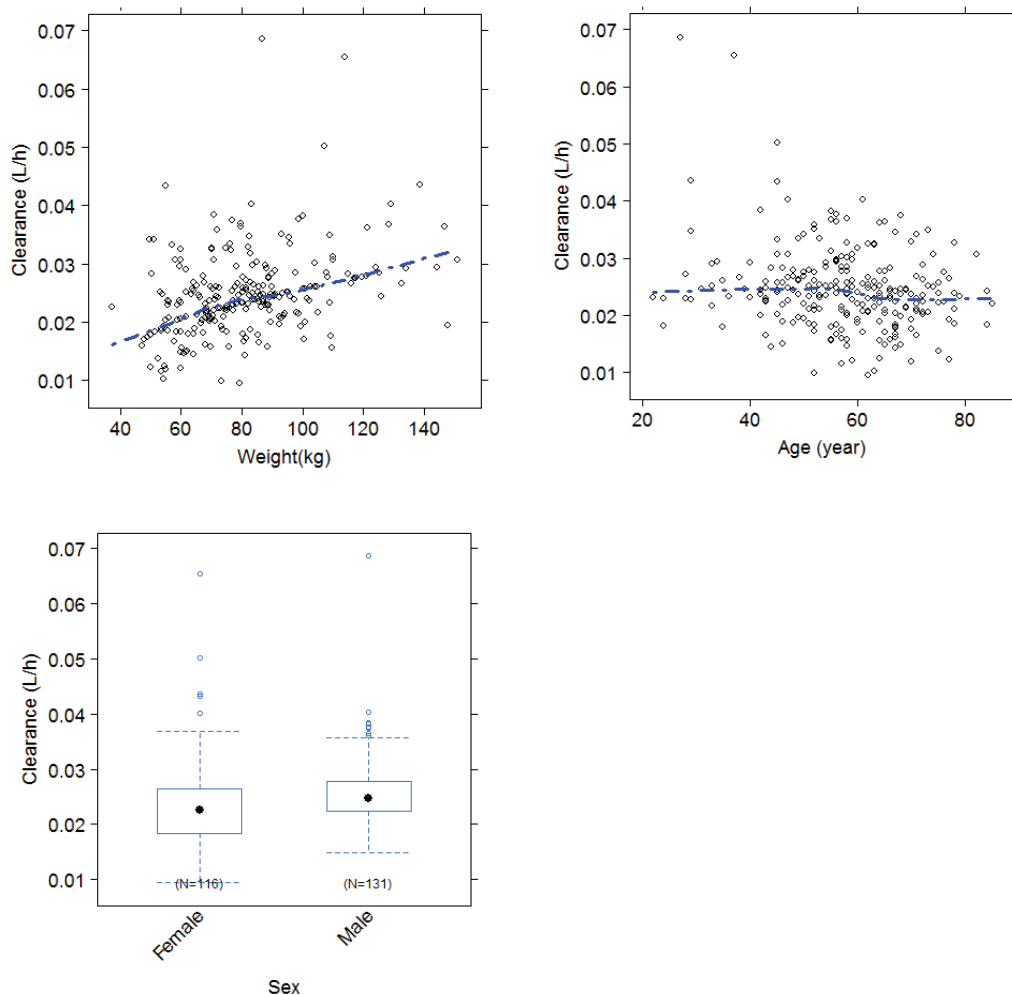
Due to the limited sample size in the Trial JGDG, the survival benefits (b) (4) will need further verification in the ongoing Trial JGDJ.

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

Multiple covariates were assessed for their effect on olaratumab PK in cancer patients in a popPK analysis. Body weight was found to have a significant effect on olaratumab clearance and volume of distribution. Body weight (range 37 to 151 kg) correlates with clearance of olaratumab, supporting body weight-based dosing. Other covariates of interest, including sex

(47% female), age (range 22 to 85 years old), and race (86% Whites, 12% Blacks), renal function (Cockcroft-Gault creatinine clearance range 14-250 mL/min), hepatic function (as assessed by alanine aminotransferase (range 4 to 88 U/L), aspartate transaminase(range 5 to 96 U/L), and total bilirubin (range 1.7 to 25.7 $\mu\text{mol/L}$) did not have significant effect on olaratumab PK. Dose adjustments based on these covariates are not necessary.

Figure 13: Relationship between Olaratumab Clearance and Covariates of Interest



Source: Figure generated by the reviewer using output of the final population PK model

Immunogenicity

Blood samples were collected from 9 olaratumab trials (JGDG, JGDA, JGDB, JGDD, JGDC, JGDF, JGDE, JGDH, and JGDI) for the analysis of anti-drug antibodies (ADAs). In addition to scheduled sampling, samples were taken for ADA assessment in the event of an infusion-related reaction

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

(IRR), at the onset of the reaction, at the resolution of the reaction, and 30 days following the resolution of the reaction.

Of 370 patients, 13 patients (3.5%) were positive for treatment-emergent ADAs. Samples were identified as treatment-emergent (TE) positive if the post-baseline sample had an increase of $\geq$ 4-fold in titer from baseline values or in the case of a baseline value that was not detected or was not present, a 1:20 titer after treatment. Neutralizing antibodies were detected in these 13 patients who tested positive for treatment-emergent anti-olaratumab antibodies (TE-ADAs).

Table 5: Immunogenicity Results for Olaratumab-Treated Patients

Trial	Evaluable ¹ (n)	Baseline ADA- Positive (%)	Post- Baseline ADA- Positive (%)	TE-ADA ² Positive (%)	Persistent ³ TE-ADA Positive	Transient ⁴ TE-ADA Positive	Neutralizing Antibody- Positive (%)
JGDG	85	11 (12.9%)	6 (7.0%)	5 (5.9%)	4 (4.7%)	1 (1.2%)	5 (5.9%)
Olaratumab plus doxorubicin	69	10 (14.5%)	5 (7.2%)	4 (5.8%)	3 (4.3%)	1 (1.4%)	4 (5.8%)
Olaratumab	16	1 (6.3%)	1 (6.3%)	1 (6.3%)	1 (6.3%)	0	1 (6.3%)
JGDA	77	3 (3.9%)	3 (3.9%)	1 (1.3%)	0	1 (1.3%)	1 (1.3%)
Olaratumab plus liposomal doxorubicin	57	2 (3.5%)	2 (3.5%)	1 (1.8%)	0	1 (1.8%)	1 (1.8%)
Olaratumab	20	1 (5.0%)	1 (5.0%)	0	0	0	0
JGDB	49	3 (6.1%)	4 (8.2%)	3 (6.1%)	1 (2.0%)	2 (4.1%)	3 (6.1%)
Olaratumab plus paclitaxel/carboplatin	45	2 (4.4%)	4 (8.9%)	3 (6.7%)	1 (2.2%)	2 (4.4%)	3 (6.7%)
Olaratumab	4	1 (25%)	0	0	0	0	0
JGDD	63	8 (12.7%)	4 (6.3%)	2 (3.2%)	1	1	2 (3.2%)
Olaratumab plus mitoxantrone	52	7 (13.5%)	4 (7.7%)	2 (3.8%)	1 (1.9%)	1 (1.9%)	2 (3.8%)
Olaratumab	11	1 (10%)	0	0	0	0	0
JGDC	18	1 (5.6%)	1 (5.6%)	1 (5.6%)	1 (5.6%)	0	1 (5.6%)
JGDF	15	0	0	0	0	0	0
JGDE	26	1 (3.8%)	0	0	0	0	0
JGDH	19	2 (10.5%)	2 (10.5%)	1 (5.3%)	1 (5.3%)	0	1 (5.3%)
JGDI	18	0	0	0	0	0	0

¹ Patients with an evaluable immunogenicity baseline sample and at least 1 evaluable post-baseline sample or patients with no evaluable baseline sample whose evaluable post-baseline samples are all ADA-negative.

² TE-ADA positive: 1) a patient with a 4-fold (2 dilutions) increase over a positive baseline antibody titer; or 2) for a negative baseline titer, a patient with an increase from the baseline to a level of 1:20.

³ TE-ADA positive results detected at ≥ 2 sample times where the first and last TE-ADA positive samples are separated by ≥ 12 weeks or if: 1) the last sample obtained while on study treatment or in the follow-up period is TE-ADA positive but with no further opportunity to assess persistence or; 2) the last sample obtained while on study treatment is TE-ADA positive and the first sample within the follow-up period is also positive.

⁴ TE-ADA positive result(s) detected that do not satisfy the conditions required of TE persistent positive ADA patients. This would include patients who are TE-ADA positive at ≥ 1 sampling time points where the time between the first and last positive sample is < 12 weeks and the last obtained sample while on study treatment or in the follow-up period is ADA-negative or if the last obtained sample during the treatment period is TE-ADA positive and does not persist into the follow-up period.

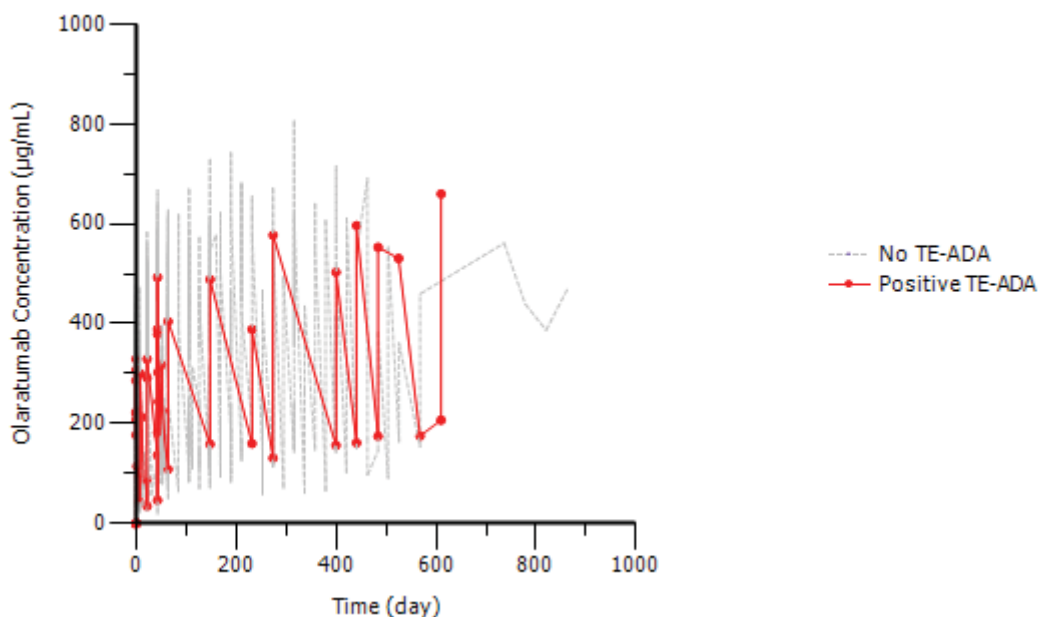
A definitive conclusion on the effect of anti-olaratumab antibodies on efficacy, safety, and exposure could not be made due to the limited number of patients with treatment-emergent anti-olaratumab antibodies. The effect of immunogenicity will need further analysis using

additional data obtained in the ongoing Study JGDJ. Analyses of Immunogenicity using data from Study JGDJ are shown below.

Effect of Immunogenicity on PK

Concentration-time profiles using intensive PK data of patients with positive TE-ADAs were within the range of those with no TE-ADAs in Trial JGDG (Figure 14).

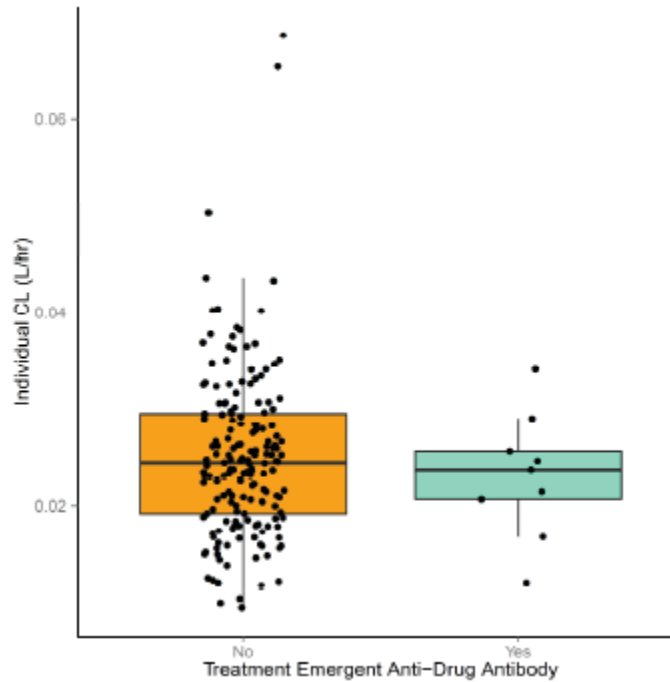
Figure 14: Olaratumab Concentration-Time Profiles for Patients with Positive Vs. Negative Treatment-Emergent Anti-Olaratumab Antibodies in Trial JGDG



Source: Reviewer's Analysis

Based on a popPK analysis using sparse samples, TE-ADAs did not appear to affect the clearance of olaratumab (Figure 15). Individual CL estimates in patients who tested for TE-ADAs did not show any difference compared to those obtained for other patients.

Figure 15: No Evident Relationship between Olaratumab Clearance and Treatment-Emergent Anti-Drug Antibody



Source: Summary of Clinical Pharmacology Studies, Figure 2.7.2.13, Page 53.

Effect of Immunogenicity on Safety

The incidence of IRR was not increased with positive ADA (Table 6). No temporal relationship between the occurrence of IRR and positive ADA was identified.

Table 6: Relationship between Immunogenicity and IRRs

Trial	Evaluable ¹ (n)	Baseline ADA- Positive (%)	Post- Baseline ADA- Positive (%)	TE-ADA ² Positive (%)	Neutralizing Antibody- Positive (%)	IRR and ADA- Positive	Overall IRR ³ (n)
JGDG	85	11 (12.9%)	6 (7.0%)	5 (5.9%)	5 (5.9%)	2 (2.4%)	16/109 (14.7%)
Olaratumab plus doxorubicin	69	10 (14.5%)	5 (7.2%)	4 (5.8%)	4 (5.8%)	1 (1.4%)	10/79 (12.7%)
Olaratumab	16	1 (6.3%)	1 (6.3%)	1 (6.3%)	1 (6.3%)	1 (6.3%)	6/30 (20%)
JGDA	77	3 (3.9%)	3 (3.9%)	1 (1.3%)	1 (1.3%)	2 (2.6%)	9/90 (10%)
Olaratumab plus liposomal doxorubicin	57	2 (3.5%)	2 (3.5%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	6/62 (9.7%)
Olaratumab	20	1 (5.0%)	1 (5.0%)	0	0	1 (5.0%)	3/28 (10.7%)
JGDB	49	3 (6.1%)	4 (8.2%)	3 (6.1%)	3 (6.1%)	2 (4.1%)	19/85 (22.4%)
Olaratumab plus paclitaxel/carboplatin	45	2 (4.4%)	4 (8.9%)	3 (6.7%)	3 (6.7%)	1 (2.2%)	17/67 (25.4%)
Olaratumab	4	1 (25%)	0	0	0	1 (25%)	2/18 (11.1%)
JGDD	63	8 (12.7%)	4 (6.3%)	2 (3.2%)	2 (3.2%)	5 (7.9%)	9/81 (11.1%)
Olaratumab plus mitoxantrone	52	7 (13.5%)	4 (7.7%)	2 (3.8%)	2 (3.8%)	4 (7.7%)	6/62 (9.7%)
Olaratumab	11	1 (10%)	0	0	0	1 (9.1%)	3/19 (15.8%)
JGDC	18	1 (5.6%)	1 (5.6%)	1 (5.6%)	1 (5.6%)	0	5/19 (26.3%)
JGDF	15	0	0	0	0	0	0/16
JGDE	26	1 (3.8%)	0	0	0	0	4/40 (10%)
JGDH	19	2 (10.5%)	2 (10.5%)	1 (5.3%)	1 (5.3%)	0	5/21 (23.8%)
JGDI	18	0	0	0	0	0	3/24 (12.5%)

¹ Patients with an evaluable immunogenicity baseline sample and at least 1 evaluable post-baseline sample or patients with no evaluable baseline sample whose evaluable post-baseline samples are all ADA-negative.

² TE-ADA positive: 1) a patient with a 4-fold (2 dilutions) increase over a positive baseline antibody titer; or 2) for a negative baseline titer, a patient with an increase from the baseline to a level of 1:20.

³ Patients who received at least 1 dose of olaratumab and experienced an infusion-related reaction (IRR) of any grade due to olaratumab.

Source: Summary of Clinical Safety, Table 2.7.4.37, Page 107.

Effect of Immunogenicity on Efficacy

In Trial JGDG, TE-ADAs were detected in 5 patients. Their PFS and OS outcomes were mostly consistent with the median PFS (by Investigator assessment) of 6.6 months (90% CI: 4.1, 8.3) and median OS of 26.5 months (90% CI: 20.9, 31.7) in the overall population.

PDGFR α Expression Status and Efficacy

Randomization for the phase 2 portion of the Trial JGDG was stratified by PDGFR α expression (positive vs. negative), number of previous lines of treatment (0 vs. 1+ lines), histological tumor type (LMS vs. synovial sarcoma vs. other tumor type), and Eastern Cooperative Oncology Group performance status (ECOG PS; 0-1 vs. 2). PDGFR α expression levels in archival or fresh biopsy specimens were assessed at a central academic laboratory using immunohistochemistry (IHC) (Assay 1); tumor samples categorized as positive had a staining result of 2+ or greater. The applicant indicated that after the trial was enrolled, it was determined that the antibody used in the IHC assay used for randomization also recognized PDGFR β , showing poor specificity. Samples were subsequently assayed with an alternative PDGFR α IHC assay (Assay 2) that, according to the applicant, was developed using a commercially available antibody highly sensitive and specific for PDGFR α . Samples with weak membranous staining of >30% of tumor cells or strong membranous staining >5% of tumor cells were considered positive. Stroma was positive if >5% of stromal cells had strong membranous staining. Samples not meeting these criteria were considered negative.

Samples were positive for PDGFR α using Assay 1 in 88% of evaluable cases, precluding meaningful assessment of heterogeneity across subgroups. Samples were evaluable (valid, nonmissing) for baseline PDGFR α expression using Assay 2 in 111 of 133 patients in the ITT population, of whom 37 (33%) had samples positive for PDGFR α expression. PDGFR α status by STS histological subtypes is listed in Table 7.

Table 7: IHC PDGFR α Status by Histology; Trial JGDG Population assessed by Assay 2 (N=111)

Subtype	PDGFRα Positive N = 37	PDGFRα Negative N = 74	Total N = 111
Angiosarcoma	0	5	5
Fibrosarcoma	1	0	1
LMS	9	34	43
Liposarcoma	9	11	20
Neurofibrosarcoma	0	0	0
Synovial Sarcoma	2	0	2
Undifferentiated Pleomorphic Sarcoma	11	11	22
Other ^a	5	13	18

Source: Applicant's table JGDG.11.19; I5B-IE-JGDG Clinical Study Report Body. LMS = leiomyosarcoma; IHC = immunohistochemistry. Data cut-off date: 16 May 2015.

PFS and OS by PDGFR α expression (Assay 2) are summarized in the table below. Based on the applicant's analyses, the interaction between PDGFR α expression and treatment was not statistically significant for OS and PFS, although longer OS was observed in the olaratumab plus doxorubicin arm compared to the control arm in patients with PDGFR α expression-negative status (30.88 vs. 16.66 months). This was not observed in patients with PDGFR α expression-positive status (Table 8).

Table 8: Progression Free Survival and Overall Survival by IHC PDGFR α Status and Treatment Arms; Trial JGDG Population Assessed by Assay 2 (N=111)

Progression Free Survival

	PDGFR α Positive		PDGFR α Negative	
	Investigational Arm N = 18	Control Arm N = 19	Investigational Arm N = 37	Control Arm N = 37
Patients with Events, n (%)	16 (88.89)	15 (78.95)	29 (78.38)	28 (75.68)
Patients Censored, n (%)	2 (11.11)	4 (21.05)	8 (21.62)	9 (24.32)
Median^a (months)	2.97	4.11	6.51	4.37
95% CI ^a	(1.41, 8.77)	(1.54, 6.21)	(4.07, 8.44)	(1.64, 7.06)
Interaction p-value ^b	0.5924			
Hazard Ratio ^c	0.91		0.71	
95% CI ^c	(0.43, 1.92)		(0.42, 1.20)	

Overall Survival

	PDGFR α Positive		PDGFR α Negative	
	Investigational Arm N = 18	Control Arm N = 19	Investigational Arm N = 37	Control Arm N = 37
Patients with Events, n (%)	14 (77.78)	17 (89.47)	19 (51.35)	26 (70.27)
Patients Censored, n (%)	4 (22.22)	2 (10.53)	18 (48.65)	11 (29.73)
Median^a (months)	14.52	15.08	30.88	16.66
95% CI ^a	(6.97, 22.74)	(3.61, 21.91)	(22.70, -)	(8.87, 25.99)
Interaction p-value ^b	0.3209			
Hazard Ratio ^c	0.64		0.40	
95% CI ^c	(0.31, 1.33)		(0.21, 0.73)	

Source: Applicant's tables JGDG.11.20 and JGDG.11.21; I5B-IE-JGDG Clinical Study Report Body. CI = confidence interval; IHC = immunohistochemistry; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category. Data cut-off date: 16 May 2015.

a. Estimated by the Kaplan-Meier method. b. Interaction p-value is based on the likelihood ratio test for the interaction term from the Cox model. c. Hazard ratio is expressed as olaratumab + doxorubicin/doxorubicin and estimated from Cox model that includes marker status, treatment, interaction between marker status and treatment, and stratification factors excluding marker status by assay

These exploratory findings are inconclusive as to whether PDGFR α expression status in tumors (positive vs negative, as determined by IHC) affects the outcome, and do not provide a means to generalize the findings in the subset of sarcomas enrolled in JGDG to other soft tissue sarcomas that express PDGFR α . According to the applicant, several technical and biological factors preclude further interpretation of the role of tumor PDFGR α expression as a marker of

response, including: (1) the IHC assay did not distinguish between PDGFR α expression in tumor cells and surrounding stromal cells, (2) use of archived biopsies from either primary or metastatic sites that may not reflect the level of PDGFR α expression at study entry, and (3) potential differences in sensitivity of the IHC assay to detect different PDGFR α dimers that may be relevant to olaratumab activity. The applicant plans to further investigate the role of PDGFR α expression on response to olaratumab in the ongoing confirmatory trial, JGDJ.

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

No clinically relevant changes in the exposure of either olaratumab or doxorubicin were observed when olaratumab 15 mg/kg and doxorubicin 75 mg/m² were coadministered in patients.

Effect of Olaratumab on Doxorubicin

The potential effect of olaratumab on doxorubicin PK was evaluated in 13 patients with STS in Trial JGDI. Coadministration of doxorubicin 75 mg/m² with olaratumab 15 mg/kg on cycle 1 day 10 did not affect the PK of doxorubicin (Table 9).

Table 9: Comparative Analysis of Doxorubicin PK Parameters on Day 1 (Without Olaratumab) and Day 10 (With Olaratumab)

Exposure parameter	Geometric Mean (%CV)		Geometric Mean Ratio* (90% CI)
	Doxorubicin alone (n=13)	Doxorubicin plus with olaratumab (n=13)	
AUC _{0-last} (ng·hr/mL)	2250 (17)	2290 (25)	1.06 (0.94, 1.19)
AUC _{0-inf} (ng·hr/mL)	2570 (17)	2610 (24)	1.05 (0.95, 1.17)
C _{max} (ng/mL)	2660 (55)	2500 (73)	0.984 (0.755, 1.28)
* Doxorubicin 75 mg/m ² alone vs. doxorubicin 75 mg/m ² plus olaratumab 15 mg/kg on day 10 Source: JGDI Final Study Report, Tables JGDI.7.1 and JGDI.7.2 Page 32.			

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Effect of Doxorubicin on Olaratumab

The potential effect of doxorubicin on olaratumab PK was evaluated by popPK analysis with olaratumab concentration data collected from patients who received olaratumab as a single agent (n=73) and in combination with doxorubicin (n=53) or paclitaxel/carboplatin (n=45). No difference in olaratumab clearance or volume of distribution was observed between patients who received olaratumab alone as compared with olaratumab plus doxorubicin or paclitaxel/carboplatin.

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Primary Reviewer

X Fang
Li -S

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Team Leader

X Jingyu
Yu -S

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Primary Reviewer

X Rosane
Charlaborbach -S

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cn=Rosane Charlaborbach -S
Date: 2016.10.19 09:34:36 -04'00'

Team Leader

X Namatiqur
Rahman -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
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cn=Namatiqur Rahman -S
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On behalf of Michael Pacanowski

Primary Reviewer

Team Leader

7 Statistical and Clinical and Evaluation

7.1 Sources of Clinical Data and Review Strategy

7.1.1 Clinical trials included in the BLA submission

Table 10 lists the clinical trials included in the BLA submission. The primary evidence to support the clinical efficacy of olaratumab in combination with doxorubicin in patients with advanced STS is from patients in the randomized portion of Trial 15B-IE-JGDG (hereafter referred to as Trial JGDG).

The primary safety data used to characterize the safety profile of olaratumab plus doxorubicin in patients with advanced soft tissue sarcomas is from the randomized portion of Trial JGDG. There were eight additional clinical trials to support the safety data which included three randomized, open-label, active-control trials in 375 patients with ovarian cancer (15B-IE-JGDA), prostate cancer (15B-IE-JGDD) or non-small cell lung cancer (15B-IE-JGDB) using different chemotherapeutic agents; four open-label, non-randomized trials which enrolled 136 patients with glioblastoma multiforme (15B-IE-JGDE), gastrointestinal stromal tumor (15B-IE-JGDH), or advanced solid tumors (15B-IE-JGDC and JGDF) who received olaratumab as a single agent, and two additional trials including the Phase 1b portion of study 15B-IE-JGDG and 15B-EW-JGDI, a single-arm study of olaratumab plus doxorubicin in 25 patients with soft tissue sarcoma.

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

7.1.2 Table of Clinical Studies

Table 10: Clinical Trials Included in the BLA

Trial	Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies for safety and efficacy						
15B-IE-JGDG: Phase 2	Phase 1b/2 Open-label Phase 2 randomized 1:1	Investigational Arm: 15 mg/kg olaratumab I.V. on D1, D8 and 75 mg/m ² doxorubicin I.V. on D1 every 21 days for up to 8 cycles In the absence of PD or other withdrawal criteria, patients continued to receive subsequent olaratumab monotherapy (15 mg/kg on D1, D8) until PD. Control Arm ¹ : 75 mg/m ² doxorubicin I.V. on D1 every 21 days and for up to 8 cycles Patients whose disease had progressed were permitted to receive subsequent olaratumab monotherapy (15 mg/kg on D1, D8) until further PD.	Primary: PFS Secondary: 3-month PFS ORR Change in tumor size from baseline to best overall response OS	Phase 1b: 15 Olaratumab Phase II: ITT: 66 (Olaratumab+ Doxorubicin) vs. 67 (Doxorubicin) Safety: 64 (Olaratumab+ Doxorubicin) vs. 65 (Doxorubicin); Doxorubicin arm receiving olaratumab monotherapy after doxorubicin stopped ² : 30	Advanced STS, not amenable to curative treatment with surgery	17-USA
Secondary Studies to Support Safety						
15B-IE-JGDG: Phase 1b	Phase 1b/2 Open-label Phase 2 randomized 1:1	15 mg/kg olaratumab I.V. on D1, D8 and 75 mg/m ² doxorubicin I.V. on D1 every 21 days for up to 8 cycles	Safety Profile	15	Advanced STS, not amenable to curative treatment with surgery	17-USA
15B-EW-JGDI	Phase 1 DDI, 2 parts, non-randomized, open-label	15 mg/kg olaratumab I.V. on D1, D8 and 75 mg/m ² doxorubicin I.V. on D1 every 21 days for up to 8 cycles	Primary: Effect of olaratumab on PK of doxorubicin Secondary: PK Safety profile Immunogenicity Antitumor Activity	25 ³	Metastatic or locally advanced STS not amenable to curative treatment with surgery or radiotherapy	7-USA
Controlled Studies to Support Safety						

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Trial	Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
15B-IE-JGDA	Phase 2, open-label	Investigational Arm: 20 mg/kg olaratumab I.V. on D1, D15 and 40 mg/m² liposomal doxorubicin I.V. on Day 1 every 28 days until PD or other withdrawal criteria were met Control Arm: 40 mg/m² liposomal doxorubicin I.V. on Day 1 every 28 days until PD or other withdrawal criteria were met. Patients whose disease had progressed were permitted to receive olaratumab monotherapy (20 mg/kg on D1, D15) until PD.	Primary: PFS Secondary: OS ORR Median duration of response Safety profile PK and immunogenicity profiles of olaratumab Descriptive pharmacodynamics profile Descriptive statistics for safety and efficacy for patients who continue on olaratumab monotherapy following disease progression on liposomal doxorubicin monotherapy	62 vs.61 Olaratumab ² Monotherapy : 28	Platinum-refractory or platinum-resistant advanced ovarian cancer	22 USA, United Kingdom, Spain
I5B-IE-JGDB	Phase 2, open-label	Investigational Arm: 15 mg/kg olaratumab I.V. on D1, D8, 200 mg/m² paclitaxel I.V. on D1, and AUC = 6 carboplatin I.V. every 21 days for up to 6 cycles until PD or other withdrawal criteria were met. In the absence of PD or other withdrawal criteria, patients received subsequent olaratumab monotherapy until PD. Control Arm: 200 mg/m² paclitaxel I.V. on D1, and AUC = 6 carboplatin I.V. every 21 days for up to 6 cycles until PD or other withdrawal criteria were met. Patients whose disease had progressed were permitted to receive olaratumab monotherapy (15 mg/kg on D1, D8) until PD.	Primary: PFS Secondary: Safety and tolerability of olaratumab ORR OS DoR PK of olaratumab Pharmacodynamics profile of olaratumab Immunogenicity of olaratumab	67 vs. 64 Olaratumab ² Monotherapy : 18	Stage IIIB or Stage IV NSCLC	22 USA, Canada

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Trial	Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
ISB-IE-JGDD -	Phase 2, open-label	Investigational Arm: 15 mg/kg olaratumab I.V. on D1, D8 and 12 mg/m² I.V. mitoxantrone every 21 days. Mitoxantrone therapy continued up to 12 cycles. In the absence of PD or other withdrawal criteria, patients received subsequent olaratumab monotherapy until PD. Control Arm: 12 mg/m² I.V. mitoxantrone every 21 days. Mitoxantrone therapy continued up to 12 cycles. Patients whose disease had progressed were permitted to receive subsequent olaratumab monotherapy (15 mg/kg on D1, D8) until PD.	Primary: PFS Secondary: OS ORR PSA doubling time PSA response rate Circulating tumor cells in whole blood PDGFRα expression and associations with efficacy endpoints PK and immunogenicity	62 vs. 59 Olaratumab ² Monotherapy : 19	metastatic castration-refractory prostate cancer	38 Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain
Non-randomized Studies to Support Safety						
ISB-IE-JGDC -	Phase 1, open-label, dose-escalation	Cohorts 1-3: 4 mg/kg olaratumab I.V. in Cohort 1 (with doses doubling between cohorts) once every wk for 4 wks followed by a 2-wk observation period for each 6-wk cycle (for a total of 4 doses per cycle) Cohorts 4-5: 15 mg/kg or 20 mg/kg olaratumab I.V. once every 2 wks for each 4-wk cycle (for a total of 2 doses per cycle) All patients received olaratumab monotherapy at cohort dose until withdrawal criteria were met.	Primary: Safety profile and MTD Secondary: PK Immunogenicity Antitumor activity Pharmacodynamics	19	Advanced cancers	USA
ISB-IE-JGDF	Phase 1, open-label, dose-escalation	Cohort 1: 10 mg/kg olaratumab I.V. on D1, D8 every 21 days Cohort 2: 20 mg/kg olaratumab I.V. on D1 every 2 wks Cohort 3: 15 mg/kg olaratumab I.V. on D1, D8 every 21 days	Primary: Safety PK Secondary: Immunogenicity	16	Advanced Cancers	1 Japan

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Trial	Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
I5B-IE-JGDE	Phase 2, open-label	Cohort 1 ⁴ : 20 mg/kg olaratumab I.V. on D1 every 2 wks Cohort 2: 8 mg/kg ramucirumab on D1 every 2 wks Treatment continued until PD or other withdrawal criteria are met.	Primary: PFS-6 month Secondary: Acute and late toxicities ORR OS PK Pharmacodynamics Immunogenicity Explore DCE-MRI imaging Blood and tumor expression of PDGFR α , PDGF, VEGFR, and VEGF PFS-6 month and median PFS by investigator assessment	40 vs. 40	Glioblastoma Multiforme	11 USA
I5B-IE-JGDH	Phase 2, open-label	20 mg/kg olaratumab I.V. on D1 every 2 wks. There was no set duration of treatment; all patients received olaratumab until withdrawal criteria were met.	Primary: Tumor response of SD, PR, or CR at 12 weeks Secondary: PFS Safety profile ORR DCR OS PK Immunogenicity	21	Unresectable or metastatic GIST	11 Belgium, Germany, Poland, Spain, Netherlands, USA

(Reviewer generated table based on: ISS Table 2.4.4.1 and Module 5.2 Tabular Listing of All Clinical Studies)

Abbreviations: PFS: progression-free survival; STS: soft tissue sarcoma; GIST = gastrointestinal stromal tumors; ID = identification; I.V. = intravenously; NSCLC = non-small cell lung cancer; PD = progressive disease; D=day; wk = week; MTD=maximum tolerated dose; PK=pharmacokinetics; OS = overall survival; ORR = overall response rate; DoR = duration of response; PSA = prostate specific antigen

- 1 During Cycles 5-8, patients who received doxorubicin may have received dexrazoxane 750 mg/m² I.V. prior to doxorubicin on Day 1, at the investigator's discretion.
- 2 Patients initially randomized to the Control Arm who received olaratumab monotherapy after discontinuation of chemotherapy.
- 3 In Study JGDI, 24 patients were treated with at least 1 dose of olaratumab, while 25 patients were treated with at least 1 dose of doxorubicin.
- 4 Only the olaratumab arm of Study JGDE is summarized in this Summary of Clinical Safety

Review Strategy

The FDA statistical and clinical BLA review consisted of one primary statistical reviewer of efficacy and two primary clinical reviewers, one primary clinical reviewer of safety and one primary clinical reviewer of efficacy.

The BLA submission contained one randomized trial, Trial JGDG, entitled “A Phase 1b/2 Randomized Phase 2 Study Evaluating the Efficacy of Doxorubicin With or Without a Human Anti-PDGRF α Antibody (IMC-3G3) in the Treatment of Advanced Soft Tissue Sarcoma” to primarily support the proposed indication. The statistical and clinical review of efficacy focuses on the randomized phase 2 portion of the trial including a detailed review and analysis of data including the clinical study report (CSR), case report forms (CRFs), statistical analysis plan (SAP), datasets, and SAS program.

The clinical review of safety primarily evaluated the safety population in Trial JGDG, defined as patients who received at least one dose of study drug, and consisted of 129 patients (64 olaratumab plus doxorubicin-treated patients and 65 doxorubicin-treated patients). The review of safety included consideration of the submitted clinical study report, SAS datasets, line-listings, CRFs, and case narratives from Trial JGDG. The review of safety also included an evaluation of eight additional trials (Table 10) which together enrolled a total of 551 patients; 391 received olaratumab as a single agent or in combination with another chemotherapeutic agent.

The statistical and clinical review of safety and efficacy included the following:

- Review of the current literature on sarcoma epidemiology and treatment
- Review of Trial JGDG, including CSR, protocol, protocol amendments, SAP, and SAP amendments.
- Review and assessment of Applicant analyses of olaratumab safety and efficacy in the clinical study report
- Review of datasets submitted as SAS transport files
- Review of patient narratives of serious adverse events and deaths
- Review of minutes of key meetings conducted during olaratumab development for STS
- Review and assessment of the Module 2 summaries including the Summary of Clinical Efficacy, and Summary of Clinical Safety, Integrated Summary of Efficacy, Integrated Summary of Safety, and proposed labeling modifications for olaratumab
- Review of consultation reports of Office of Scientific Investigations
- Requests for additional information from the Applicant and review of Applicant responses
- Formulation of the benefit-risk analysis and recommendations
- Review and evaluation of proposed labeling.

Data Sources

The electronic submission including Protocols, SAP, CSRs, SAS transport datasets in legacy, SDTM, and ADAM format, and SAS codes for the BLA submission are located in the following network paths:

- Original submission: \\cdsesub1\evsprod\bla761038\0002\

Data and Analysis Quality

Upon further clarifications from the applicant's per FDA's information requests (IRs), the reviewer was able to:

- Reproduce the applicant's analysis dataset and analysis results from legacy dataset
- Evaluate documentation of data quality control/assurance procedures
- Find the blinding and un-blinding procedures
- Verify the randomized treatment assignments
- Conduct FDA analyses for PFS and OS

7.2 Review of Relevant Individual Trials Used to Support Efficacy

7.2.1 Trial JGDG (Protocol version 6)

Trial Design and Endpoints

Trial JGDG is a two-stage, open-label, multicenter trial designed to evaluate the anti-tumor activity of olaratumab, when administered in combination with doxorubicin, compared with single-agent doxorubicin for the treatment of patients with advanced soft tissue sarcoma (STS) whose disease is not amenable to treatment with surgery or radiation, and who had not received prior anthracycline therapy.

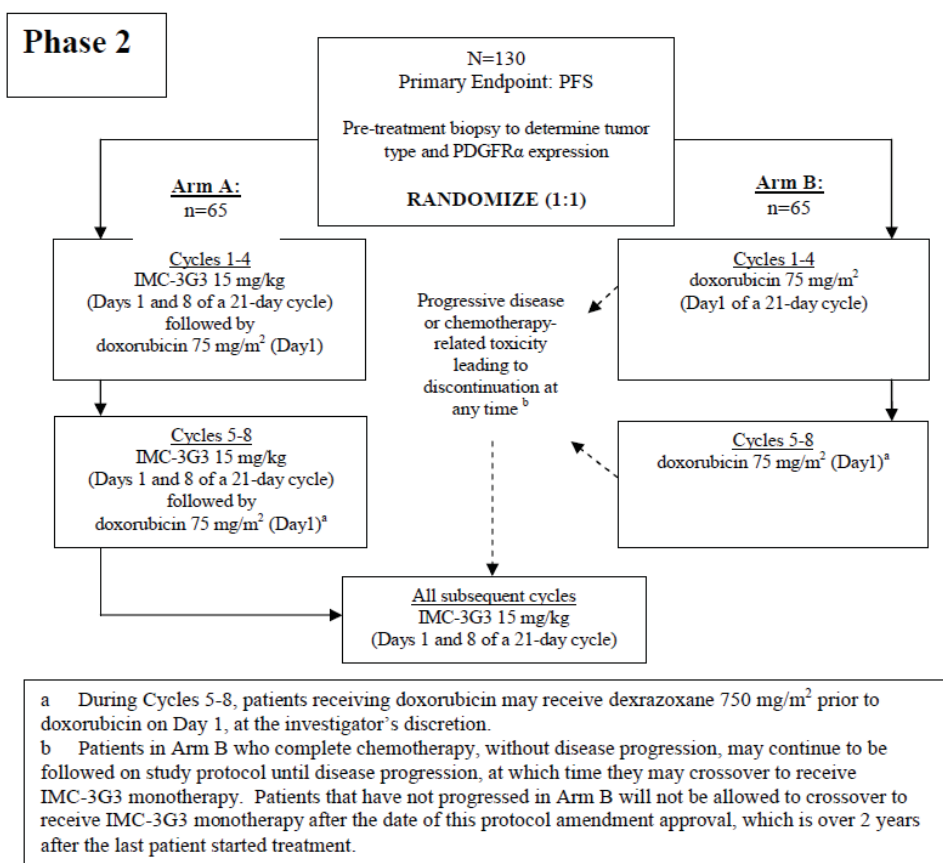
The first stage of the trial was a single-arm assessment of the tolerability of olaratumab, given in combination with doxorubicin in patients with advanced STS. The second stage of this trial was an open-label, randomized, two-arm, active-controlled study. See Figure 16. Patients were randomized (1:1) to one of two arms:

- olaratumab + doxorubicin: doxorubicin 75 mg/m² followed by olaratumab 15 mg/kg on day 1 and 8 of each 21-day cycle
- doxorubicin: doxorubicin 75 mg/m² on day 1 of each 21-day cycle

Treatment continued for up to eight cycles or until disease progression or unacceptable treatment-related toxicity. During Cycles 5 through 8, dexrazoxane [750mg/m² (10:1 ratio to doxorubicin) within 30 minutes prior to doxorubicin infusion] could be administered prior to doxorubicin at the discretion of the treating physician. In the absence of disease progression or other withdrawal criteria, patients in experimental arm who completed 8 cycles of doxorubicin could continue to receive olaratumab as a single agent at the same dose and schedule until

progression, death, intolerable toxicity, or other discontinuation criteria were met. Patients on the control arm were eligible to receive single-agent olaratumab upon disease progression. Disease assessments were conducted every 6 weeks until the primary endpoint of the trial (PFS) was assessed, and then every 12 weeks for patients who remained on trial.

Figure 16 Study Schema



(Source: Trial JGDG Protocol V6)

Randomization was stratified by PDGFR- α expression by IHC (positive vs. negative according to an IHC assay using Santa Cruz Biotechnology rabbit polyclonal antibody Sc-338), prior lines of treatment (0 vs. ≥ 1), histological tumor type (leiomyosarcoma vs. synovial sarcoma vs. other), and ECOG performance status (0-1 vs. 2) via dynamic minimization randomization method per interactive voice response system (IVRS).

In the phase 2 portion, the primary objective was to compare the PFS per investigator (INV) assessment in patients treated with olaratumab in combination with doxorubicin vs. doxorubicin alone. The secondary objectives were to evaluate 3-months PFS rate, objective response rate (ORR), overall survival (OS), tumor size change from baseline to best overall response, PK, and immunogenicity.

FDA's review of efficacy is limited to analyses of PFS, OS, ORR, and duration of response (DoR) for the phase 2 portion of Trial JGDG. The clinical data cutoff dates for the final PFS analysis and the final OS analysis were August 15, 2014, and May 16, 2015, respectively.

Eligibility Criteria

Inclusion criteria:

1. Histologically- or cytologically-confirmed malignant STS (excluding Kaposi's sarcoma)
2. Measurable disease
3. Advanced STS, not amenable to treatment with surgery or radiotherapy; no limit on number of prior therapies
4. Eastern Cooperative Oncology Group (ECOG) performance status 0-2
5. Available tumor tissue from either the primary or metastatic tumor for determination of PDGFR α expression
6. Age at study entry $\geq$ 18 years
7. Adequate hematologic function as defined by an absolute neutrophil count (ANC) $\geq$ 1500 μ L, hemoglobin $\geq$ 9.0 g/dL, and a platelet count of 100,000/ μ L obtained within 2 weeks prior to study entry
8. Adequate hepatic function as defined by a total bilirubin $\leq$ 1.5 mg/dL, and AST and ALT $\leq$ 3.0 $\times$ the upper limit of normal (ULN)
9. Adequate renal function as defined by serum creatinine $\leq$ 1.5 $\times$ the institutional ULN. If creatinine is above the ULN, creatinine clearance must be $\geq$ 45 mL/min
10. Adequate coagulation function, as defined by international normalized ratio (INR) $\leq$ 1.5 and a partial thromboplastin time (PTT) $\leq$ 5 seconds above the ULN if not receiving anticoagulation therapy. Patients on full-dose anticoagulation must be on a stable dose of oral anticoagulant or low molecular weight heparin, have therapeutic INR, no active bleeding (defined as within 14 days prior to first dose of study medication), and no pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices).
11. Prestudy echocardiogram (ECHO) or multigated acquisition (MUGA) scan with an actual left ventricular ejection fraction (LVEF) $\geq$ 50%, within 21 days prior to first dose of study medication
12. Women of childbearing potential and sexually active males agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation
13. Resolution to Grade $\leq$ 1 by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4 (NCI-CTCAE v 4.0) of all clinically significant toxic effects of prior locoregional therapy, surgery, chemoembolization, or other anticancer therapy,
14. Life expectancy of $\geq$ 3 months
15. Signed informed consent

Exclusion criteria:

1. Histologically- or cytologically-confirmed Kaposi's sarcoma

2. Untreated central nervous system metastases. Patients with treated CNS metastases are eligible if they are clinically stable, off all steroids after cranial irradiation ending at least 2 weeks prior to study entry, or after surgical resection performed at least 4 weeks prior to study entry.
3. Prior treatment with doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthracenediones (i.e., mitoxantrone)
4. Prior radiation therapy to the mediastinal/pericardial area
5. History of another primary cancer, with the exception of a) curatively resected nonmelanomatous skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid tumor treated with curative intent, no known active disease present, and no treatment administered during the last 3 years prior to study entry
6. Receiving concurrent treatment with other anticancer therapy, including other chemotherapy, immunotherapy, hormonal therapy, radiotherapy, chemoembolization, targeted therapy, or an investigational agent within 4 weeks prior to study entry
7. Elective or a planned major surgery to be performed during the course of the study
8. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, requiring parenteral antibiotics, symptomatic congestive heart failure, severe myocardial insufficiency, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements
9. Unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction 6 months prior to study entry
10. Known immunodeficiency virus (HIV) infection
11. Pregnant or lactating
12. Received previous therapy with any agent that targets the PDGF or PDGFR
13. Known allergy to any of the treatment components
14. History of allergic reactions attributed to compounds of chemical or biologic composition similar to that of olaratumab
15. Currently enrolled in, or discontinued within the last 28 days from, a clinical trial involving an investigational product or non-approved use of a drug or device (other than the study drug used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

Dose Modification and Management Algorithms

Olaratumab

- Infusion-related reactions
 - Grade 1: slow infusion rate by 50%; for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent); additional premedication may be administered at the investigator's discretion
 - Grade 2: stop the infusion; administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally for fever, and oxygen; resume the infusion at 50% of the prior rate once the infusion reaction has resolved or

decreased to Grade 1 (the infusion duration should not exceed 2 hours); for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent); additional premedication may be administered at the investigator's discretion

For a second Grade 1 or 2 infusion reaction, administer dexamethasone 10 mg I.V. (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally, and dexamethasone 10 mg I.V. (or equivalent).

- Grade 3: stop the infusion; administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), dexamethasone 10 mg I.V. (or equivalent), bronchodilators for bronchospasm, and other medications/treatment as medically indicated (patients who have a Grade 3 infusion reaction will not receive further IMC-3G3 treatment)
 - Grade 4: Stop the infusion; administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), dexamethasone 10 mg I.V. (or equivalent), and other medications/treatment as medically indicated; give epinephrine or bronchodilators as indicated; hospital admission for observation may be indicated (patients who have a Grade 4 infusion reaction will not receive further IMC-3G3 treatment)
- Hematologic toxicity
 - Grade 1 or 2: no dose-modification is required
 - Grade 3 (not adequately controlled with appropriate supportive care, including hematopoietic growth factors, if indicated): withhold dose until toxicity $\leq$ Grade 2, or has returned to pretreatment baseline; restart at reduced dose of 12 mg/kg
 - Grade 4: withhold the dose until toxicity is $\leq$ Grade 2; restart at reduced dose of 10 mg/kg
 - Non-hematologic toxicity
 - Grade 1: no dose-modification is required
 - Grade 2: At the investigator's discretion, the patient may continue to receive olaratumab per protocol, provided that the event does not pose a serious health risk or is easily treated. If necessary, the patient may be dose reduced up to two times (to 12 mg/kg and subsequently to 10 mg/kg) during the study.
 - Grade 3: For a Grade 3 toxicity not adequately controlled with appropriate supportive care, the dose must be withheld until toxicity is $\leq$ Grade 1 or has returned to pretreatment baseline; then treatment may resume at a reduced dose of 12 mg/kg. If toxicity recurs after therapy resumes, a second dose reduction (to 10 mg/kg) is permitted. If more than two toxicity-related olaratumab dose reductions are required, treatment will be permanently discontinued
 - Grade 4: The dose must be withheld until dose toxicity is $\leq$ Grade 1 or has returned to baseline. Treatment may then resume with the dose reduced to 10 mg/kg. If toxicity recurs after therapy resumes, treatment will be discontinued

If treatment with olaratumab was withheld for more than 6 continuous weeks due to an olaratumab-related toxicity that does not resolve, olaratumab was to be permanently discontinued.

Doxorubicin

- Hematologic toxicity
 - ANC < 1,000/ μ L: no doxorubicin administered: treatment cycle delayed
 - $\geq$ Grade 3 neutropenic fever/infection: reduce doxorubicin to 60 mg/m²
 - Grade 4 neutropenia lasting longer than 1 week: reduce doxorubicin to 60 mg/m²
 - Second incidence of:
 - either $\geq$ Grade 3 neutropenic fever/infection or Grade 4 neutropenia lasting longer than 1 week: reduce doxorubicin to 45 mg/m²
 - reversible Grade 3 neutropenia with fever/infection or Grade 4 ANC: retreatment with doxorubicin at investigator's discretion

- Cardiovascular toxicity
 - If an ECHO/MUGA scan conducted on study indicates a resting LVEF is < 50%, then the ECHO or MUGA scan was to be repeated. If there is an absolute decrease in LVEF of > 10% from the previous evaluation, or if the actual LVEF decreases to $\leq$ 40%, then doxorubicin was to be discontinued. Doxorubicin was also to be discontinued if the patient developed Grade 3 or 4 left ventricular systolic dysfunction (symptomatic congestive heart failure).

If treatment with doxorubicin was withheld for more than 6 continuous weeks due to a doxorubicin-related toxicity that does not resolve, treatment with doxorubicin was to be permanently discontinued.

In the case each drug was delayed for toxicity, the schedule of the other drug was to be maintained.

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Monitoring Plan

Day	Pre-treatment	Treatment Period ^a					End of Therapy ^b	Follow-up		
		Cycles 1-8			Cycle 9 Onward			30-day Follow-up ^b	End-of-study Follow-up	Extended Follow-up
		Day 1 ^{c,d}	Day 8 ^{c,d}	Day 15 ^c	Day 1 ^{c,d}	Day 8 ^{c,d}				
NA										
Eligibility Assessments										
Informed Consent ^e	X									
Tumor PDGFR α expression ^f	X									
Medical History	X ^g									
Pregnancy Test	X ^h	X ^{i,j,k}			X ^l		X			
ECG	X ⁱ	X ^m					X			
ECOG performance status	X ^g	X ⁿ			X ⁿ		X	X		
Echocardiogram or MUGA	X ⁱ	X ^{l,k}					X			
Safety Assessments										
Physical Exam	X ^g	X ⁿ			X ⁿ		X	X		
Vital Signs	X ^g	X ^{o,p}	X ^{o,p}		X ^{o,p}	X ^{o,p}	X	X		
Adverse Event Assessment		X ⁿ			X ⁿ		X ^q	X ^q	X ^q	X ^q
Concomitant Medication Assessment ^r	X ^g	X ⁿ			X ⁿ		X	X ^r		
Immunogenicity ^s	(Please see 7.10.2 for specific timepoints) ^t							X ^r		
Laboratory Assessments										
Hematology Profile	X ^g	X ⁿ	X		X ⁿ	X ^p	X	X		
Coagulation Profile	X ^g	X ^{k,u,v}			X ^{u,v}		X ^u	X ^w		
Chemistry Profile	X ^g	X ⁿ			X ⁿ		X	X		
Urinalysis	X ^g	X ^{k,u,v}			X ^{u,v}		X	X		
Efficacy Assessments										
Imaging Studies (CT/MRI)	X ^l	X ^{l,k}			X ^l		X ^l	X ^l	X ^l	X ^l
Tumor Assessments	X ^l	X ^{l,k}			X ^l		X ^l	X ^l	X ^l	X ^l
Survival Data										X ^l
Other Assessments										
PK sampling	(Please see 7.10.2 for specific timepoints) ^t							X ^{aa}		
Pharmacodynamic Assessment	(Please see 7.10.2 for specific timepoints) ^t							X		
Biopsy/Tumor Tissue Submission ^{bb}	X			X ^{cc}						
Clinical Drug Supplies										
Administer IMC-3G3 ^{dd}		X ^{ee}	X ^{ee}		X ^{ee}	X ^{ee}				
Administer doxorubicin ^{dd}		X								

BLA 761038 Multi-disciplinary Review and Evaluation
 LARTRUVO (Olaratumab)

Day	Pre-treatment	Treatment Period ^a					End of Therapy ^b	Follow-up		
		Cycles 1-8			Cycle 9 Onward			30-day Follow-up ^b	End-of-study Follow-up	Extended Follow-up
		Day 1 ^{c,d}	Day 8 ^{c,d}	Day 15 ^c	Day 1 ^{c,d}	Day 8 ^{c,d}				
Administer dexrazoxane (only at investigator's discretion) ^{dd}	NA	X ⁱⁱ								

(Source: Trial JGDG Protocol V6)

Abbreviations: CT = computed tomography, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, MRI = magnetic resonance imaging, MUGA = multigated acquisition (scan), NA = not applicable, PDGFRα = platelet-derived growth factor receptor alpha, PK = pharmacokinetic(s).

- a Treatment period includes patients from both arms, receiving chemotherapy (with or without IMC-3G3); patients from both arms who continue on or crossover to IMC-3G3 monotherapy following initial chemotherapy; and patients from Arm B who experience stable disease or better on chemotherapy, complete chemotherapy and are followed until disease progression.
- b End-of-therapy evaluations will be performed at the discontinuation of all study therapy (including IMC-3G3 monotherapy) or for Arm B patients who complete chemotherapy treatment without disease progression at the time it is decided that the patient will not crossover to IMC-3G3 monotherapy; patients will be followed for at least 30 days following cessation of all study therapy to ensure sufficient safety monitoring. For Arm B patients who complete chemotherapy treatment without disease progression, the end-of-therapy visit will suffice for the follow-up evaluation, provided a decision to not continue the patient on IMC-3G3 monotherapy is made at least 30 days after the last dose of study therapy. Otherwise, both the end-of-therapy and follow-up evaluations will take place.
- c Procedures may be performed within 3 days prior to each scheduled timepoint; however, vital signs must be taken at the time of study therapy infusions. Any pretreatment evaluations performed within 3 days prior to start of treatment on Day 1, Cycle 1 do not have to be repeated.
- d In the case of dose interruptions, these procedures will also be performed at minimum frequency of every 21 days (±3 days).
- e Written informed consent must be obtained prior to any study-specific pretreatment evaluations.
- f PDGFRα determined from biopsy and tumor tissue submission (previously archived tumor tissue acceptable for Phase 2 patients) performed within 21 days prior to enrollment/randomization.
- g Performed within 14 days prior to enrollment/randomization.
- h WOCBP must receive a serum pregnancy test within 7 days prior to enrollment/randomization.
- i Serum or urine pregnancy test every 6 weeks (±3 days) or in accordance with local regulations, whichever is of shorter duration.
- j Performed every 6 weeks (±3days) irrespective of treatment cycles. For patients that have not progressed after the data cut-off for the primary analysis imaging will be performed every 12 weeks or according to good clinical practice (whichever interval is shorter).
- k These evaluations do not have to be performed on Day 1, Cycle1.
- l Performed within 21 days prior to enrollment/randomization.
- m An ECG and ECHO/MUGA scan must be performed at Cycles 5 and 7 within 3 days prior to any treatment administration (≤ 3 days) in these respective cycles.
- n Performed every cycle.
- o Vital sign measurements will be obtained prior to and at the completion of each IMC-3G3 infusion (Arm A and any patients receiving crossover IMC-3G3 monotherapy). Arm A patients will also have vital signs taken 1 hour following the doxorubicin infusion. For patients receiving doxorubicin alone (Arm B), vital signs will be taken prior to the doxorubicin infusion in Cycles 1-4, and prior to dexrazoxane in Cycles 5-8, and 1 hour following the doxorubicin infusion in Cycles 1-8.
- p For patients who experience stable disease or better on chemotherapy, complete chemotherapy and are followed until disease progression Day 8 procedures will not be performed, vitals sign measurements will be performed once on Day 1, and blood sampling for PK/pharmacodynamics/immunogenicity will not be performed.
- q All AEs considered at least possibly related to IMC-3G3 will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.
- r Concomitant medications will be recorded including any taken within 30 days prior to study medication and those taken during the 30 days after the last dose of study medication.

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

- s Immunogenicity samples will also be obtained in the setting of an IMC-3G3 infusion reaction. Where possible, blood for immunogenicity analysis will be taken from the blood drawn for PK analysis. Refer to Section 9.1.1 for a description of these procedures.
- t The immunogenicity sample collected at the 30-day follow-up may also be used for PK analysis as needed.
- u Performed every 2 cycles.
- v To be performed more frequently if clinically indicated.
- w If clinically indicated.
- x For patients who discontinued for reasons other than PD.
- y Imaging studies and tumor assessments have been obtained every 6 weeks ($\pm$ 3days) until documented progression for patients with CR, PR, or SD, and/or for patients who have discontinued study therapy due to toxicity or reasons other than PD. For patients that have not progressed after the data cut-off for the primary analysis imaging will be performed every 12 weeks or according to good clinical practice (whichever interval is shorter).
- z Following objectively determined progression, patients will be contacted every 2 months until completion of the study to obtain survival information and subsequent anticancer therapy (if applicable).
- aa For those patients who have been treated with IMC-3G3 combination or crossover therapy.
- bb Tumor tissue samples collected from biopsy for patients in both Phase 1b and Phase 2 (previously archived samples acceptable for patients in Phase 2) will be collected within 21 days prior to enrollment/randomization. If at any time during the study tumor tissue is obtained through a biopsy, fine needle aspiration, or resection as routine clinical care, ImClone requests a portion of the sample for analysis of potentially relevant surrogate biomarkers. Remaining tissues will be stored at a secure central laboratory.
- cc On-study tumor biopsy performed on Cycle 1, Day 15 ($\pm$ 3 days) for Phase 1b patients only.
- dd Study therapy may be administered $\pm$ 3 days of scheduled timepoint.
- ee For all patients in Phase 1b and Phase 2, Arm A and for patients in Arm B who crossover to IMC-3G3 monotherapy.
- ff From Cycles 5-8 for patients receiving doxorubicin.

Adverse Event Collection

Adverse events (AEs) were graded according to NCI-CTCAE v.4.0. All AEs occurring after the patient received the first dose of study treatment until 30 days following the decision to discontinue study treatment were to be reported the sponsor via the electronic case report forms. AEs were to be evaluated at each visit and patients were instructed to call their physician to report any AEs between visits.

Sample Size Considerations

The sample size for the Phase 1b part of Trial JGDG was based on evaluating the safety and tolerability of the combination of olaratumab + doxorubicin. Ten patients were planned to be accrued. For the Phase 2 portion, assuming a hazard ratio of 0.67 with a median PFS of 2 months in the control arm and 3 months in the experimental arm, a total of 130 patients with 110 events for the final analysis were needed to provide 80% power at a 2-sided alpha level of 20%. An interim analysis of PFS was planned after 80 PFS events. The Applicant states that this interim analysis was non-binding, [REDACTED] (b) (4) [REDACTED]. The Applicant further stated that a positive result may lead to the planning of a phase 3 study, but the results would not lead to any early stopping of the trial. Two-sided nominal alpha of 0.0001 and 0.1999 were allocated to the interim and final analysis for PFS. No pre-specified statistical criteria, power analysis, or statistical procedure to adjust for multiplicity was planned in the original protocol for the key secondary endpoints of OS and ORR.

In protocol V5, an interim analysis of OS was added at the time of the final PFS analysis. A non-binding alpha-spending approach of the O'Brien-Fleming boundary was proposed to adjust alpha based on actual number of deaths for OS interim analysis assuming 91 deaths was the required number of deaths for the final OS analysis.

Analysis sets

Per the final SAP, the primary efficacy analysis population would be limited to the Phase 2 portion in the modified intent-to-treat (mITT) population, which includes all randomized patients who received any amount of study drug. Patients would be categorized by the treatment arm to which they were randomized, regardless of the actual treatment received.

The safety analysis population would include all patients who receive any amount of study drug. Analysis of safety data would be performed according to the actual treatment a patient has received.

Efficacy Measures

PFS was defined as the time from the date of randomization to the earliest date of documented tumor progression or death from any cause.

OS was defined as the time from randomization to death from any cause. Patients who did not die at the end of the extended follow-up period, or are lost to follow-up during the study will be censored at the last date known alive.

The ORR was defined as the proportion of all randomized patients with the best overall response of partial response (PR) or complete response (CR). The applicant planned to provide both confirmed and unconfirmed ORR. The final SAP also states that the ORR includes CR or PR from either the Phase 1b or Phase 2 portions. FDA's ORR endpoint is defined as confirmed CR or PR from the Phase 2 portion in the ITT population.

Efficacy Analysis Methods

PFS

The analysis for PFS would be performed using a log-rank test. Only when there were a sufficient number of patients in each stratum, the stratified analysis may be performed. The median PFS with corresponding two-sided 90% CIs and survival curves were to be estimated using the Kaplan-Meier (KM) method.

Tumor response was assessed every 6 weeks per INV assessment and per BICR using RECIST v.1.1 until disease progression. Tumor response for patients who have not progressed after the data cut-off for the primary analysis would be assessed every 12 weeks or until disease progression. Per the final SAP, the primary PFS analysis was PFS per INV assessment.

Table 11 summarizes the PFS censoring rules.

Table 11 PFS Definition and Censoring Rules

Situation	Date of progression or Censoring	Outcome 1	Outcome 2
No baseline tumor assessment	Randomization	Censored	Censored
No post baseline tumor assessments	Randomization	Censored	Censored
Progression documented between scheduled visits	Earliest date of documented PD	Progressed	Progressed
No progression	Date of last adequate assessment	Censored	Censored
Treatment discontinuation for reasons other than PD and no further assessment	Date of last assessment before Treatment discontinuation	Censored	Censored
New anticancer treatment started before progression	Outcome 1: Date of last assessment prior to new anti-cancer therapy Outcome 2: Progressed at start date of new anticancer therapy	Censored	Progressed
Death before the first PD assessment or between adequate assessment visits	Date of Death	Progressed	Progressed
Death or progression after two or more missed visits	Outcome 1: Date of last assessment prior to missing visit Outcome 2: Date of death or progression	Censored	Progressed
Patient is lost to follow-up without progression	Date of last assessment	Censored	Progressed

(Source: Final SAP P18 Table 1)

In Table 11, outcome 1 is the primary PFS analysis, and outcome 2 is the sensitivity analysis S1 defined in the protocol. Two additional sensitivity analyses S2 (outcome 3) and S3 (outcome 4) for PFS were planned. The S2 would evaluate the actual reported date of progression or death, regardless of missing assessments, treatment discontinuation or new anticancer treatment. Outcome S3 would include clinical progression (symptomatic deteriorations) as progressive events and primary PFS events.

OS

The OS analysis method is identical to that for PFS analysis. Two sensitivity analyses were included in the protocol to evaluate potential impact of crossover: S1) patients would be censored at the date of starting new anti-cancer treatment (including crossover to olaratumab monotherapy), since the OS endpoint was confounded by new anti-cancer treatment, S2) exclude patients who crossover to olaratumab monotherapy. However, analysis S1 includes informative censoring and analysis S2 is not conducted in the ITT population.

ORR

The analysis for ORR would be compared using the Fisher exact test. If there was sufficient number of patients in each stratum, the ORR would be adjusted by the stratification Cochran-Mantel-Haenszel (CMH) test. Two-sided 90% exact CI will be determined. FDA's ORR analysis

includes confirmed ORR per BICR assessment with two-sided 95% exact CI. Without pre-specified multiplicity adjustment method, FDA considers the ORR analysis as exploratory.

Protocol and SAP Amendments

Substantial protocol and SAP amendments are summarized below:

- Protocol V2 (July 2010): no major clinical or statistical changes
- Protocol V3 (February 2012):
 - Sample size increased from 120 to 130 based on modified PFS estimates
 - Modifications to allow patients on the doxorubicin arm who discontinue study therapy due to therapy-related toxicity or complete doxorubicin treatment and experience stable disease (or better) to stay on study schedule and assessments until PD is documented and then receive single agent olaratumab
- Protocol V4 (July 2013): an interim efficacy analysis for PFS was pre-specified after 80 PFS events. Data lock for this PFS interim analysis occurred on 17 January 2014.
- Protocol V5 (August 2014):
 - A data cutoff date of 15 August 2014 for the final analysis of PFS was set instead of the originally planned 110 events due to the high rate of censoring.
 - The final OS analysis after 91 OS events or 2 years after the last patient enrollment was to be conducted with a non-binding alpha spending using the OBF boundary method.
 - Further clarification for the significance level for statistical testing of the efficacy analysis (efficacy analysis was powered for a one-sided log-rank test at the 0.1 significance level. A two-sided p-value will also be computed, which can be compared with the traditional threshold of 0.05.)

The following analyses that were presented in the CSR were not reflected in any protocol or SAP amendments.

1. The primary efficacy population was changed to the ITT population (defined as all randomized patients) from the mITT population.
2. 95% CIs were presented instead of 90% CIs.
3. PFS and ORR analyses per BICR assessment were provided to evaluate for potential systematic bias.
4. Subgroup analyses were based on information from the CRF, rather than IVRS.
5. The stratified log-rank test was stratified by histologic tumor types (LMS vs. non-LMS) per CRF and number of lines of previous treatment (0 vs. ≥ 1) from the IVRS database.

7.2.2 Study Results

Compliance with Good Clinical Practices

The Applicant stated in the BLA clinical study report for Trial JGDG that the study was

conducted in accordance with:

1. Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2. The International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guidelines [E6]
3. Applicable laws and regulations
4. The protocol
5. Food and Drug Administration (FDA) GCP guidelines, FDA Financial Disclosure regulations

Financial Disclosure

The Applicant submitted a list of investigators (BLA Module 1.3.4) and FDA form 3454 certifying that all of the investigators on the list had no financial arrangements as defined in 21 CFR 54.2 (a, b, and f) that could affect the outcome of the trial. No financial disclosures were submitted for any investigator in this BLA. See Appendix 13.2.

Demographic Characteristics

Trial JGDG was conducted at 16 centers in the U.S. A total of 133 patients were randomized in a 1:1 allocation (olaratumab + doxorubicin: 66; doxorubicin: 67). The demographics and baseline disease characteristics of patients in the randomized portion of trial JGDG appear to be balanced as summarized in Table 12, except that there were more females on the olaratumab + doxorubicin arm (61% vs. 51%) and there were more patients age 65 and older on the doxorubicin arm (36% vs. 27%). The majority of the patients treated on this trial were White. The most common single STS histology was leiomyosarcoma (38% in the olaratumab arm and 39% in the doxorubicin arm), and 59% of all patients had a STS histology that fell under the category of “other”. At the time of enrollment, the majority of patients had an ECOG status of 0 or 1 (94%) and most (59% vs. 54%) had received one or more prior therapies (including adjuvant or neoadjuvant therapy). When considering only systemic therapy for advanced disease, the majority of patients had not received any prior therapy; this percentage was higher in the doxorubicin arm (70% vs. 61%). There was no requirement that patients have progressive disease within a certain time period prior to study enrollment and the Applicant did not capture this information. The duration of disease was similar between arms (median of 15 months).

Table 12 summarizes the demographics and baseline disease characteristics for patients treated in the randomized portion of Trial JGDG.

Table 12: Demographics and Baseline Disease Characteristics

Variable	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Population		
ITT	66	67
mITT	64 (97)	65 (97)
Age		
Mean (SD)	56.8 (12.5)	58.3 (12.5)
Median (min-max)	58.5 (22-85)	58.0 (29-86)
18-<65	48 (73)	43 (64)
≥65	18 (27)	24 (35)
Sex		
Male	26 (39)	33 (49)
Female	40 (61)	34 (51)
Race		
White	55 (83)	60 (90)
Black	6 (9)	5 (7)
Asian	2 (3)	2 (3)
Other	3 (5)	0
Country		
U.S.	66 (100)	67 (100)
ECOG performance status^a		
0-1	62 (94)	63 (94)
2	4 (6)	4 (6)
Tumor PDGFRα status^a		
Positive	58 (88)	59 (88)
Negative	8 (12)	8 (12)
Tumor histology^a		
Leiomyosarcoma	25 (38)	26 (39)
Synovial sarcoma	1 (1)	2 (3)
Other	40 (61)	39 (58)
Prior systemic therapy^{a,b}		
0	27 (41)	31 (46)
1 or more	39 (59)	36 (54)
Tumor grade		
Grade 1	7 (11)	8 (12)
Grade 2	5 (8)	7 (10)
Grade 3	29 (44)	29 (43)
Grade cannot be assessed or unknown	25 (38)	23 (34)

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Variable	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Duration of disease (months)		
Mean (SD)	31.9 (41.4)	34.7 (53.1)
Median (range)	15 (0.5-223.5)	14.9 (0.3-258.6)
Metastatic disease	66 (100)	67 (100)
Sites of metastatic disease		
Lung	42 (64)	42 (63)
Soft tissue	22 (33)	33 (49)
Liver	26 (39)	22 (33)
Peritoneal	15 (23)	23 (34)
Lymph nodes	16 (24)	21 (31)
Bone	10 (15)	18 (27)
Other	8 (12)	16 (24)
Pleural	10 (15)	9 (13)
Skin	3 (5)	0

(Source: ADSL.xpt, DM.xpt, FA.xpt, XM.xpt, SUPPMH.xpt, ADPTDC.xpt)

Abbreviations: ITT= intent-to-treat; mITT=modified ITT

^a Randomization factors based on IVRS

^b Includes adjuvant and neoadjuvant therapy

Stratification Factors

Table 13 presents the distribution for stratification factors per IVRS database, CRFs, and independent review of the original pathology reports (Path).

Table 13: Stratification Factors per IVRS, CRF, and Independent Review

Variable	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Tumor histology Per IVRS		
Leiomyosarcoma	25 (38)	26 (39)
Synovial sarcoma	1 (1)	2 (3)
Other	40 (61)	39 (58)
Histology Per CRF		
Leiomyosarcoma	24 (36)	27 (40)
Synovial sarcoma	1 (2)	2 (3)
Other	41 (62)	38 (57)
Histology Per independent review of pathology forms		
Leiomyosarcoma	25 (38)	25 (37)
Synovial sarcoma	1 (2)	1 (2)
Other	40 (61)	41 (61)

Variable	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Prior systemic therapy Per IVRS ^a		
0	27 (41)	31 (46)
1 or more	39 (59)	36 (54)
Prior systemic therapy Per CRF		
0	40 (61)	47 (70)
1 or more	26 (39)	20 (30)
ECOG performance status Per IVRS		
0-1	62 (94)	63 (94)
2	4 (6)	4 (6)
ECOG performance status Per CRF		
0-1	62 (94)	64 (96)
2	4 (6)	3 (4)
Tumor PDGFR α status Per IVRS		
Positive	58 (88)	59 (88)
Negative	8 (12)	8 (12)

^a Includes adjuvant and neoadjuvant therapy
 (Source: adstrata.xpt, path.xpt, adsl.xpt, adptdc.xpt, adlb.xpt, ds.xpt,)

There were 35 (26%) patients with stratification factors discordant across the IVRS database, CRF, and independent review of the original pathology reports. Specifically, there were 3 (2%), 29 (22%), and 8 (6%) discordance due to ECOG, prior line of therapy, and tumor histology, respectively. The Applicant stated that the discordance in prior lines of therapy between the IVRS and CRF is related to a difference in the interpretation of the definition of this variable. Study sites included adjuvant and neoadjuvant therapy for the IVRS stratification, but the CRF specifically requested number of lines of systemic therapy given for advanced disease. The definition used in the CRF is generally considered the more clinically relevant parameter.

The majority of patients had an ECOG status of 0 or 1 (> 94%), and positive tumor PDGFR α (88%), and there were very limited numbers of patients either with performance status 2 or PDGFR α negative status. The Applicant stated that the PDGFR α IHC assay used for stratification purposes was subsequently found to have poor specificity as the antibody used in the assay bound to PDGFR β as well as PDGFR α . An alternative assay was developed and the Applicant conducted a retrospective analysis of PDGFR α status for patients who had available tissue (n=111). Eighteen (32.7%) patients and 19 (33.9%) patients randomized to the olaratumab + doxorubicin arm and doxorubicin arm, respectively, were PDGFR α positive, and 37 were negative in each arm.

Histology

Trial eligibility was determined and randomization was based upon the histology entered by the enrolling site in the IVRS randomization system. Histology was also recorded in the case report

forms (CRFs). In addition, the Applicant conducted an independent review of the original pathology reports from the sites by two independent pathologists and an adjudicator blinded to trial arm and previous pathologic diagnosis. No central histologic review of tumor tissue was conducted. The results from the independent review of pathology reports most likely represents the most accurate source for determining sarcoma histologic subtype, and this is the source that is used by FDA for efficacy analysis.

There was disagreement in interpretation of the institutional pathology reports among the IVRS, CRF, and independent review for eight patients (6%), seven on the doxorubicin arm and one on the olaratumab + doxorubicin arm. For the independent review, the two pathology reviewers did not agree in two cases (one on each arm) and adjudication was required.

Table 14 summarizes the differences between the histology entered in the IVRS and CRF by the treating institution and review of the pathology reports by the independent pathologists. Table 14 summarizes the histologies as reported by the independent review of pathology reports and includes the specific histology for the “other” category, which was the largest group of patients treated on Trial JGDG. The large number of different sarcoma subtypes demonstrates the heterogeneity of histologies of patients treated in this trial.

Table 14: Detailed Histology by Independent Review of Pathology Forms

Histology	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
“Other”		
Liposarcoma	8 (12.1)	14 (20.9)
Dedifferentiated	4	6
Myxoid	2	3
Well-differentiated	1	3
Pleomorphic	1	1
Liposarcoma NOS	0	1
Undifferentiated pleomorphic sarcoma	7 (10.6)	8 (11.9)
Angiosarcoma	4 (6.1)	3 (4.5)
Undifferentiated sarcoma NOS	2 (3)	4 (6)
Extraskeletal myxoid chondrosarcoma	2 (3)	2 (3)
Malignant peripheral nerve sheath tumor	3 (4.5)	0
Myxofibrosarcoma	2 (3)	1 (1.5)
Malignant solitary fibrous tumor	2 (3)	1 (1.5)
Endometrial stromal sarcoma ^a	2 (3)	1 (1.5)
Chondrosarcoma	0	2 (3)
Epithelioid sarcoma	2 (3)	0
Fibrosarcoma	1 (1.5)	1 (1.5)
Low-grade fibromyxoid sarcoma	1 (1.5)	1 (1.5)
Alveolar soft part sarcoma	1 (1.5)	0

Histology	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Chondroblastic osteosarcoma	0	1 (1.5)
Clear cell sarcoma of soft tissue	1 (1.5)	0
Extra-renal rhabdoid tumor	0	1 (1.5)
Extraskeletal osteosarcoma	0	1 (1.5)
Undifferentiated round cell sarcoma	1 (1.5)	0
Leiomyosarcoma	25 (37.9)	25 (37.3)
Synovial sarcoma	1 (1.5)	1 (1.5)

(Source: path.xpt)

Abbreviations in table: NOS=not otherwise specified

^aTwo cases listed as undifferentiated stromal sarcoma (one in each arm), other not further classified

Previous Therapy

Table 15 summarizes the number and types of previous anticancer therapy and Table 16 summarizes the prior systemic therapy received by more than 3% of patients in Trial JGDG. Patients may have received more than one type of therapy prior to enrollment. The two most common prior therapies were gemcitabine and docetaxel. No patients received an anthracycline prior to enrollment. As mentioned previously, more patients on the doxorubicin arm had not received any systemic therapy prior to enrollment (70% vs. 61%), so although this was a less treatment-refractory group, this difference did not appear to have an impact on the main efficacy outcomes. There were no notable differences in the types of systemic regimens received by patients on either arm.

Table 15: Previous Anticancer Therapy

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Lines of therapy (excluding adjuvant and neoadjuvant)		
0	40 (60.6)	47 (70.1)
1	14 (21.2)	12 (17.9)
2	8 (12.1)	7 (10.4)
3	2 (3)	1 (1.5)
4	2 (3)	0
Type of previous anticancer therapy		
Neoadjuvant	3 (4.5)	10 (14.9)
Adjuvant	17 (25.8)	10 (14.9)
Previous surgery		
Yes	55 (83)	57 (85.1)
No	11 (16.7)	10 (14.9)
Previous radiotherapy		
Yes	31 (47)	32 (47.8)
No	35 (53)	35 (52.2)

(Source: CM.xpt)

Table 16: Prior Chemotherapy in ≥3% of Patients in Either Arm

Therapy	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Gemcitabine	29 (43.9)	30 (44.8)
Docetaxel	28 (42.4)	30 (44.8)
Paclitaxel	3 (4.5)	2 (3)
Bevacizumab	2 (3)	3 (4.5)
Investigational drug	4 (6.1)	1 (1.5)
Ifosfamide	3 (4.5)	1 (1.5)
Trabectedin	3 (4.5)	2 (3)
Letrozole	3 (4.5)	1 (1.5)
Palbociclib	2 (3)	2 (3)
Fluorouracil	0	2 (3)

(Source: CM.xpt)

Patient Disposition

The first patient was enrolled on Trial JGDG on October 6, 2010. A total of 183 patients were enrolled at 16 sites, all in the U.S.

Of the 183 enrolled patients, 15 were treated on the phase 1b portion. One hundred and thirty-three patients were randomized in the phase 2 portion, and of those, 129 (97%) were treated with study drug. Two patients in each arm were randomized and not treated. On the olaratumab + doxorubicin arm one patient withdrew consent due to potential side effects and one went into hospice care. On the doxorubicin arm, one patient was beyond maximum weight and one patient is listed as having not met inclusion/exclusion criteria. The primary population for the FDA efficacy evaluation for this BLA is the ITT population. Table 17 summarizes the populations in Trial JGDG used in the analyses.

Table 17: Analysis populations, Trial JGDG

Population	Olaratumab + Doxorubicin	Doxorubicin	Total
All Screened Population	-	-	183
Patients in phase 1 portion ^a	15	-	15
ITT Population: all randomized patients in the phase 2 portion	66	67	133
Safety Population: all patients in the phase 2 portion who received at least one dose of study drug	64	65	129

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Population	Olaratumab + Doxorubicin	Doxorubicin	Total
Olaratumab monotherapy after doxorubicin treatment: patients on the control arm in the phase 2 portion who received olaratumab following disease progression	-	30	30

^aOne screen failure in phase 1b portion

Thirty-five (21%) patients were not randomized. The most common reason for screen failure was that the inclusion/exclusion criteria were not met (65.7%), followed by withdrawal of consent (31.4%). Table 18 summarizes the screen failures for patients in the phase 2 portion of Trial JGDG. These screen failures are not expected to affect the interpretation of the efficacy or safety data for Trial JGDG.

Table 18: Reason for Screen failures in the Phase 2 Portion

Patients	N (%)
Total enrolled	167
Randomized	133 (79.6)
Not randomized	35 (21)
Reason not randomized	
Inclusion/exclusion criteria not met	23 (65.7)
Patient withdrew consent	11 (31.4)
Did not complete screening procedures within required window	1 (2.9)

(Source: DS.xpt, July 20, 2016 response to FDA IR)

Table 19 summarizes the eligibility criteria not met by the patients enrolled but not randomized. The most common (>10%) reason for screen failure was not having a prestudy echo or MUGA with LVEF $\geq$ 50% prior to study entry.

Table 19: Inclusion/Exclusion Criteria Not Met by Patients Enrolled, Not Randomized

Inclusion/Exclusion Criteria Not Met^a	N=23
Inclusion #11a and #12: The patient has a prestudy echocardiogram or multigated acquisition (MUGA) scan with an actual left ventricular ejection fraction (LVEF) $\geq$ 50%, within 21 days prior to first dose of study medication.	5
Inclusion #8: The patient has adequate hepatic function as defined by a total bilirubin $\leq$ 1.5 mg/dL, and AST and ALT $\leq$ 3.0 x the upper limit of normal (ULN).	3
Inclusion #11: Adequate coagulation function (INR $\leq$ 1.5 and PTT $\leq$ 1.5xULN). If on full-dose anticoagulation, must be stable dose, and for warfarin: therapeutic INR and no active bleeding and no high risk of bleeding.	3
Inclusion #7: Has adequate hematologic function as defined by an absolute neutrophil count (ANC) $\geq$ 1500 uL, hemoglobin $\geq$ 9.0 g/dL, and a platelet count of 100,000/uL obtained within 2 weeks prior to study entry.	3
Inclusion #9: The patient has adequate renal function as defined by serum creatinine $\leq$ 1.5 x the institutional ULN. If creatinine is above the ULN, the patient's creatinine clearance is $\geq$ 45 mL/min.	3
Exclusion #8: Uncontrolled intercurrent illness or psychiatric illness/social situations that would limit compliance with study requirements.	3
Inclusion #2: Measurable disease. Previously irradiated tumors will be designated as "nontarget" unless PD is documented or a biopsy is obtained to confirm persistence $\geq$ 90 days after radiation therapy.	2
Inclusion #13a and #14: Resolution to Gr $\leq$ 1 by the NCI-CTCAE v 4.02 of all clinically significant toxic effects of all prior anticancer therapies. Except events pertain to the lab values allowed in these inclusion criteria.	2
Inclusion #4: The patient's Eastern Cooperative Oncology Group (ECOG) performance status is 0-2.	1
Inclusion #10: Patient has urinary protein $\leq$ 1+ on dipstick/routine urinalysis; if urine dipstick or routine analysis is $\geq$ 2+, 24hr urine for protein must demonstrate $<$ 1g of protein in 24hr to allow participation.	1
Inclusion #7a: Adequate hematologic function as defined by an (ANC) $\geq$ 1500 uL, hemoglobin $\geq$ 9.0 g/dL, platelet count of 100,000/uL obtained within 2 weeks prior to study entry.(G-CSFs) should not be administered	1
Exclusion #3: The patient received prior treatment with doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthracenediones (ie, mitoxantrone).	1
Exclusion #4: The patient received prior radiation therapy to the mediastinal/pericardial area.	1
Exclusion #6a: Concurrent treatment with other anticancer therapies like chemo, immuno, hormonal therapy, radio, chemoemobilization, targeted therapy, or an investigational agent within 4 weeks to study entry.	1
Exclusion #12: The patient has received previous therapy with any agent that targets the PDGF or PDGFR.	1
Inclusion #1: The patient has histologically- or cytologically-confirmed malignant soft tissue sarcoma (STS), including uterine leiomyosarcoma. Patients with Kaposi's sarcoma will be excluded.	1
Inclusion #5: Tumor tissue available from either the primary or metastatic tumor for	1

Inclusion/Exclusion Criteria Not Met ^a	N=23
determination of PDGFR [?] expression. (Biopsy tissue sample in Ph 1b; biopsy tissue or previously archived tissue sample in Ph 2).	
Inclusion #14a: The patient has a life expectancy of >= 3 months	1

(Source: IE.xpt, TI.xpt)

^a Patients may have not met more than one criteria

At the time of final OS data cut-off, no patients were receiving protocol therapy, and follow-up for survival was ongoing for 23 patients in the olaratumab + doxorubicin arm and for eight patients in the doxorubicin arm. Radiographic progression of disease was the most common reason for treatment discontinuation (64% vs. 40%). More patients on the doxorubicin arm discontinued treatment for symptomatic progression (10% vs. 4%), two of them subsequently received olaratumab monotherapy. One additional patient received olaratumab monotherapy without documented disease progression for a total of 4.5% of patients in this open-label study who received olaratumab without document radiographic progression of disease. Eight percent of patients in the olaratumab + doxorubicin arm and 16% in the doxorubicin arm discontinued treatment for study drug toxicity and 8% and 9%, respectively discontinued therapy for withdrawal of consent. Table 20 summarizes the summary of treatment discontinuations for patients in Trial JGDG.

Table 20: Summary of Patient Disposition by Treatment Discontinuation

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Progressive disease, radiographic	42 (63.6)	27 (40.3)
Adverse event ^a	5 (7.6)	11 (16.4)
Completed treatment ^b	0	11 (16.4)
Withdrawal of consent	5 (7.6)	6 (9)
Progressive disease, symptomatic	3 (4.5)	7 (10.4)
Physician decision	6 (9.1)	0
Randomized but not treated	2 (3)	2 (3)
Death	2 (3)	1 (1.5)
Other ^c	1 (1.5)	2 (3)

(Source: ADSL.xpt)

^a See

Table 37 for a listing of AEs that required discontinuation

^b Completed 8 cycles of doxorubicin

^c Other reasons for discontinuation: Olaratumab + doxorubicin=gradual increase in lesions that did not meet RECIST criteria; Doxorubicin=patient crossed over to study drug, non-compliance, each n=1

Protocol Violations/Deviations

The Applicant defined an important protocol deviation as a deviation that significantly impacts subject safety, the quality or the integrity of the study data, and/or the subject's willingness to participate in the study. These were divided into the following categories: inclusion/exclusion criteria violated, incorrect response assessment, medication errors, out of window

visits/procedures, protocol procedures/visits not performed/missing, and “other”. There were 39 protocol deviations in 33 randomized patients. After reviewing the actual deviations, the “other” category included issues with incomplete informed consent documentation for all instances except one and this category was added in Table 21, which summarizes the major protocol deviations in the phase 2 portion of Trial JGDG. Five protocol deviations were considered to have the potential to impact the analyses of INV-assessed PFS, two on the doxorubicin arm (incorrect response assessment and protocol procedures not performed) and three on the olaratumab + doxorubicin arm (incorrect response assessment n=2, protocol procedures not performed); however, upon review, it was determined that there was likely minimal impact of these deviations on the interpretation of efficacy in this application. In addition, PFS results according to the blinded independent review were similar to the INV (see Section Table 23 and Table 24).

Table 21: Major Protocol Deviations

Protocol Violation	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Patients with major protocol violation (%)	17 (25.8)	16 (23.9)
Total number of major protocol violations	20	19
Issues with informed consent	7 (35)	7 (36.8)
Protocol procedures/visits not performed/missing ^a	7 (35)	4 (21.1)
Inclusion/Exclusion criteria violated ^b	2 (10)	5 (26.3)
Incorrect response assessment ^c	2 (10)	1 (5.3)
Out of window visits/procedure	0	2 (10.5)
Medication errors	1 (5)	0
Other ^d	1 (5)	0

(Source: DV.xpt, RS.xpt, TU.xpt)

^a doxorubicin: patient CP15-0806/001-1007 had liver ablation to target lesion #2 and continued on therapy, doxorubicin + olaratumab: Patient CP15-0806/015-1011 end of treatment date was 2/5/2013 when investigator (INV) determined PD/PFS event date was 11/9/2012

^b Includes two patients in the doxorubicin arm who had chondrosarcoma. Sponsor stated in CSR these were identified during the submission preparation and not included in the table in the CSR

^c Olaratumab + doxorubicin: Patient CP15-0806/011-1001 end of treatment date 12/19/2011 when INV determined PD/PFS date was 10/27/2011, Patient CP15-0806/012-1012 had PD by protocol measurements on 11/2/2011 and INV PFS date was 12/19/2011 (BICR did not agree with PD and censored the patient on 12/19/2011); doxorubicin: Patient CP15-0806/004-1007 had INV PD/PFS date recorded on 4/24/2013, but by protocol recorded measurements should have been SD; however, BICR agreed with PD on 4/24/2013.

^d Other: patient found to be pregnant while in survival follow-up period

Post-Progression Therapy

As summarized in Table 22, the number of patients with any systemic therapy in both arms was similar (67% vs. 69%) if olaratumab was counted as post-progression therapy, as was the number of patients with 1 to >4 regimens. As allowed by the protocol, 45% of the patients in the doxorubicin arm received olaratumab monotherapy after they stopped doxorubicin therapy. This accounted for a substantial amount of the treatment for patients on the doxorubicin arm, and if olaratumab is not counted as post-progression therapy, more patients

in the olaratumab arm received post-progression therapy, 67% vs. 49%. Table 22 also summarizes post-treatment regimens received by at least 3% of patients in either arm. There were differences in post-trial therapy between the arms, specifically more patients in the olaratumab + doxorubicin arm received therapies that are approved (pazopanib 23% vs. 15%, trabectedin 17% vs. 4%, eribulin 4% vs. 3%) or commonly used for STS (gemcitabine 23% vs. 16%, docetaxel 21% vs. 12%, and dacarbazine 18% vs. 12%). None of these drugs have demonstrated an improvement in OS except eribulin for patients with liposarcoma, and the advantages in PFS for have been modest; therefore, the degree of impact of post-progression therapy on the large improvement in OS seen in patients on the olaratumab + doxorubicin arm is unclear, but this imbalance in a small clinical trial with a heterogeneous population is one factor that contributes to the uncertainty in the interpretation of the magnitude of clinical benefit of olaratumab in this population.

Table 22: Post-study Therapy in ≥ 3% of Patients in Either Arm

Therapy	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Any systemic therapy	44 (66.7)	46 (68.7)
1 regimen	18 (27.3)	20 (29.9)
2 regimens	12 (18.2)	14 (20.9)
3 regimens	9 (13.6)	6 (9)
4 regimens	1 (1.5)	2 (3)
>4 regimens	4 (6.1)	4 (6)
Olaratumab ^a	0	30 (44.8)
Gemcitabine	15 (22.7)	11 (16.4)
Pazopanib	15 (22.7)	10 (14.9)
Docetaxel	14 (21.2)	8 (11.9)
Dacarbazine	12 (18.2)	8 (11.9)
Trabectedin	11 (16.7)	3 (4.5)
Ifosfamide	8 (12.1)	8 (11.9)
Investigational drug	8 (12.1)	2 (3)
Doxorubicin	1 (1.5)	5 (7.5)
Eribulin	3 (4.5)	2 (3)
Everolimus	2 (3)	2 (3)
Vinorelbine	2 (3)	2 (3)
Alisertib	1 (1.5)	2 (3)
Etoposide	1 (1.5)	2 (3)
Paclitaxel	2 (3)	1 (1.5)
Sorafenib	2 (3)	0
Sunitinib	2 (3)	0

(Source: CM.xpt)

^a Olaratumab received by patients on doxorubicin arm as allowed per protocol in trial JGDG

Efficacy Results – Primary Endpoint PFS

Although the mITT was the primary analysis population per the final SAP, efficacy analyses were based on the ITT population in the CSR.

Table 23 presents efficacy analysis results for the final PFS per INV assessment based on 103 events on the ITT population, and sensitivity analyses conducted by the applicant or FDA. The statistical reviewer was able to reproduce the applicant’s analysis results.

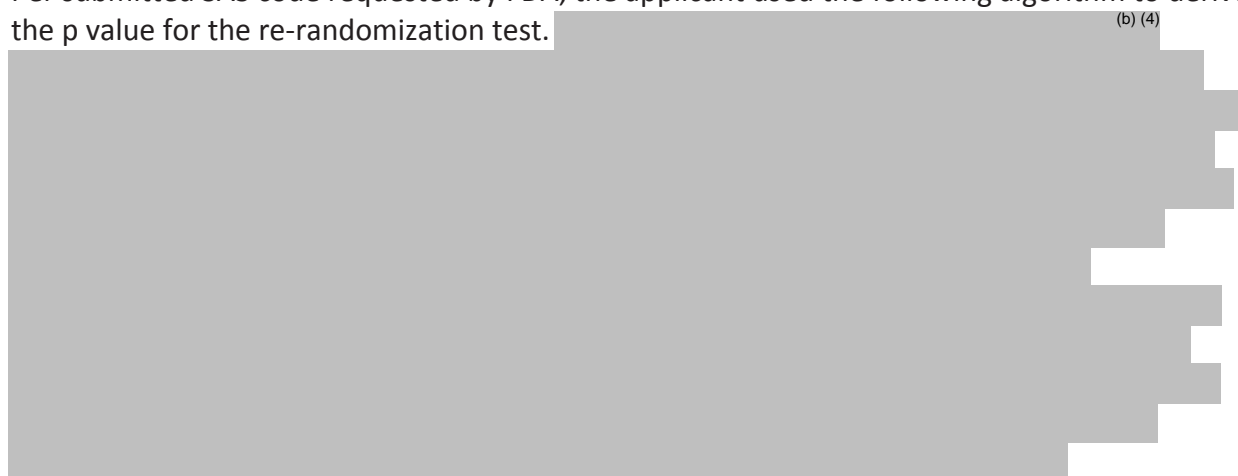
The median PFS was 6.6 months (95% CI: 4.1 8.3) for the olaratumab + doxorubicin arm and 4.1 months (95% CI: 2.8, 5.4) for the doxorubicin arm. The corresponding stratified HR was 0.67 (95% CI: 0.44, 1.02) in the olaratumab + doxorubicin arm compared to the doxorubicin arm. The estimated HRs for sensitivity analyses using different censoring methods (see Efficacy Analysis Methods for PFS for details) range from 0.62 to 0.81.

Per the applicant’s analysis, the olaratumab + doxorubicin arm demonstrated an improvement in PFS compared with the doxorubicin arm. The stratified log-rank test P value of 0.06 was less than pre-planned final two-sided significance level of 0.1999 specified in the SAP.

The dynamic minimization randomization technique was used for randomization, which could determine future patient enrollment based on the current distribution of stratification factors to achieve a balance in stratification factors and treatment arms. This is essentially a deterministic method that may cause selection bias, because the next assignment can be predicted in some situations (Scott, McPherson, et al., 2002). For this reason, FDA usually conducts a re-randomization test if a dynamic minimization method is used during the randomization. The re-randomization method compares the evaluation of data from a randomized experiment with analogous evaluations of the same data calculated as though other experimental plans had been chosen (Cox and Kempthorne, 1963).

Per submitted SAS code requested by FDA, the applicant used the following algorithm to derive the p value for the re-randomization test.

(b) (4)



Also, due to the small sample size with four stratification factors (24 strata), to capture the most accurate result, FDA’s re-randomization test used two stratification factors: prior systemic therapy per CRF and histology per independent review of pathology forms (see histology section for details), which was different than the stratification factors (prior systemic therapy per IVRS and histology per CRF) used in the stratified log-rank test in the CSR. Using the above algorithm, FDA derived a p-value for the re-randomization of 0.06. Although a two-sided significance level of 0.20 for the primary endpoint of PFS does not generally meet the regulatory standard for providing adequate evidence of effectiveness, it met the protocol specified criteria.

Table 23: PFS Analyses, Per INV assessment

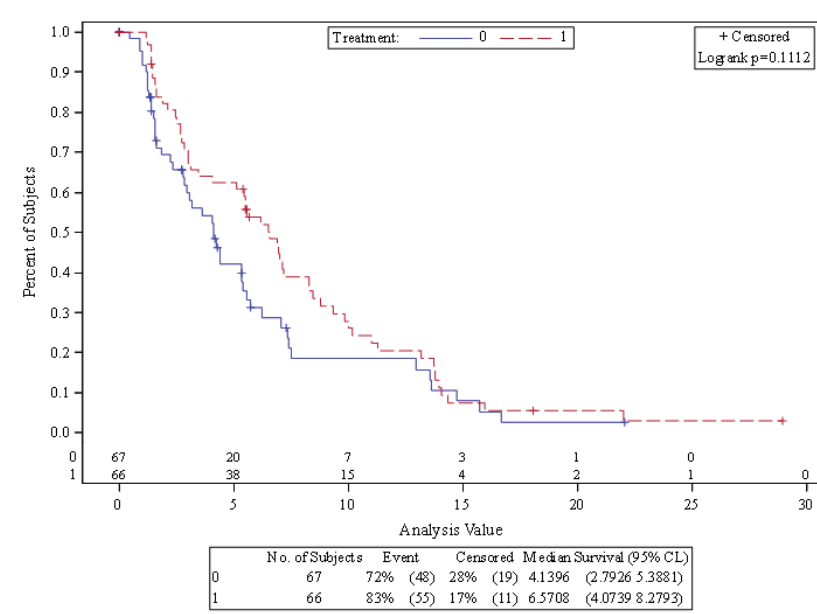
	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Applicant’s Analyses		
Number of Events, n (%)	55 (83)	48 (72)
PD, n (%)	54(82)	43 (64)
Death, n (%)	1 (2)	5 (7)
Number of Censored, n (%)	11 (17)	19 (28)
No Tumor Assessment, n (%)	3 (5)	4 (6)
Due to >=2 missing, n (%)	1 (2)	2 (3)
New anticancer therapy, n (%)	5 (8)	5 (8)
No documented PD, n (%)	2 (3)	6 (9)
Withdrew Consent Form, n (%)	0	1 (2)
Median PFS (months), 95% CI	6.6 (4.1, 8.3)	4.1 (2.8, 5.4)
Cox Stratified HR (95% CI) ^a	0.67 (0.44, 1.02)	
P value, stratified log-rank test ^a	0.06	
Cox Un-Stratified (95% CI)	0.73 (0.49, 1.08)	
P value, Unstratified log-rank	0.11	
FDA Analyses		
P value, re-randomization ^b	0.06	

^a Applicant’s stratification stratum: prior systemic therapy per IVRS and histology per CRF

^b prior systemic therapy per CRF and histology per independent review of pathology forms

Figure 17 presents the Kaplan-Meier (K-M) Curves for applicant’s PFS analysis per INV assessment.

Figure 17: K-M Curves for PFS per INV Assessment



In general, PFS is subject to ascertainment bias, especially in an open-label trial. Therefore, results of PFS assessed by INV should be consistent with that by BICR to rule out this type of bias.

Table 24 presents the efficacy analyses for the final PFS based on 71 events as determined by BICR. The re-randomization test has a p-value of 0.1065. The median PFS was 8.2 months (95% CI: 5.5, 9.8) for the olaratumab + doxorubicin arm and 4.4 months (95% CI: 3.1, 7.4) for the doxorubicin arm. The corresponding stratified HR was 0.67 (95% CI: 0.40, 1.12) in the olaratumab + doxorubicin arm compared to the doxorubicin arm. The p-value and HR by BICR are similar to that by INV. There were more censored observations (potentially due to informed censoring) in the PFS analysis per BICR assessment.

Table 24: PFS Analyses, Per BICR assessment

	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Applicant's Analyses		
Number of Events, n (%)	37 (56)	34 (51)
PD, n (%)	36(55)	32 (48)
Death, n (%)	1 (2)	2 (3)
Number of Censored, n (%)	29 (44)	33 (49)
No Tumor Assessment, n (%)	7 (11)	10 (15)
Due to >=2 missing, n (%)	2 (3)	5 (8)
New anticancer therapy, n (%)	18 (27)	6 (9)
No documented PD, n (%)	2 (3)	11 (16)

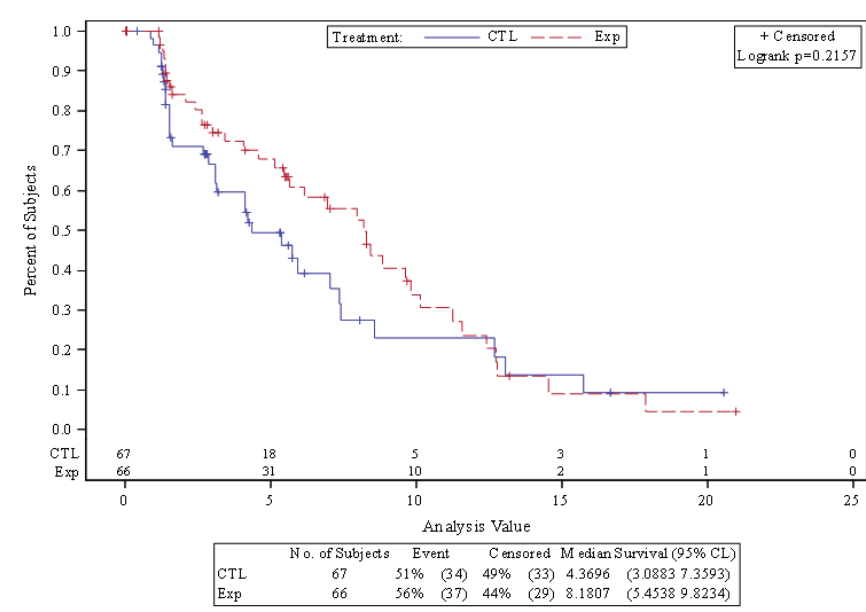
	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Withdrew Consent Form, n (%)	0	1 (2)
Median PFS (months), 95% CI	8.2 (5.5, 9.8)	4.4 (3.1, 7.4)
Cox Stratified HR (95% CI) ^a	0.67 (0.40, 1.12)	
P value, stratified log-rank test ^a	0.12	
Cox Un-Stratified (95% CI)	0.74 (0.46, 1.19)	
P value, Unstratified log-rank	0.22	
FDA Analyses		
P value, re-randomization ^b	0.11	

^a Applicant's stratification stratum: prior systemic therapy per IVRS and histology per CRF

^b prior systemic therapy per CRF and histology per independent review of pathology forms

Figure 18 presents the Kaplan-Meier (K-M) Curves for BICR PFS.

Figure 18: K-M Curves for PFS per BICR Assessment



FDA also evaluated discordance between PFS per INV assessment and per BICR assessment (see [Table 25](#)). Specifically, there were 21% vs. 16% discordance due to censored status (censored vs. PD or death) and 39% vs. 31% due to duration (from randomization to PD or death) in the olaratumab + doxorubicin arm and doxorubicin arm. Overall, there were 61% and 48% disagreement for PFS due to different assessments in the olaratumab + doxorubicin arm and doxorubicin arm. Despite the discordance, the PFS results by INV and BICR were similar, suggesting that there was not systemic bias in INV assessment of PFS.

Table 25: Discordance in determination of PFS events or time of censoring between INV and BICR

Discordance	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Any	40 (61)	32 (48)
Due to Censoring status only	14 (21)	11 (16)
Due to Duration only	26 (39)	21 (31)
Due to Censoring status and duration	6 (9)	7 (10)

Efficacy Results – OS

The final OS analysis was analyzed when approximately 91 deaths occurred. There were 30 (45%) patients in the doxorubicin arm who crossed over to olaratumab therapy.

Although the statistical analysis plan was amended to conduct an interim OS analysis at the final PFS analysis, there was also one unplanned OS interim analysis at 55 events. Based on the actual OS events for two interim analyses at 55 and 84 events and amended OBF boundaries, FDA used two-sided alpha of 0.005 for the final OS analysis with 91 death events.

Table 26 presents the primary analyses for the final OS with a total of 91 (100%) required deaths. The statistical reviewer was able to reproduce applicant’s analysis results. The re-randomization test gives a p value of 0.0002 which is less than 0.005, the adjusted alpha level for the final OS analysis. Per FDA’s analysis, the p value from the re-randomization test was 0.0004, which is similar to the applicant’s re-randomization test result. The median OS was 26.5 months (95% CI: 20.9, 31.7) and 14.7 months (95% CI: 9.2, 17.1) in the olaratumab + doxorubicin arm and doxorubicin arm respectively. The corresponding stratified HR was 0.46 with 95% CI (0.30, 0.71) for the olaratumab + doxorubicin arm compared to the doxorubicin arm.

Table 26: OS Analyses

	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Applicant’s Analyses		
Number of Deaths, n (%)	39 (59)	52 (78)
Median OS in months, (95% CI)	26.5 (20.9, 31.7)	14.7 (9.2, 17.1)
Cox Stratified HR (95% CI) ^a	0.46 (0.30, 0.71)	
P value, stratified log-rank test ^a	0.0003	
Cox Un-Stratified HR (95% CI)	0.52 (0.34, 0.79)	
P value, Unstratified log-rank	0.0017	
FDA Analyses		

	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
P value, re-randomization ^b	0.0004	

^a Applicant's stratification stratum: prior systemic therapy per IVRS and histology per CRF

^b prior systemic therapy per CRF and histology per independent review of pathology forms

Figure 19: K-M Curves for OS presents the KM Curves for OS.

Figure 19: K-M Curves for OS

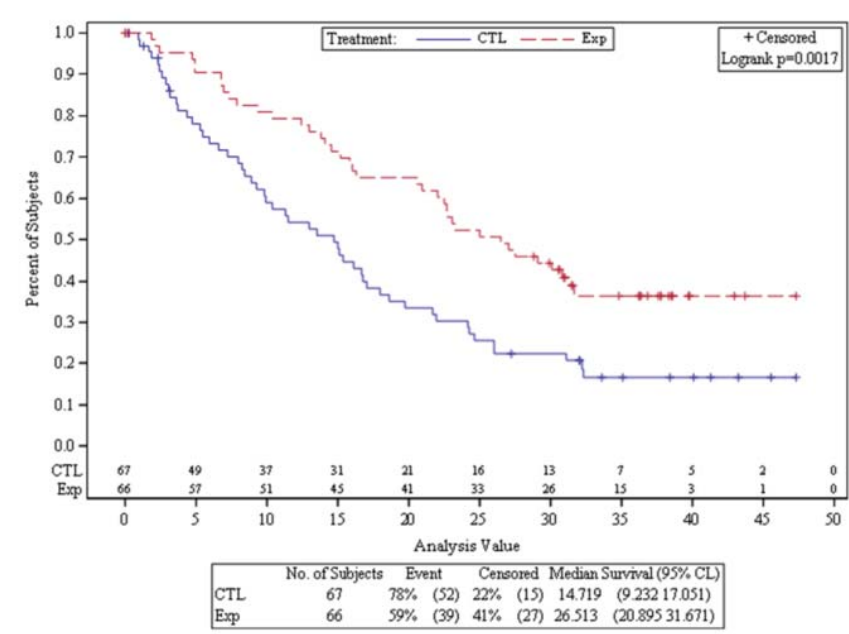


Table 27 presents OS sensitivity analyses including post-PD OS analyses per INV and BICR, censored at the initiation of subsequent anti-cancer therapy, and by number of doxorubicin cycles received. The estimated HRs range between 0.43 and 0.55, which are similar to that of the primary OS analysis.

Table 27: OS Sensitivity Analyses

	Olaratumab + Doxorubicin N=66 HR (95%)	Doxorubicin N=67 HR (95%)
Post PD (BICR) OS ^{a,b,c}	0.46 (0.26, 0.81)	
Post PD (INV) OS ^{a,b,c}	0.55 (0.34, 0.89)	
Censored at any subsequent anti-cancer therapy ^a	0.49 (0.23, 1.04)	
Censored at subsequent specific anti-cancer therapy ^{a,d}	0.43 (0.24, 0.76)	
Exclude < 8 cycles of doxorubicin therapy ^{a, c}	0.38 (0.17, 0.86)	
Exclude < 7 cycles of doxorubicin therapy ^{a,c}	0.42 (0.19, 0.91)	

	Olaratumab + Doxorubicin N=66 HR (95%)	Doxorubicin N=67 HR (95%)
Exclude < 6 cycles of doxorubicin therapy ^{a, c}	0.41 (0.21, 0.81)	
Exclude < 5 cycles of doxorubicin therapy ^{a, c}	0.42 (0.22, 0.80)	
Exclude < 4 cycles of doxorubicin therapy ^{a, c}	0.35 (0.20, 0.64)	

^a Stratified by prior systemic therapy per CRF and histology per independent review of pathology forms

^b From the date of documented PD to the date of death from any cause

^c Based on a subgroup of patients

^d Limited to pazopanib, eribulin, gemcitabine + docetaxel, doxorubicin, and trabectedin

While trial JGDG was not designed with the objective of demonstrating an OS benefit and the sample size of the study is relatively small, the observed OS benefit with olaratumab is statistically significant. Because of the small sample size, the confidence interval for the HR is wide, and the true estimate of treatment effect could be small (HR = 0.71) or large (HR = 0.30). The treatment effect cannot be estimated precisely; however, in the worst case scenario, the improvement in median overall survival could be 3.8 months (difference between lower limit in the olaratumab arm (20.9 months) and upper limit in the doxorubicin arm (17.1 months)). If the true HR is indeed 0.46, using a two-sided alpha of 0.05, there is 95% chance to detect a HR of 0.46 with 91 events based on FDA's simulation (10,000 iterations, EAST 6.2). Since the magnitude of the improvement of OS is large (both HR and the difference in medians), the results suggest that the findings purely due to chance is very small.

However, there remains clinical uncertainty due to the heterogeneous population included in this small study and lack of adequate evidence to generalize to all the subgroup of patients, particularly those with non-leiomyosarcoma. To confirm the clinical benefit of olaratumab in all patients, a second randomized trial is deemed necessary.

Efficacy Results – ORR

Table 28 and Table 29 present the confirmed ORR analyses based on the INV assessment and BICR assessment respectively. Per INV assessment, the ORRs were 18% (95% CI: 9.8%, 29.6%), and 12% (95% CI: 2.5%, 16.6%) in the olaratumab + doxorubicin arm and doxorubicin arm, respectively. The DoR are 8.3 months (95% CI: 2.7, 12.7) and 8.2 (95% CI: 2.8, 14.5) for the olaratumab + doxorubicin arm and doxorubicin arm, respectively. Per BICR assessment, the ORRs were 18% (95% CI: 9.8, 29.6), and 8% (95% CI: 2.5%, 16.6%) in olaratumab + doxorubicin arm and doxorubicin arm, respectively.

Table 28: ORR Results Based on the INV Measurements

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Overall Response	12 (18)	8 (12)
CR	2 (3)	1 (2)
PR	10 (15)	7 (10)
Binomial 95% CI	(9.8, 29.6)	(5.3, 22.2)
p-value ^a	0.3421	
DoR, median in months (95% CI)	8.3 (2.7, 12.7)	8.2 (2.8, 14.5)

^a Fisher's exact test (two-sided)

Table 29: ORR Results Based on the BICR Measurements

	Olaratumab + Doxorubicin N=66 n (%)	Doxorubicin N=67 n (%)
Overall Response	12 (18)	5 (8)
CR	3 (5)	1 (2)
PR	9 (14)	4 (6)
Binomial 95% CI	(9.8, 29.6)	(2.5, 16.6)
p-value ^a	0.074	

^a Fisher's exact test (two-sided)

Additional Subgroup Analyses Conducted for OS

Table 30 presents OS subgroup analysis results by demographics, stratification factors, and important disease characteristics. No outlier subgroups were identified.

Included in Table 31 are OS subgroup analysis result by independent review of pathology forms, IVRS, and CRF. There was disagreement in interpretation of the institutional pathology reports among the IVRS, CRF, and independent review for eight patients (6%), seven on the doxorubicin arm and one on the olaratumab + doxorubicin arm.

Table 30: OS Subgroup Analyses

	Sample Size (EVTS/N)	HR_(95% CI)
Overall	39/66 : 52/67	0.52 (0.34, 0.79)
Age		
<=65	30/48 : 33/43	0.54 (0.33, 0.89)
>65	9/18 : 19/24	0.48 (0.22, 1.07)

BLA 761038 Multi-disciplinary Review and Evaluation
 LARTRUVO (Olaratumab)

	Sample Size (EVTS/N)	HR_(95% CI)
Gender		
F	23/40 : 24/34	0.53 (0.3, 0.94)
M	16/26 : 28/33	0.55 (0.3, 1.02)
Race		
Asian	1/2 : 2/2	0.62 (0.05, 7)
Black Or African American	3/6 : 3/5	0.5 (0.1, 2.49)
White	32/55 : 47/60	0.52 (0.33, 0.81)
Histological Tumor (Path)		
Leiomyosarcoma	16/25 : 23/25	0.34 (0.17, 0.65)
Non-Leiomyosarcoma	23/41 : 29/42	0.62 (0.36, 1.08)
Histological Tumor (IVRS)		
Leiomyosarcoma	16/25 : 24/26	0.33 (0.17, 0.63)
Non-leiomyosarcoma	23/41 : 28/41	0.64 (0.37, 1.12)
Histological Tumor (CRF)		
Leiomyosarcoma	16/24 : 24/27	0.47 (0.25, 0.9)
Non-leiomyosarcoma	23/42 : 28/40	0.56 (0.32, 0.97)
PDGFR alpha (IVRS)		
Negative	4/8 : 6/8	0.39 (0.11, 1.41)
Positive	35/58 : 46/59	0.54 (0.35, 0.84)
ECOG PS		
0	20/36 : 30/38	0.51 (0.29, 0.91)
1	16/26 : 19/26	0.46 (0.24, 0.91)
2	3/4 : 3/3	0.18 (0.02, 1.84)
Prior Line of Therapy		
0	21/40 : 36/47	0.47 (0.27, 0.81)
1 Or More	18/26 : 16/20	0.55 (0.28, 1.1)
EGFR		
Negative	4/8 : 6/8	0.39 (0.11, 1.41)
Positive	35/58 : 46/59	0.54 (0.35, 0.84)

	Sample Size (EVTS/N)	HR_(95% CI)
Platelet (10E9/L)		
<=300	26/49 : 29/41	0.5 (0.29, 0.86)
>300	13/17 : 23/26	0.73 (0.37, 1.44)
WBC (10E9/L)		
<=10	34/59 : 38/52	0.55 (0.34, 0.87)
>10	5/7 : 14/15	0.74 (0.26, 2.06)
Weight Group		
81.4	20/37 : 21/29	0.52 (0.28, 0.97)
<=81.4	19/29 : 31/38	0.57 (0.32, 1.02)

7.3 Review of Safety

7.3.1 Safety Review Approach

The clinical review of safety of olaratumab in patients with STS focused on evaluation of the Phase 2 portion of Trial JGDG, an open-label, randomized, multicenter, active-controlled trial in addition to eight supportive studies. In Trial JGDG, of the 133 subjects randomized, 129 received at least one dose of any study treatment. Two patients in each arm were randomized but never received the study drug(s). Sixty-four patients received olaratumab + doxorubicin in the olaratumab + doxorubicin arm and 65 patients received single-agent doxorubicin. These 129 patients define the safety population for this trial. The safety monitoring period was from the time of randomized treatment assignment until 30 days following discontinuation of assigned treatment for all AEs or related serious AEs (SAEs) reported beyond the 30 days were also collected. Safety data from patients in the olaratumab + doxorubicin arm who received single-agent olaratumab after completing eight cycles of study therapy are summarized under the olaratumab + doxorubicin data. Patients receiving single-agent olaratumab after discontinuation of single-agent doxorubicin were analyzed separately.

Evaluation of eight additional trials supported the safety review; however, data from these studies were not pooled due to differences in trial design, drug regimen, and tumor type. (Refer to Table 10 in Section 7.1.1 for details) The reviewer conducted an extensive analysis of these studies and no additional safety signals were identified. The same tools and methods that were used to analyze the safety data in Trial JGDG were used to assess the safety data across the eight supportive studies. The eight supportive studies included three randomized, open-label, active-controlled trials in ovarian cancer (JGDA), prostate cancer (JGDD), and non-small cell lung cancer (JGDB) using different chemotherapeutic agents in which 256 patients received at least one dose of olaratumab; four open-label, non-randomized trials which enrolled 136 patients who received olaratumab as a single-agent in glioblastoma multiforme (JGDE), gastrointestinal

stromal tumor (JGDH), and advanced solid tumors (JGDC and JGDF); and two additional trials including the Phase 1b portion of study JGDG (15 patients) and JGDI, a single-arm study of olaratumab + doxorubicin in 25 patients with soft tissue sarcoma. Due to the differences in trial design, treatment regimens, and tumor types, there was no pooling of safety data. In total, 485 subjects received at least one dose of olaratumab across all studies:

- 103 patients with STS received olaratumab plus doxorubicin in two studies (JGDG, JGDI)
- 191 patients received olaratumab in combination with chemotherapy other than doxorubicin in three studies (JGDA, JGDB, JGDD)
- 96 patients received olaratumab as a single agent in four studies (JGDC, JGDE, JGDF, JGDH)
- 95 patients initially randomized to a Control Arm in four studies received single-agent olaratumab after discontinuation of chemotherapy

The review of safety included analysis of the submitted study report, datasets, line-listings, case narratives, and case report forms (CRFs) from Trial JGDG and the eight supportive studies. The review tools used included JMP, JReview, and MedDRA based Adverse Events Diagnostics tool (MAED) software. *A priori* the Applicant identified IRRs as a potential safety concern for olaratumab and possible potentiation of cardiac toxicities from the administration of olaratumab with doxorubicin. Neutropenia was analyzed based on AEs listings for the purpose of describing SAEs and clinically important events (dose delays, reductions, discontinuations) but evaluated using the laboratory dataset for incidence and severity.

7.3.2 Review of the Safety Database

Overall Exposure

In Study JGDG, 64 patients received at least one dose of olaratumab in the olaratumab + doxorubicin arm. As shown in Table 31, the median duration of exposure to olaratumab was 26 weeks (range 3 weeks to 128 weeks). A total of 36 (56.2%) patients received olaratumab for ≥ 6 months and 10 (15.6%) patients received olaratumab for ≥ 12 months. Patients received a median of 16.5 olaratumab infusions; the median cumulative dose was 230 mg/kg.

Table 31: Exposure to Olaratumab, Trial JGDG

	Olaratumab + Doxorubicin N=64 n (%)	Single-agent Olaratumab after Single-agent Doxorubicin ¹ N = 30 n (%)
Duration of Olaratumab Treatment (weeks)		
Median duration	26.1	7.0

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

	Olaratumab + Doxorubicin N=64 n (%)	Single-agent Olaratumab after Single-agent Doxorubicin ¹ N = 30 n (%)
Range	3.0-128.8	3.0-134.0
Number of Infusions, n		
Median	16.5	4.0
Range	1.0-83.0	1.0-81.0
Cumulative Dose level (mg/kg)		
Median	230.1	61.0
Range	0.7-1217.1	0.2-1232.0
Relative Dose Intensity (%)		
Median	88.7	85.8
Range	2.4-101.9	0.6-96.8

(Reviewer generated table based on: EX.xpt, AE.xpt, ADEX.xpt)

N = number of treated patients; n = number of patients in category.

Note: Exposure to olaratumab in the olaratumab + doxorubicin arm includes single-agent olaratumab following discontinuation of single-agent doxorubicin after 8 cycles of combination therapy.

1. Patients initially randomized to the single-agent doxorubicin arm who received single-agent olaratumab after discontinuation of doxorubicin.

Overall exposure to doxorubicin was higher in the olaratumab + doxorubicin arm vs. the single-agent doxorubicin arm as shown in Table 32: Exposure to Doxorubicin, Trial JGDG. The Applicant attributes this to longer progression-free survival (median of 2.5 months) for patients in the olaratumab + doxorubicin arm. The reviewer agrees with this. Median duration of exposure was 21 weeks (range 3 to 29 weeks) vs. 12 weeks (range 3 to 25 weeks). Patients in the olaratumab + doxorubicin arm received a median of seven cycles of doxorubicin vs. four cycles in the single-arm doxorubicin arm. Cumulative exposure to doxorubicin was 488 mg/m² vs. 300 mg/m² in the olaratumab + doxorubicin arm and single-agent doxorubicin arm, respectively. The addition of olaratumab did not impact the ability of patients to receive doxorubicin as prescribed as the relative dose intensity of doxorubicin was similar in both arms.

Table 32: Exposure to Doxorubicin, Trial JGDG

	Olaratumab + Doxorubicin N=64 n (%)	Doxorubicin N=65 n (%)
Duration of Doxorubicin Treatment (weeks)		
Median duration	21.3	12.3
Range	3.0-29.0	3.0-25.4
Number of Infusions, n		
Median	7.0	4.0
Range	1.0-8.0	1.0-8.0
Cumulative Dose level (mg/kg)		
Median	487.6	299.6
Range	73.9-617.0	74.9-751.3
Relative Dose Intensity (%)		

	Olaratumab + Doxorubicin N=64 n (%)	Doxorubicin N=65 n (%)
Median	98.7	99.0
Range	66.8-103.3	73.5-106.5

(Reviewer generated table based on: EX.xpt, ADSL.xpt, ADEX.xpt)
 N = number of treated patients; n = number of patients in category

Duration of exposure to olaratumab across the eight supportive studies was less as compared to Trial JGDG. A total of 80 of 391 (20.4 %) patients received olaratumab for ≥ 6 months and 14 of 377 (3.7%) patients received olaratumab for ≥ 12 months. The reviewer agrees with the Applicant’s assessment to not pool exposure data since exposure in Trial JGDG was higher than in the eight secondary and supportive studies combined

Relevant characteristics of the safety population:

The Applicant provided the safety data by gender, age, and racial subgroups from the CRFs. There were minor differences between demographics and baseline characteristics between treatment arms. There was a greater proportion of females in the olaratumab + doxorubicin arm, 59% vs. 51%, more non-white patients (17% vs. 9%), and more patients age <65 years (73% vs. 61%). Eastern Cooperative Oncology Group performance status (ECOG PS) and histological tumor type were well balanced between arms.

Adequacy of the safety database:

Overall, the reviewer feels the safety database submitted by the Applicant was adequate. No major deficiencies were found. The size of the safety database was sufficient to identify adverse events that occur at an incidence of approximately $\geq 1\%$.

7.3.3 Adequacy of Applicant’s Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data quality submitted was well-organized and adequate to perform a complete review of the safety of olaratumab plus doxorubicin. Several information requests were sent to the Applicant during the review of safety to confirm data or clarify minor discrepancies. In collaboration with the Office of Computational Sciences, a data fitness assessment was performed. Key findings included:

- The domain Action Taken with Study Treatment did not allow the reviewer to distinguish if a study drug was held or modified. To remedy this, the Applicant provided a table with a per patient breakdown of study drug reduced, held, delayed, and interrupted.

- Time to disposition event analysis was not able to be computed given the missing data in domains DSSTDTC, DSDTC, and DSSTDY.

Categorization of Adverse Events

The Applicant used the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 to map verbatim terms from the CRFs to preferred terms (PTs) to code all AEs reported by the Investigator. The Applicant defined treatment-emergent AEs (TEAEs) as AEs that first occurred or worsened any time between the first dose of study treatment and 30 days after the last dose of study treatment, and related SAEs reported beyond 30 days after the last dose of study treatment. National Cancer Institute (NCI) CTCAE v 4.0 was used to grade AEs. For all TEAEs, the Investigator provided his/her opinion regarding the relationship of the event to olaratumab and doxorubicin. All events were assessed for causality to the study drug(s) by the Investigator based on five tiers: definite/certain, probable, possible, not likely, or unrelated to study therapy. All TEAEs assessed by the Investigator as at least possibly related to study drug were reported in the datasets as “related.” AEs were collected at every visit regardless of relationship to study drug. All patients were followed until resolution or stabilization of any study related AE. TEAEs were summarized by the MedDRA (Version 17.1), System Organ Class (SOC) and PT. The incidence and percentage of patients with at least one occurrence of a PT were included, according to the most severe NCI –CTCAE version 4.0 grade. Verbatim terms in the AEs dataset were analyzed to determine the correctness of the coding of the MedDRA PTs. A manual analysis of the 2,932 PT from Trial JGDG adequately represented the verbatim terms. In addition, 50 of the 98 CRFs in Trial JGDG were audited to determine if verbatim terms, toxicity grading, intervention, and characterization of the seriousness of the AEs were accurately entered into the database. In general, this reviewer found few discrepancies between the CRFs, narratives, and database entries. These issues were resolved upon receiving clarification from the Applicant. In some instances, PTs were combined into one consolidated PT within a table. These included neutropenia, anemia, fatigue, musculoskeletal pain, infections and infestations, thrombocytopenia, mucositis, abdominal pain, infusion-related reaction (IRR), cardiac arrhythmias, and cardiac dysfunction. The reviewer did not agree with the PT used in the consolidated PT neutropenia which included neutropenia, leukopenia, white blood cell count decreased, and neutrophil count decreased. The PTs of leukopenia and white blood cell count are not the same as neutropenia and neutrophil count decreased. These PTs were separated in the consolidated PT leukopenia (preferred term leukopenia and white blood cell count decreased) and the consolidate term neutropenia (preferred term neutropenia and neutrophil count decreased).

Routine Clinical Tests

Laboratory assessments were performed within 14 days of enrollment/randomization, at regularly scheduled intervals, and when medically necessary during Trial JGDG. Vital sign measurements were obtained prior to and at the completion of each dose of olaratumab and prior to each cycle. Monitoring for cardiac-related toxicities included ECGs and ECHOs at

baseline, prior to Cycles 5 and 7, at the end of therapy, and when clinically indicated by the Investigator. Neutropenia was assessed at baseline, on Day 1 and Day 8 of each cycle, at the end of therapy, and when clinically indicated. (Refer to the Monitoring Plan in section 7.2.1 for details.)

7.3.4 Safety Results

Deaths

The Applicant performed an analysis of the cause of death for all patients who had died as of the data cut-off of May 16, 2015, with an emphasis on patients who died within 30 days of the last dose of study drug or whose death was associated with an AE in Trial JGDG. The Applicant provided detailed narratives of all patient deaths occurring within 30 days for both treatment arms, irrespective of whether the deaths were associated with a TEAE.

Table 33 summarizes the primary cause of death reported for patients in Trial JGDG. There were a total of 39 (60.9%) deaths in the olaratumab + doxorubicin arm and 51 (78.5%) deaths in the single-agent doxorubicin arm. In both arms, the leading cause of death was disease progression (39 [60.9%] in the olaratumab + doxorubicin arm and 44 [67.7%] in the single-agent doxorubicin arm). The proportion of deaths that occurred within 30 days of the last dose of treatment was higher in the single-agent doxorubicin arm (9.2%) vs. (4.7%) in the olaratumab + doxorubicin arm. Death due to an AE was the primary cause of death in the single-arm doxorubicin arm in four (6.2%) patients. All deaths in the olaratumab + doxorubicin arm were due to progressive disease; no deaths occurred due to an AE in the olaratumab + doxorubicin arm.

The Applicant's approach to the follow-up and evaluation of deaths appears reasonable. The reviewer conducted analyses of the narrative summaries and AEs to verify the cause of death described by the Applicant for all deaths that occurred within 30 days of last dose of with study therapy. The Applicant categorized the primary cause of death for one patient in the single-agent doxorubicin arm as "other". This reviewer conducted an analysis of the death whose cause was attributed to "other". This patient in the single-agent doxorubicin arm died 5 months after administration of the last dose of study therapy and no information was available on cause of death per the Applicant. Attribution to study drug could not be determined.

Table 33 Summary of Deaths, Trial JGDG

Deaths	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Doxorubicin ¹ N=65 n(%)	Single-agent Olaratumab Following Single-agent Doxorubicin ¹ N=30 n(%)
All Deaths	39 (60.9)	51 (78.5)	23 (76.7)

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Primary Cause			
Disease Progression	39 (60.9)	44 (67.7)	22 (73.3%)
Adverse Event	0	6 (9.2)	1 (3.3)
Other		1 (1.5)	0
Death on Study or within 30 days of Last Dose	3 (4.7)	6 (10.8)	1 (3.3)
Primary Cause			
Disease Progression	3 (4.7)	2 (3.1)	0
Adverse Event	0	4 (6.2)	1 (3.3)
Other	0	0	0

(Reviewer generated table based on: DS.xpt, ADSL.xpt, narratives)

Abbreviation: N = number of treated patients.

1. Deaths include those occurring during both the single-agent doxorubicin treatment period and, if applicable, subsequently during single-agent olaratumab treatment period

2. Data in this column represents a subset of the data in the doxorubicin column

Table 34 provides a tabular listing of AEs leading to death that occurred within 30 days of receipt of study treatment.

Table 34 Treatment-Emergent Adverse Events with an Outcome of Death by System Organ Class and Preferred Terms, Trial JGDG

System Organ Class/Preferred Term	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Doxorubicin N=65 n(%)	Single-agent Olaratumab Following Single-agent Doxorubicin N=30 n(%)
Patients with AE	0	5 (7.7)	1 (3.3)
Cardiac Disorder			
Cardiac Arrest	0	0	1 (3.3)
Infection and Infestations			
Sepsis	0	1 (1.5)	0
Septic Shock	0	1 (1.5)	0
Respiratory, Thoracic, and Mediastinal Disorders			
Pneumonia Aspiration	0	1(1.5)	0
Respiratory Failure	0	1 (1.5)	0

(Reviewer generated table based on: DS.xpt, ADSL.xpt, narratives)

Abbreviation: N = number of treated patients,

Table 35 presents a brief description of the cause of death for the 10 patients that died within 30 days of study therapy.

Table 35 Probable cause of Death Occurring within 30 Days of Last Dose of Study Drug, Trial JGDG

Patient ID	Age/Sex	Study Arm	Related	Brief Description of Probable Cause of Death
004-1002	67/M	Olaratumab + Doxorubicin	N	Progressive disease

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Patient ID	Age/Sex	Study Arm	Related	Brief Description of Probable Cause of Death
011-1006	52/M	Olaratumab + Doxorubicin	N	Febrile with productive cough. Imaging showed bilateral pulmonary infiltrates and no disease progression in the lungs. Progressive disease.
012-1024	65/M	Olaratumab + Doxorubicin	N	Progressive Disease
001-1009	51/M	Single-agent Doxorubicin	Y	Aspirational pneumonia after altered mental status and respiratory distress.
005-1010	63/F	Single-agent Doxorubicin	N	Progressive disease
006-1001	78/M	Single-agent Doxorubicin	Y	E. coli urinary tract urosepsis with respiratory distress.
006-1013	71/M	Single-agent Doxorubicin	N	Respiratory failure
008-1006	74/M	Single-agent Olaratumab after discontinuation of single-agent doxorubicin	Y	Infusion related reaction on C1D1 after crossover to single-agent olaratumab. Significant cardiac history. Cardiac arrest 11 minutes into infusion.
012-1010	54/M	Single-agent Doxorubicin	N	Progressive disease
012-1013	76, M	Single-agent Doxorubicin	Y	Decreased ejection fraction with neutropenia and thrombocytopenia leading to disseminated intravascular coagulation and septic shock.

(Reviewer generated table based on: Patient Narratives)

This reviewer conducted analyses of the narrative summaries and AE listings to verify the cause of death by the Applicant for all deaths attributed to a TEAE or other death that occurred within 30 days of the last dose of study therapy regardless of attribution. The reviewer agreed with the attribution by the Applicant in all but one case. The Investigator and Applicant categorized patient 011-1006's death due to progressive disease and that AEs of respiratory failure and pneumonia were not unrelated to olaratumab and doxorubicin. After reviewing the narrative and CRF, this reviewer does not agree that the information provided supports the attribution of progressive disease as the cause for this patient's death; the reviewer's attribution of this adverse event is possibly related to olaratumab and doxorubicin. This patient presented with fever, absolute neutrophil count of 1.1 k/ul, and pneumonia found on chest x-ray. Imaging by CT scan of the chest and subsequent chest x-ray demonstrated bilateral pulmonary infiltrates; however, there was no finding of progressive disease in the lungs. The patient experienced acute respiratory distress and hypoxemia leading to intubation, and expired shortly thereafter. Additional information including further details of this case was provided in a narrative for this patient by the Applicant and did not support progressive disease as the cause of death.

Patient 008-1006 died from an IRR during the first infusion of olaratumab after crossing over from the single-agent doxorubicin arm. This adverse reaction is described in detail in Section 7.3.6.

Summary of Review of Deaths from ISS Database

In the ISS database, there were a total of 22 of 485 (4.5%) patients who died within 30 days of the last dose of olaratumab. Across the eight supportive studies, 18 of the 391 (4.6%) patients had died within 30 days of the last dose of olaratumab. The majority of deaths were due to progressive disease (11 of 18 [61.1%]). No deaths occurred due to AEs in the nonrandomized

studies (JGDI, Phase 1b of JGDG, JGDC, JGDE, JGDF, and JGDH). In the three randomized studies (JGDA, JGDB, JGDD), there were seven separate TEAEs that led to death in the olaratumab-containing arms in seven patients (multi-organ failure, stroke and weakness, myocardial infarction, bronchopleural fistula, interstitial lung disease, sepsis, and pulmonary embolism [PE]). The reviewer analyzed the narratives for the seven patients who experienced a TEAE leading to death. The event of neutropenic sepsis occurred 6 days after the first cycle of olaratumab, paclitaxel, and carboplatin. Neutropenia is an expected event for both paclitaxel and carboplatin, and the time dependent relatedness to the administration of olaratumab and increased incidence of Grade 3-4 neutropenia with the addition of olaratumab to doxorubicin observed in Trial JGDG makes it possibly related to olaratumab as well. In addition, a chest x-ray taken shortly after admission showed evidence of progressive disease. Four of the seven patients had progressive disease leading to the TEAEs of multi-organ failure, cerebrovascular event, bronchopulmonary fistula, and interstitial lung disease. The patient who died from a myocardial infarction had an extensive pre-existing cardiac history. The patient with the PE experienced the PE 14 days after the first cycle of olaratumab and liposomal doxorubicin. There was no prior history other than hypertension as a risk factor for PE. Underlying malignancy is a risk for thrombus formation. In addition, the patient had an 8.1cm adnexal mass on the left that likely contributed to the formation of deep vein thrombosis (DVT) in the left lower extremity.

Serious Adverse Events

The rate of non-fatal SAEs was comparable between arms. SAEs occurred in 27 (42.2%) patients in the olaratumab + doxorubicin arm compared to 25 (38.5%) patients in the single-agent doxorubicin arm. The rate of Grade 3 SAEs was higher in the olaratumab + doxorubicin arm (31.3% vs. 21.5%). The most commonly occurring SAEs in the olaratumab + doxorubicin arm were febrile neutropenia (12.5%), musculoskeletal pain (4.7%), and neutropenia (4.7%). Musculoskeletal pain occurred more frequently in the olaratumab + doxorubicin arm (4.7% vs. 1.5% in the single-agent doxorubicin arm).

The analysis of SAEs presented by the Applicant are based on the reporting database and include randomized patients who reported an AE that met any of the serious criteria, whether or not the event was judged to be related to study drug. The Applicant stated that the majority of SAEs in the olaratumab + doxorubicin were whole or in part attributed to doxorubicin. The Applicant's definition of serious adverse events (SAEs) is any AEs that result in one of the following outcomes:

- Death
- initial or prolonged inpatient hospitalization
- life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered important by the investigator for any other reason

The definition of SAE is in accordance with 21 CFR 312.32(a). Table 36 lists SAEs regardless of causality by PT in order of decreasing frequency.

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Table 36 Serious Adverse Events by Preferred Term, Trial JGDG

Preferred Term Consolidated TEAE Category	Olaratumab + Doxorubicin N=64 n(%)			Single-agent Doxorubicin N=65 n(%)			Single-agent Olaratumab after Doxorubicin Treatment N=30 n(%)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Patients with SAE	27 (42.2)	20 (31.3)	7 (10.9)	25 (38.5)	14 (21.5)	8 (12.3)	11 (33.3)	8 (26.7)	3 (10.0)
Febrile Neutropenia	8 (12.5)	7 (10.9)	1 (1.6)	8 (12.3)	8 (12.3)	0	0	0	0
Musculoskeletal Pain ¹	3 (4.7)	3 (4.7)	0	1 (1.5)	0	0	3 (10.0)	3 (10.0)	0
Neutropenia ²	3 (4.7)	0	3 (4.7)	3 (4.6)	0	3 (4.6)	0	0	0
Abdominal Pain ³	2 (3.1)	2 (3.1)	0	1 (1.5)	0	0	0	0	0
Pneumothorax	2 (3.1)	1 (1.6)	0	2 (3.1)	2 (3.1)	0	0	0	0
Urinary Tract Infection	1 (1.6)	1 (1.6)	0	3 (4.6)	3 (4.6)	0	0	0	0
Infections and Infestations ⁴	0	0	0	4 (6.2)	1 (1.5)	1 (1.5)			
Gastrointestinal hemorrhage	0	0	0	2 (3.1)	2 (3.1)	0			
Thrombocytopenia	0	0	0	2 (3.1)	1 (1.5)	1 (1.5)	0	0	0
Dyspnea	0	0	0	2 (3.1)	1 (1.5)	0			
Nausea	0	0	0	2 (3.1)	1 (1.5)	0			
Patient with SAE AESIs									
Infusion-related Reaction ⁵	2 (3.1)	0	2 (3.1)	0	0	0	1 (3.3)	0	1 (3.3)
Cardiac Arrhythmias ⁶	1 (1.6)	0	0	1 (1.5)	1 (1.5)	0	0	0	0

(Reviewer generated table base on: ADSL.xpt, AE.xpt)

SAE were included if they occurred in 2 or more patients

Abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event; AESIs = adverse events of special interest; N = number of treated patients; n = number of patients with given event

1. Preferred terms reported were: back pain, pain in extremity, musculoskeletal chest pain.

2. Preferred terms reported were: neutropenia and white blood cell count decreased.

3. Preferred terms reported were: abdominal pain and abdominal pain upper.

4. Includes all preferred terms within the MedDRA system organ class of Infections and Infestations

5. Preferred terms reported were: 48 IRR preferred terms from the core.

6. Preferred terms reported were: tachycardia, bradycardia, bundle branch block left, electrocardiogram QT prolonged, heart rate increased, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, supraventricular extrasystoles, atrial fibrillation, syncope

Musculoskeletal pain was an unexpected adverse event in patients receiving olaratumab. The SAE of musculoskeletal pain occurred in more patients who received single-agent olaratumab after discontinuation of single-agent doxorubicin or olaratumab plus doxorubicin than in the single-agent doxorubicin arm. One patient who received single-agent olaratumab discontinued therapy due to pain in the extremity. Musculoskeletal pain is discussed in more detail in Section 7.3.9.

There were no SAEs attributed to cardiac dysfunction in either arm. The event of cardiac arrhythmia that occurred in patient 016-1005 in the olaratumab + doxorubicin arm was Grade 2 sinus bradycardia. The patient was initially randomized to the single-agent doxorubicin arm. Doxorubicin therapy was discontinued after the patient was found to have decreased left ventricular ejection fraction (LVEF) and was started on single-agent olaratumab. After the Cycle 6 Day 8 olaratumab infusion, the patient complained of fatigue, headache, and dizziness. An electrocardiogram (ECG) showed Grade 2 sinus bradycardia with premature ventricular complexes and the patient was hospitalized. Elevated cardiac troponins were noted; however, cardiac function was normal by ECHO. The patient was discontinued from olaratumab due to this SAE. The Applicant assessed the SAE of sinus bradycardia as possibly related to olaratumab and this reviewer agrees given the temporal relationship. Refer to Section 7.3.8 for further details on cardiac arrhythmias.

Analyses of SAEs from ISS Database

In the ISS database, there was a total of 155 of 485 (32.0%) patients with any grade SAEs. Some of the SAEs were reflective of the nature of the tumor type and different chemotherapies received. In Trial JGDI and the Phase 1b portion of Trial JGDG SAEs occurred in seven (18%) patients. The most common were febrile neutropenia in two (5%) patients and neutropenia in two (5%) patients. There were a total of four (2.9%) patients with SAEs in the four non-randomized studies (JGDC, JGDE, JGDF, JGDH) including one patient who experienced Grade 2 hepatic function abnormal and Grade 2 hemorrhage, one patient with Grade 3 tumor hemorrhage, one patient with glioblastoma multiforme experienced Grade 2 DVT and Grade 2 intracranial hemorrhage, and one patient with Grade 3 syncope. The reviewer assessed the SAEs as related to progressive disease. In the supportive randomized studies (JGDA, JGDB, JGDD), SAEs varied across studies. A total of 83 (43.4%) patients in the olaratumab + chemotherapy arms, 61 (33.0%) patients in the control arms, and 23 (32.8%) patients who received olaratumab after discontinuation of chemotherapy experienced an SAE. The most commonly reported SAEs differed from those in Trial JGDG and included pulmonary embolism (seven [3.7%] patients in the olaratumab-containing arms vs. eight [4.3%] patients in the control arms), anemia (five [8.1%] patients in the olaratumab-containing arms vs. three [5.1%] patients in the chemotherapy arms), intestinal obstruction [four (6.5%) patients in the olaratumab-containing arms vs. six (9.8%) patients in the chemotherapy arms], and febrile neutropenia (four [6.0%]) in the olaratumab-containing arms vs. none in the control arms. The four events of febrile neutropenia occurred in Trial JGDB. This may reflect tumor type and

chemotherapeutic agents used. In addition, neutropenia occurred at a higher rate in Trial JGDB than in Trials JGDA and JGDD.

Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations

Progressive disease was the most common reason for discontinuation of study therapy in both treatment arms. AEs leading to discontinuation of any study drug occurred in more patients in the single-agent doxorubicin arm.

Table 37 lists the AEs that led to discontinuation of study therapy. In the olaratumab + doxorubicin arm, TEAES leading to discontinuation occurred in five (7.8%) patients receiving olaratumab and seven (10.9%) patients receiving doxorubicin. Of the five patients who discontinued olaratumab in the olaratumab + doxorubicin arm, four of the five patients also discontinued doxorubicin. Patients who discontinued therapy could have experienced more than one AE. The most common AE leading to discontinuation of either study drug was ejection fraction decreased in three (4.7%) patients in the olaratumab + doxorubicin arm and four (6.2%) patients in the single-agent doxorubicin arm.

In the olaratumab + doxorubicin arm, hypersensitivity, respiratory failure, and sinus bradycardia were reported as SAEs in patients who discontinued study therapy. None of these AEs had a fatal outcome. In the single-agent doxorubicin arm, six patients had SAEs leading to treatment discontinuation (one patient each with sepsis, respiratory failure, obstruction of the small intestine, thrombocytopenia, neutropenic sepsis, and procedural pain). In addition, three patients had an AE with fatal outcome (sepsis, respiratory failure, and obstruction of the small intestine).

Table 37 Adverse Events Leading to Discontinuation of Study Therapy, Trial JGDG

	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Doxorubicin N=65 n(%)	Single-agent Olaratumab after Doxorubicin Treatment N=30 n(%)
Patients with any TEAE leading to discontinuation of:			
Any study drug	8 (12.5)	11 (16.9)	2 (6.7)
Olaratumab	5 (7.8)	NA	2 (6.7)
Doxorubicin	7 (10.9)	11 (16.9)	NA
TEAES leading to any study drug discontinuation ¹			
Ejection fraction decreased	3 (4.7)	4 (6.2)	0
Infusion related reaction ²	2 (3.1)	0	1 (3.3)
Respiratory failure	1 (1.6)	1 (1.5)	0
Congestive cardiac failure	1 (1.6)	0	0
Left ventricular dysfunction	1 (1.6)	0	0

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Doxorubicin N=65 n(%)	Single-agent Olaratumab after Doxorubicin Treatment N=30 n(%)
Sinus bradycardia	1 (1.6)	0	0
Pneumonia	1 (1.6)	0	0
Mucositis ³	1 (1.6)	0	0
Neutropenia	0	1 (1.5)	0
Thrombocytopenia	0	2 (3.1)	0
Intestinal obstruction ⁴	0	1 (1.5)	0
Hypotension	0	1 (1.5)	0
Neutropenic sepsis	0	1 (1.5)	0
Sepsis	0	1 (1.5)	0
Procedural pain	0	1 (1.5)	0
Phantom pain	0	1 (1.5)	0
Pain in Extremity	0	0	1 (3.3)
TEAEs leading to olaratumab discontinuation			
Infusion related reaction ¹	2 (3.1)	NA	1 (3.3)
Pneumonia	1 (1.6)	NA	0
Ejection fraction decreased	1 (1.6)	NA	0
Respiratory failure	1 (1.6)	NA	0
Sinus bradycardia	1 (1.6)	NA	0
TEAEs leading to doxorubicin discontinuation			
Ejection fraction decreased	3 (4.7)	4 (6.2)	NA
Thrombocytopenia	0	2 (3.1)	NA
Respiratory failure	1 (1.6)	1 (1.5)	NA
Infusion related reaction ²	1 (1.6)	0	NA
Congestive cardiac failure	1 (1.6)	0	NA
Left ventricular dysfunction	1 (1.6)	0	NA
Sinus bradycardia	1 (1.6)	0	NA
Pneumonia	1 (1.6)	0	NA
Mucositis ³	1 (1.6)	0	NA
Neutropenia	0	1 (1.5)	NA
Intestinal obstruction ⁴	0	1 (1.5)	NA
Hypotension	0	1 (1.5)	NA
Neutropenic sepsis	0	1 (1.5)	NA
Sepsis	0	1 (1.5)	NA
Procedural pain	0	1 (1.5)	NA

(Reviewer generated table based on: ADSL.xpt, DS.xpt, AE.xpt)

Abbreviations: TEAE = treatment-emergent adverse events; N = number of treated patients; n = number of patients with given event.
Events; NA = not applicable

1. Some patients may have experienced more than AE
2. AESI of IRR comprising the following preferred term (based on the core IRR analysis [48 IRR preferred terms]): hypersensitivity.
3. Preferred terms reported was: mucosal inflammation.
4. Preferred terms reported was: small intestinal obstruction.

The Applicant reported that patient 010-1001 in the single-agent doxorubicin arm experienced phantom pain that led to discontinuation of study therapy. In reviewing the narrative for this patient, the patient withdrew from study therapy to undergo placement of a spinal neural

stimulator placement for the phantom limb pain. This reviewer attributes discontinuation of the study therapy due to the need to undergo the surgical procedure and not due to a TEAE.

The reviewer performed additional analyses on musculoskeletal pain as a cause for discontinuation of study therapy. Patient 015-1010 discontinued study therapy due to the TEAE of musculoskeletal pain. This patient had Grade 3 intractable leg pain that resulted in hospitalization. MRI revealed extensive metastatic disease in the spine, sacrum, and cord compression which were noted on an MRI performed 4 months prior to this AE. He was treated with dexamethasone and was discharged 5 days later. This reviewer found no other patients across the other eight trials who discontinued olaratumab due to the consolidated PT of musculoskeletal pain.

Narratives for the following patients were reviewed to further evaluate cardiac dysfunction as a cause for discontinuation of study therapy:

- Patient 002-1004 discontinued both olaratumab and doxorubicin for Grade 2 decrease in left ventricular ejection fraction (LVEF) to 45% (baseline ECHO 50%) found on post Cycle 5 Day 1 ECHO. No follow-up ECHO was performed and the patient died 4 months later.
- Patient 008-1001 was randomized to the olaratumab + doxorubicin arm and discontinued doxorubicin only post Cycle 4 Day 1 due to Grade 2 decrease in LVEF from 64% to 53%. This patient went onto receive single-agent olaratumab. Post Cycle 6 Day 8, the patient's LVEF was noted to be 48%.
- Patient 006-1005 discontinued doxorubicin only after ECHO post Cycle 4 demonstrated a LVEF of 40% (baseline ECHO 60%). He was treated with carvedilol and later switched to metoprolol. Olaratumab was continued as a single-agent in this patient. A repeat ECHO after Cycle 5 showed improved LVEF to 55%.
- Patient 003-1004 randomized to the olaratumab + doxorubicin arm discontinued doxorubicin only post Cycle 6 Day 8 due to Grade 3 cardiac congestive failure and Grade 3 ejection fraction decrease to 42% from a baseline of 64%. The patient was treated with carvedilol, furosemide, lisinopril, and metoprolol. This patient went onto receive four cycles of single-agent olaratumab until experiencing disease progression. The last reported LVEF on ECHO was 34%. No treatment was given for this decrease in LVEF. Three months after olaratumab discontinuation the patient was reported as having a resolution of Grade 3 ejection fraction decrease, but ongoing cardiac congestive failure.

Analysis of Discontinuations in the ISS Database

In the ISS database, there were a total of 56 of 485 (11.5%) patients who discontinued study therapy due to an AE. Across the eight supportive studies, the most common reason for discontinuation was progressive disease. AEs that led to discontinuation varied depending on the chemotherapy received. There were no discontinuations of olaratumab due to an AE in Trials JGDI, Phase 1b of JGDG, JGDC, JGDF, and JGDH. Three patients discontinued olaratumab in Trial JGDE (glioblastoma multiforme) due to an AE: one patient with intracranial hemorrhage

into the area of tumor necrosis while on aspirin and enoxaparin, and two patients with thrombocytopenia. All events were Grade 2. In the three supportive randomized trials (JGDA, JGDB, JGDD), 38 (19.9%) patients in the olaratumab-containing arms vs. 33 (17.9%) patients in the chemotherapy arms discontinued therapy due to an AE. A total of 20 patients discontinued olaratumab and 32 patients discontinued chemotherapy. In patients who received olaratumab after discontinuation of chemotherapy, five (7.7%) patients had an AE that led to discontinuation.

Dosage Modifications

The majority of dose modifications in both treatment arms were due to AEs. Other causes included patient request, physician decision, or equipment malfunction. Dose modifications of any reason were higher in the olaratumab + doxorubicin arm vs. the single-agent doxorubicin arm as shown in

Table 38. The patients with interruptions in the infusion of olaratumab were due to IRRs in all cases except two patients (one each for vomiting and dyspepsia). The patient who had doxorubicin infusion interrupted was due to equipment failure. In addition to dose modifications, infusion rate modifications were reported for three patients (4.7%) on the olaratumab + doxorubicin arm, two of which were due to a Grade 2 IRR.

The Applicant states that the higher rate of modification of doxorubicin in the olaratumab + doxorubicin arm was consistent with the longer exposure to doxorubicin in the former arm (median 7 infusions vs. 4 infusions).

Table 38 Summary of Olaratumab and Doxorubicin Dose and Administration Modifications, Trial JGDG

	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Doxorubicin Arm N=65 n(%)	Single-agent Olaratumab after Doxorubicin Treatment N=30 n(%)
Olaratumab			
Patients with Dose Delay	37 (57.8)	n/a	8 (26.7)
Patients with Dose Reduced	16 (25.0)	n/a	1 (3.3)
Patients with Dose Held	20 (31.3)	n/a	2 (6.7)
Patients with Infusion Interrupted	8 (12.5)	n/a	4 (13.3)
Doxorubicin			
Patients with Dose Delay	16 (25.0)	12 (18.5)	n/a
Patients with Dose Reduced	16 (25.0)	10 (15.4)	n/a
Patients with Dose Held	8 (12.5)	3 (4.6)	n/a
Patients with Infusion Interrupted	0	1 (1.5)	n/a

(Reviewer generated table based on: AD_SL.xpt, ADEX.xpt, line-listings provided by the Applicant)

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Each patient may have had more than one dose modification during study therapy and more than one AE may have led to the dose modification.

Abbreviation: N = number of treated patients; n = number of patients in category, n/a: not applicable.

The most common TEAEs leading to dose modifications of olaratumab regardless of relationship to study therapy were neutropenia (31 [48.4%] patients) and thrombocytopenia (8 [12.5%] patients). There were more patients with AEs leading to modification of doxorubicin in the olaratumab + doxorubicin arm (23 [35.9%] patients) than in the single-agent doxorubicin arm (17 [26.2%] patients). The most common AEs leading to modification of doxorubicin were neutropenia (13 [20.3%] vs. six [9.2%] patients in the olaratumab + doxorubicin arm vs. the single-agent doxorubicin arm) and febrile neutropenia (three [4.7%] vs. four [6.2%] patients). In the single-agent olaratumab after discontinuation of single-agent doxorubicin, there were five (16.7%) patients who had 10 AEs that led to dose modifications.

Table 39 and Table 40 show the AEs that led to dose reductions in both arms of Trial JGDG. The most common reason for dose reduction in either arm was neutropenia. SAEs leading to dose reduction of both drugs in the olaratumab + doxorubicin arm occurred in one patient with febrile neutropenia. The SAE of neutropenia led to delay in one patient in the single-agent doxorubicin arm. Of the 14 patients that experienced neutropenia, five (35.7%) patients had recurrent neutropenia. In one patient, subsequent episode of neutropenia was a lower grade. Two patients had subsequent neutropenia after receiving an additional two cycles of therapy without neutropenia. One patient had neutropenia with each cycle. One patient experienced neutropenia in only one subsequent cycle.

Table 39 Summary of Adverse Events Leading to Olaratumab Dose Reductions, Trial JGDG

	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Olaratumab after Doxorubicin N=30 n(%)
Neutropenia	14 (21.8)	0
Febrile neutropenia	1 (1.6)	0
Thrombocytopenia	1 (1.6)	0
Mucositis	1 (1.6)	0
Weight decreased	0	1 (3.3)

(Reviewer generated table based on: ADSL.xpt, ADEX.xpt, line-listings provided by the Applicant)

For each patient, more than one AE may have led to the dose reduction

Abbreviation: N = number of treated patients; n = number of events in category

Table 40 Summary of Adverse Events Leading to Doxorubicin Dose Reductions, Trial JGDG

	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Doxorubicin Arm N=65 n(%)
Neutropenia	10 (15.6)	6 (9.2)
Febrile Neutropenia	2 (3.1)	4 (6.2)
Thrombocytopenia	3 (4.7)	2 (3.1)

	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Doxorubicin Arm N=65 n(%)
Mucositis	1 (1.6)	3 (4.6)
Fatigue	1 (1.6)	2 (3.1)

(Reviewer generated table based on: ADSL.xpt, ADEX.xpt, line-listings provided by the Applicant)
For each patient, more than one AE may have led to the dose reduction
Abbreviation: N = number of treated patients; n = number of events in category

Table 41 and Table 42 show AEs that led to dose delays in Trial JGDG. The most common AE that led to dose delays in either arm was neutropenia. SAEs that led to dose delay in the olaratumab + doxorubicin arm were wound infection (olaratumab and doxorubicin delayed); diarrhea and dehydration led to delay in a patient who received single-agent olaratumab after single-agent doxorubicin. In the single-agent doxorubicin arm, two patients had an SAE leading to delay (one each with neutropenia and febrile neutropenia).

Table 41 Summary of Adverse Events Leading to Olaratumab Dose Delays, Trial JGDG

	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Olaratumab after Single-agent Doxorubicin N=30 n(%)
Neutropenia	21 (32.8)	0
Thrombocytopenia	5 (7.8)	0
Infections and Infestations	4 (6.3)	2 (6.7)
Anemia	3 (4.7)	0
Diarrhea	3 (4.7)	1 (3.3)
Hypokalemia	2 (3.1)	0
Febrile Neutropenia	1 (1.6)	0
Diarrhea	0	1 (3.3)
Fatigue	0	1 (3.3)

(Reviewer generated table based on: ADSL.xpt, ADEX.xpt, line-listings provided by the Applicant)
For each patient, more than one AE may have led to the dose delay
Abbreviation: N = number of treated patients; n = number of patients in category

Table 42 Summary of Adverse Events Leading to Doxorubicin Dose Delays, Trial JGDG

	Olaratumab + Doxorubicin N=64 n(%)	Single-arm Doxorubicin Arm N=65 n(%)
Neutropenia	11 (17.2)	5 (7.7)
Thrombocytopenia	1 (1.6)	0
Infections and Infestations	3 (4.7)	2 (3.1)
Anemia	1 (1.6)	0
Diarrhea	0	0
Hypokalemia	2 (3.1)	0
Febrile Neutropenia	1 (1.6)	2 (3.1)

(Reviewer generated table based on: ADSL.xpt, ADEX.xpt, line-listings provided by the Applicant)
For each patient, more than one AE may have led to the dose delay

Abbreviation: N = number of treated patients; n = number of patients in category

The reviewer noted that the majority of dose modifications leading to dose reductions or delays were due to neutropenia. In addition, thrombocytopenia and anemia were additional cytopenias leading to dose modifications in both treatment arms. The reviewer does not agree with attribution by the Investigator and Applicant of neutropenia, thrombocytopenia, and anemia solely to doxorubicin in the majority of cases. Although cytopenias are a well-characterized adverse reaction to doxorubicin with nadir occurring 7 to 10 days after administration, the temporal relationship of these AEs to the administration of olaratumab plus doxorubicin make it difficult to discount olaratumab as possibly related.

Significant Adverse Events

The ICH E3 guidance recommends that marked laboratory abnormalities not meeting the definition of SAEs also be considered significant AEs. These laboratory abnormalities are described in Laboratory Findings in Section 7.4.4.

In addition, the ICH E3 guidance considers other potentially important abnormalities, such as severe AEs (i.e., $\geq$ Grade 3 by CTCAE that do not meet the definition of a serious AE) as potentially significant. Overall, a higher incidence of patients in the olaratumab + doxorubicin arm (79.7%) experienced any Grade 3 or 4 TEAE than in the single-agent doxorubicin arm (69.3%).

Table 43 shows the most frequent Grade 3 or 4 TEAEs including neutropenia (53.2% in the olaratumab + doxorubicin arm vs. 32.2% in the single-agent doxorubicin arm) and anemia (12.5% vs. 9.2%).

Table 43 Summary of Overall TEAEs and Consolidated TEAE Categories (Grade 3 and Grade $\geq$ 4, Including AESIs), Trial JGDG

Preferred Term Consolidated TEAE Category	Olaratumab + Doxorubicin N=64 n(%)		Single-agent Doxorubicin N=65 n(%)		Single-agent Olaratumab after Single-agent Doxorubicin Treatment N=30 n(%)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Patients with any AE	24 (37.5)	27 (42.2)	25 (38.5)	20 (30.8)	8 (17.8)	0
Neutropenia ¹	12 (18.8)	22 (34.4)	5 (7.7)	16 (24.6)	0	0
Anemia ²	8 (12.5)	0	6 (9.2)	0	1 (3.3)	0
Febrile Neutropenia	7 (10.9)	1 (1.6)	9 (13.8)	0	0	0
Fatigue ³	6 (9.4)	0	2 (3.1)	0	2 (6.7)	0
Musculoskeletal Pain ⁴	5 (7.8)	0	1 (1.5)	0	2 (6.7)	0
Infections and Infestation ⁵	5 (7.8)	0	4 (6.2)	3 (4.6)	0	0
Thrombocytopenia ⁶	5 (7.8)	2 (3.1)	3 (4.6)	2 (3.1)	0	0

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Preferred Term Consolidated TEAE Category	Olaratumab + Doxorubicin N=64 n(%)		Single-agent Doxorubicin N=65 n(%)		Single-agent Olaratumab after Single-agent Doxorubicin Treatment N=30 n(%)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Mucositis ⁷	2 (3.1)	0	3 (4.6)	0	0	0
Hypokalemia	2 (3.1)	0	1 (1.5)	1 (1.5)	1 (3.3)	0
Lymphopenia	2 (3.1)	0	1 (1.5)	0	0	0
Abdominal Pain ⁸	2 (3.1)	0	0	0	0	0
Diarrhea	2 (3.1)	0	0	0	0	0
Nausea	1 (1.6)	0	2 (3.1)	0	1 (3.3)	0
Decreased Appetite	1 (1.6)	0	0	0	2 (6.7)	0
Dry Mouth	1 (1.6)	0	0	0	0	0
Dehydration	1 (1.6)	0	0	0	1 (3.3)	0
Constipation	0	0	1 (1.5)	0	0	0
Dyspnea	0	0	1 (1.5)	0	1 (3.3)	0
AESI						
Infusion-related Reaction ⁹	0	2 (3.1)	0	0	0	0
Cardiac Arrhythmias ¹⁰	0	0	1 (1.5)	0	0	0
Cardiac Dysfunction ¹¹	1 (1.6)	0	0	0	0	0

(Reviewer generated table based on: ADSL.xpt, AE.xpt)

Abbreviations: AESIs = adverse events of special interest; TEAE = treatment-emergent adverse events; N = number of treated patients; n = number of patients with given event

1. Preferred terms reported were: neutropenia, leukopenia, neutrophil count decreased, white blood cell count decreased.

2. Preferred terms reported were: anemia, hemoglobin decreased.

3. Preferred terms reported were: fatigue, asthenia.

4. Preferred terms reported were: back pain, musculoskeletal chest pain, musculoskeletal pain.

5. System Organ Class

6. Preferred terms reported were: thrombocytopenia, platelet count decreased.

7. Preferred terms reported were: mucosal inflammation, oropharyngeal pain, stomatitis.

8. Preferred terms reported were: abdominal pain upper, abdominal pain.

9. Preferred terms patients experienced were face edema, hypersensitivity, infusion related reaction

10. Preferred terms patients experienced were tachycardia, bradycardia, bundle branch block left, electrocardiogram QT prolonged, heart rate increased, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, supraventricular extrasystoles, atrial fibrillation, syncope

11. Preferred terms patients experienced edema peripheral, ejection fraction decreased, cardiac failure congestive, hepatjugular reflux, jugular vein distention, left ventricular dysfunction

Significant Adverse Events from the ISS database

In the ISS database, a total of 231 of 485 (47.6%) patients had a Grade 3 or 4 event. For the 391 patients in the eight supportive studies who received at least one dose of olaratumab, 172 (44.0%) had a Grade 3 or 4 event. The most common events were neutropenia (60 [15.3%] patients), fatigue (27 [6.9%] patients) and anemia (21 [5.4%] patients). Other significant adverse events were dependent upon tumor type and chemotherapy administered with olaratumab. In Trial JGDE (glioblastoma multiforme), convulsion and gait disturbance were the most common significant adverse events. In patients with ovarian cancer in Trial JGDA, palmar-plantar erythrodysesthesia syndrome was common.

Treatment Emergent Adverse Events and Adverse Reactions

The most common TEAEs observed are shown in Table 44. In the olaratumab + doxorubicin arm, the most common TEAEs were nausea (73.4%), fatigue (68.8%), musculoskeletal pain (64.1%), neutropenia (57.8%), and mucositis (53.1%). In the single-agent doxorubicin arm, the most common TEAEs observed were fatigue (69.2%), nausea (52.3%), alopecia (40.0%), anemia (36.9%), neutropenia (35.4%), and mucositis (35.4%). The most frequently reported TEAEs occurring at a $\geq 20\%$ higher incidence in the olaratumab + doxorubicin arm than in the single-agent doxorubicin arm were musculoskeletal pain (64.1% vs. 24.6%), nausea (73.4% vs. 52.3%), neutropenia (57.8% vs. 35.4%), and vomiting (45.3% vs. 18.5%).

Grade ≥ 3 TEAEs were reported in 79.7% of patients in the olaratumab + doxorubicin arm and 69.2% of patients in the single-agent doxorubicin arm. The most common Grade ≥ 3 TEAEs occurring in patients in the olaratumab + doxorubicin arm included neutropenia, anemia, febrile neutropenia, and thrombocytopenia. In the single-agent doxorubicin arm, the most common Grade ≥ 3 AEs included neutropenia and febrile neutropenia. The most common Grade 4 TEAE on both study arms was neutropenia 22 (34.4%) vs. 16 (24.6%).

For the 30 patients who received single-agent olaratumab after discontinuation of single-agent doxorubicin, the TEAEs most frequently reported were musculoskeletal pain [seven patients (23.3%)] and fatigue and nausea (each with six patients [20.0%]). Grade ≥ 3 TEAEs reported in two or more patients were fatigue, musculoskeletal pain, and decreased appetite (each with two patients [6.7%]).

Refer to Sections 7.3.6 to 7.3.8 for a more comprehensive review on adverse events of special interest (AESIs), musculoskeletal pain, and neutropenia.

Table 44 Summary of Overall TEAEs and Consolidated TEAE Categories (Any Grade, Including AESIs), Trial JGDG

Preferred Term Consolidated TEAE Category	Olaratumab + Doxorubicin N=64 n(%)		Single-agent Doxorubicin N=65 n(%)		Single-agent Olaratumab after Single-agent Doxorubicin Treatment N=30 n(%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Patients with any AE	63 (98.4)	51 (79.7)	64 (98.5)	45 (69.2)	26 (80.0)	8 (17.8)
Nausea	47 (73.4)	1 (1.6)	34 (52.3)	2 (3.1)	6 (20.0)	1 (3.3)
Fatigue ¹	44 (68.8)	6 (9.4)	45 (69.2)	2 (3.1)	6 (20.0)	2 (6.7)
Musculoskeletal Pain ²	41 (64.1)	5 (7.8)	16 (24.6)	1 (1.5)	7 (23.3)	2 (6.7)
Neutropenia ^{3,4}	37 (57.8)	34 (53.2)	23 (35.4)	22 (32.3)	0	0
Mucositis ⁵	34 (53.1)	2 (3.1)	23 (35.4)	3 (4.6)	2 (6.7)	0
Alopecia	33 (51.6)	0	26 (40.0)	0	2 (6.7)	0
Vomiting	29 (45.3)	0	12 (18.5)	0	5 (16.7)	0

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Preferred Term Consolidated TEAE Category	Olaratumab + Doxorubicin N=64 n(%)		Single-agent Doxorubicin N=65 n(%)		Single-agent Olaratumab after Single-agent Doxorubicin Treatment N=30 n(%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Infections and Infestations ⁶	27 (42.2)	5 (7.8)	27 (41.5)	7 (10.8)	7 (23.3)	0
Anemia ^{4,7}	26 (40.6)	8 (12.5)	24 (36.9)	6 (9.2)	5 (16.7)	1 (3.3)
Leukopenia ⁸	26 (40.6)	0	12 (18.5)	0	1 (3.3)	0
Constipation	22 (34.4)	0	21 (32.3)	1 (1.5)	3 (10.0)	0
Diarrhea	22 (34.4)	2 (3.1)	15 (23.1)	0	5 (16.7)	0
Decreased Appetite	20 (31.3)	1 (1.6)	13 (20.0)	0	3 (10.0)	2 (6.7)
Abdominal Pain ⁹	15 (23.4)	2 (3.1)	9 (13.8)	0	3 (10.0)	0
Pyrexia	15 (23.4)	0	12 (18.5)	0	3 (10.0)	0
Thrombocytopenia ^{4,10}	16 (25.0)	7 (10.9)	14 (21.5)	5 (7.7)	0	0
Neuropathy ¹¹	14 (21.9)	0	7 (10.8)	0	3 (10.0)	0
Headache	13 (20.3)	0	6 (9.2)	0	1 (3.3)	0
Cough	14 (21.9)	0	12 (18.5)	0	3 (10.0)	0
Dyspnea	11 (17.2)	0	12 (18.5)	1 (1.5)	1 (3.3)	1 (3.3)
Hypokalemia	9 (14.1)	2 (3.1)	6 (9.2)	2 (3.0)	1 (3.3)	1 (3.3)
Febrile Neutropenia	8 (12.5)	8 (12.5)	9 (13.8)	9 (13.8)	0	0
Insomnia	8 (12.5)	0	6 (9.2)	0	2 (6.7)	0
Non-cardiac Chest Pain	8 (12.5)	0	4 (6.2)	0	1 (3.3)	0
Lymphopenia ^{4,12}	8 (12.5)	2 (3.1)	3 (4.6)	1 (1.5)	0	0
Weight Decreased	7 (10.9)	0	7 (10.8)	0	2 (6.7)	0
Dehydration	7 (10.9)	1 (1.6)	6 (9.2)	0	2 (6.7)	1 (3.3)
Hypomagnesemia ¹³	7 (10.9)	0	1 (1.5)	0	0	0
Dry Eye	7 (10.9)	0	2 (3.1)	0	0	0
Dry Mouth	7 (10.9)	1 (1.6)	6 (9.2)	0	1 (3.3)	0
Anxiety	7 (10.9)	0	2 (3.1)	0	0	0
Dizziness	6 (9.4)	0	10 (15.4)	0	5 (16.7)	0
Rash ¹⁴	6 (9.4)	0	5 (7.7)	0	5 (16.7)	0
Abdominal distention	6 (9.4)	0	1 (1.5)	0	1	0
Dysgeusia	6 (9.4)	0	3 (4.6)	0	0	0
Dyspepsia	6 (9.4)	0	1 (1.5)	0	0	0
Hypocalcemia	6 (9.4)	0	2 (3.1)	0	0	0
Depression	4 (6.3)	0	2 (3.1)	0	0	0
Chills	4 (6.3)	0	2 (3.1)	0	3 (10.0)	0
Dry skin	4 (6.3)	0	3 (4.6)	0	1 (3.3)	0
Epistaxis	4 (6.3)	0	2 (3.1)	0	0	0
Gastroesophageal reflux	4 (6.3)	1 (1.6)	3 (4.6)	0	1 (3.3)	0
Hyperglycemia	4 (6.3)	1 (1.6)	0	0	1 (3.3)	0
Hypoalbuminemia	4 (6.3)	0	3 (4.6)	0	1 (3.3)	0
Lacrimation increased	4 (6.3)	0	1 (1.5)	0	0	0
Pollakiuria	4 (6.3)	0	0	0	0	0
AST increased	3 (4.7)	0	1 (1.5)	0	0	0
Erythema	3 (4.7)	0	1 (1.5)	0	0	0
Flatulence	3 (4.7)	0	1 (1.5)	0	1 (3.3)	0
Hiccups	3 (4.7)	0	2 (3.1)	0	0	0

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Preferred Term Consolidated TEAE Category	Olaratumab + Doxorubicin N=64 n(%)		Single-agent Doxorubicin N=65 n(%)		Single-agent Olaratumab after Single-agent Doxorubicin Treatment N=30 n(%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hyponatremia	3 (4.7)	1 (1.6)	4 (6.2)	2 (3.1)	1 (3.3)	0
Malaise	3 (4.7)	0	0	0	0	0
Nail discoloration	3 (4.7)	0	1 (1.5)	0	0	0
Onychomadesis	3 (4.7)	0	2 (3.1)	0	1 (3.3)	0
Palmar-plantar erythrodysesthesia syndrome	3 (4.7)	0	0	0	0	0
Pulmonary embolism	3 (4.7)	1 (1.6)	3 (4.6)	2 (3.1)	0	0
Vaginal hemorrhage	3 (4.7)	0	0	0	0	0
Vision blurred	3 (4.7)	0	0	0	0	0
Vitreous floaters	3 (4.7)	0	0	0	0	0
AESIs						
Infusion-related Reactions ¹⁵	8 (12.5)	2 (3.1)	0	0	3 (10.0)	1 (3.3)
Cardiac Arrhythmias ¹⁶	10 (15.6)	0	10 (15.4)	1 (1.5)	4 (13.3)	0
Cardiac Dysfunction ¹⁷	15 (23.4)	1 (1.6)	12 (16.9)	0	4 (13.3)	0

(Reviewer generated table based on: ADSL.xpt, AE.xpt)

Abbreviations: TEAE = treatment-emergent adverse events; AESI = adverse event of special interest; N = number of treated patients; n = number of patients with given event

1. Preferred terms patients experienced were fatigue and asthenia.
2. Preferred terms patients experienced were arthralgia, back pain, bone pain, flank pain, groin pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and pain in extremity.
3. Preferred terms patients experienced were neutropenia and neutrophil count decreased.
4. As reported by the Investigator. These do not represent actual laboratory values.
5. Preferred terms patients experienced were mucosal inflammation, oropharyngeal pain, and stomatitis.
6. Includes all preferred terms within the MedDRA system organ class of Infections and Infestations
7. Preferred terms patients experienced were anemia and hemoglobin decreased.
8. Preferred terms patients experienced were leukopenia and white blood cell count decreased.
9. Preferred terms patients experienced were abdominal pain upper, abdominal pain, and abdominal pain lower.
10. Preferred terms patients experienced were thrombocytopenia and platelet count decreased.
11. Preferred terms patients experienced were neuropathy peripheral, paresthesia, peripheral sensory neuropathy, and hypoesthesia.
12. Preferred terms patients experienced were lymphocyte count decreased and lymphopenia.
13. Preferred terms patients experienced were hypomagnesaemia and magnesium deficiency.
14. Preferred terms patients experienced were rash, rash papular, dermatitis, dermatitis acneiform, rash macular, and rash pruritic
15. Preferred terms patients experienced were face edema, hypersensitivity, infusion related reaction
16. Preferred terms patients experienced were tachycardia, bradycardia, bundle branch block left, electrocardiogram QT prolonged, heart rate increased, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, supraventricular extrasystoles, atrial fibrillation, syncope
17. Preferred terms patients experienced edema peripheral, ejection fraction decreased, cardiac failure congestive, hepatjugular reflux, jugular vein distention, left ventricular

Although the incidence of neutropenia reported as an adverse event was increased in the olaratumab + doxorubicin arm, the combination of olaratumab and doxorubicin did not result in an increased incidence of febrile neutropenia or infections. The Applicant defined neutropenia with the PTs neutropenia, neutrophil count decreased, leukopenia, and white blood cell count decreased. These terms are not synonymous. The reviewer did not agree with combining these four PTs under the consolidated term neutropenia. The consolidated PTs terms neutropenia (neutropenia and neutrophil count decreased) and leukopenia (leukopenia and white blood cell count decreased) were used separately.

The following describes a review of the Trial JGDG database using standardized MedDRA queries (SMQs). Using FDA MAED software, narrow scope MedDRA SMPs were analyzed to look for potential safety signals not identified through analyses of AEs by MedDRA system organ class, high level term, high level group term, or preferred term. Table 45 provides a listing of AEs identified by narrow scope MedDRA SMQ.

Table 45 Adverse Events by Narrow Scope MedDRA SMQ, Trial JGDG

SMQ	Olaratumab + Doxorubicin N=64 n(%)			Single-agent Doxorubicin N=65			Olaratumab + Doxorubicin vs. Single- agent Doxorubicin
	Events	Patients	Rate %	Events	Patients	Rate %	Odds Ratio
(1) Gastrointestinal and nonspecific inflammation and dysfunctional conditions	256	56	87.5	148	52	80	1.75
(2) Gastrointestinal and nonspecific symptoms and therapeutic procedures	256	56	87.5	142	50	76.92	2.1
(1) Hematopoietic cytopenias	307	40	62.5	91	34	52.31	1.52
(2) Hematopoietic leukopenia	238	40	62.5	72	31	47.69	1.828
(1) Oropharyngeal disorders	44	28	43.75	28	19	29.23	1.883
(2) Oropharyngeal conditions (excluding neoplasms, infections and allergies)	41	26	40.63	27	19	29.23	1.657
(1) Noninfectious diarrhea	34	21	32.81	22	15	23.08	1.628
(2) Hematopoietic thrombocytopenia	67	16	25	19	14	21.54	1.214
(1) Hemorrhages	23	15	23.44	7	6	9.23	3.01
(2) Hemorrhage terms (excluding laboratory terms)	22	14	21.88	7	6	9.23	2.753
(1) Hemodynamic edema, effusions and fluid overload	19	14	21.88	18	12	18.46	1.237
(1) Hypersensitivity	15	13	20.31	14	11	16.92	1.251
(1) Peripheral neuropathy	13	11	19.19	7	6	9.23	2.041
(1) Lacrimal disorders	12	11	17.19	3	3	4.62	4.289
(2) Gastrointestinal nonspecific dysfunction	11	10	15.63	4	4	6.15	2.844
(1) Hepatic disorders	14	8	12.5	5	3	4.62	2.952
(2) Drug related hepatic disorders - comprehensive search	14	8	12.5	5	3	4.62	2.952
(1) Agranulocytosis	10	8	12.5	12	10	15.38	0.786
(1) Conjunctival disorders	8	7	10.94	2	2	3.08	3.686
(1) Taste and smell disorders	7	6	9.38	3	3	4.62	2.138
(1) Embolic and thrombotic events	8	6	9.38	8	7	10.77	0.857
(1) Cardiac failure	7	5	7.81	4	4	6.15	1.292

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

SMQ	Olaratumab + Doxorubicin N=64 n(%)			Single-agent Doxorubicin N=65			Olaratumab + Doxorubicin vs. Single- agent Doxorubicin
	Events	Patients	Rate %	Events	Patients	Rate %	Odds Ratio
(3) Liver related investigations, signs and symptoms	11	5	7.81	3	2	3.08	2.669
(1) Cardiac arrhythmias	6	5	7.81	6	6	9.23	0.833
(2) Cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias)	6	5	7.81	6	6	9.23	0.833
(2) Embolic and thrombotic events, venous	7	5	7.81	3	3	4.62	1.751
(1) Gastrointestinal perforation, ulceration, hemorrhage or obstruction	10	5	7.81	6	4	6.15	1.292
(1) Cardiomyopathy	5	5	7.81	4	4	6.15	1.292
(1) Depression and suicide/self-injury	4	4	6.25	2	2	3.08	2.1
(2) Depression (excluding suicide and self-injury)	4	4	6.25	2	2	3.08	2.1
(1) Hyperglycemia/new onset diabetes mellitus	10	4	6.25	0	0	0	9.744
(3) Bradyarrhythmias (including conduction defects and disorders of sinus node function)	4	4	6.25	1	1	1.54	4.267
(1) Hyponatremia/SIADH	5	4	6.25	7	6	9.23	0.656

(Reviewer generated table based on: ADSL.xpt, AE.xpt, MAED)

N = number of treated patients; n = number of patients with given event

SMQs with an odds ratio (OR) cut-off >2 were further evaluated to identify additional adverse reactions of olaratumab not identified as an adverse reaction in other analyses of Trial JGDG. The following adverse events were further evaluated using this cut-off: gastrointestinal and nonspecific symptoms and therapeutic procedures, peripheral neuropathy, lacrimal disorders, gastrointestinal nonspecific dysfunction, hepatic disorders, drug related hepatic disorders - comprehensive search, conjunctival disorders, taste and smell disorder, liver related investigations signs and symptoms, depression and suicide/self-injury, depression (excluding suicide and self-injury), hyperglycemia/new onset diabetes mellitus, and bradyarrhythmias (including conduction defects and disorders of sinus node function). When available, narratives were reviewed to determine whether there was a causal relationship between olaratumab and the adverse event. Hyperglycemia had the highest OR of 9.744. The difference in laboratory values for hyperglycemia was 52% in the olaratumab + doxorubicin arm vs. 32% in the single-agent doxorubicin arm. The level 1 term hemorrhage had an OR of 3.01. In review of the PTs associated with this (injection site hemorrhage, gastrointestinal hemorrhage, vaginal hemorrhage, hepatic hemorrhage, and rectal hemorrhage), the majority appear to be hemorrhage due to tumor. The OR was greater than 2 for hepatic disorders, drug-related hepatic disorders, and liver-related investigations, signs and symptoms -comprehensive search.

As noted in the laboratory evaluation (refer to Table 49), there were differences between the two arms for prolonged activated partial thromboplastin time (aPTT). This reviewer did not identify any additional adverse events.

This reviewer analyzed common TEAEs in Trial JGDG based upon system organ class (SOC), high-level term, and high-level group term of the MedDRA hierarchy. Table 46 shows the most common AEs by SOC in Trial JGDG. Gastrointestinal disorders were the most common TEAEs in the olaratumab + doxorubicin arm (87.5% vs. 84.6% in the single-agent doxorubicin arm).

Table 46 Most Common Treatment Emergent Adverse Events by MedDRA System Organ Class, Trial JGDG

System Organ Class	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Doxorubicin N=65 n(%)
Gastrointestinal disorders	56 (87.5)	55 (84.6)
General disorders and administration site conditions	55 (85.9)	57 (87.7)
Blood and lymphatic system disorders	45 (70.3)	41 (63.1)
Skin and subcutaneous tissue disorders	44 (68.8)	33 (50.8)
Respiratory, thoracic and mediastinal disorders	43 (67.2)	31 (47.7)
Musculoskeletal and connective tissue disorders	42 (65.6)	18 (27.7)
Investigations	33 (51.6)	25 (38.5)
Metabolism and nutrition disorders	33 (51.6)	29 (44.6)
Nervous system disorders	31 (48.4)	26 (40.0)
Infections and infestations	27 (42.2)	28 (43.1)
Psychiatric disorders	17 (26.6)	12 (18.5)
Eye disorders	15 (23.4)	3 (4.6)
Cardiac disorders	10 (15.6)	10 (15.4)
Vascular disorders	10 (15.6)	14 (21.5)
Injury, poisoning and procedural complications	9 (14.1)	6 (9.2)
Renal and urinary disorders	9 (14.1)	8 (12.3)

(Reviewer generated table based on: ADSL.xpt, AE.xpt, MAED)

N = number of treated patients; n = number of patients with given event

Table 47 summarizes the incidence of high-level group terms in the olaratumab + doxorubicin arm as compared to the single-agent doxorubicin arm. The most common TEAEs by high-level group term are gastrointestinal sign and disorders (84.4% in the olaratumab + doxorubicin arm vs. 66.2% in the single-agent doxorubicin arm), general system disorders NEC (79.7% in the olaratumab + doxorubicin arm vs. 86.2% in the single-agent doxorubicin arm), and skin appendage conditions (62.5% in the olaratumab + doxorubicin arm vs. 46.2% in the single-agent doxorubicin arm).

Table 47 Most Common Treatment Emergent Adverse Events by MedDRA High-Level Group Term, Trial JGDG

High Level Group Term	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Doxorubicin N=65 n(%)
Gastrointestinal signs and disorders	54 (84.4)	43 (66.2)
General system disorders NEC	51 (79.7)	56 (86.2)
Skin appendage conditions	40 (62.5)	30 (46.2)
Respiratory disorders NEC	38 (59.4)	28 (43.1)
White blood cell disorders	35 (54.7)	24 (36.9)
Gastrointestinal motility and defecation conditions	34 (53.1)	32 (49.2)
Musculoskeletal and connective tissue disorder NEC	30 (46.9)	12 (18.5)
Anemias non hemolytic and marrow depression	27 (42.2)	24 (36.9)
Hematology investigations (incl blood groups)	22 (34.4)	14 (21.5)
Appetite and general nutritional disorders	20 (31.3)	14 (21.5)
Infections-pathogen unspecified	20 (31.3)	21 (32.3)
Epidermal and dermal conditions	18 (28.1)	12 (18.5)
Electrolyte and fluid balance conditions	16 (25.0)	15 (23.1)
Body temperature conditions	15 (23.4)	12 (18.5)
Muscle disorders	15 (23.4)	4 (6.15)
Platelet disorders	15 (23.4)	12 (18.5)
Neurologic disorders NEC	14 (21.9)	19 (29.2)
Oral soft tissue conditions	14 (21.9)	12 (18.5)
Headaches	13 (20.3)	7 (10.8)
Bone, calcium, magnesium and phosphorous metabolism disorders	12 (20.3)	5 (7.7)
Eye disorders NEC	11 (17.2)	3 (4.6)
Peripheral neuropathies	11 (17.2)	6 (9.2)
Joint disorders	9 (14.1)	4 (6.2)
Physical examination and organ system status topics	9 (14.1)	8 (12.3)
Upper respiratory tract disorders (excl infections)	9 (14.1)	7 (10.8)
Urinary tract signs and symptoms	9 (14.1)	6 (9.2)
Cardiac arrhythmias	8 (12.5)	10 (15.4)
Sleep disorders and disturbances	8 (12.5)	6 (9.2)
Anxiety disorders and symptoms	7 (10.9)	2 (3.1)
Cardiac and vascular investigations (excl enzyme tests)	7 (10.9)	4 (6.2)
Salivary gland conditions	7 (10.9)	5 (7.7)

(Reviewer generated table based on: ADSL.xpt, AE.xpt, MAED)

N = number of treated patients; n = number of patients with given event; NEC = not elsewhere classified

Table 48 summarizes the incidence of TEAEs by high level term in patients in the olaratumab + doxorubicin arm as compared to the patients in the single-agent doxorubicin arm. The most common TEAEs by high level term are nausea and vomiting symptoms (79.7% in the olaratumab + doxorubicin arm vs. 53.9% in the single-agent doxorubicin arm), asthenic conditions (70.3% in the olaratumab + doxorubicin arm vs. 69.2% in the single-agent doxorubicin arm), neutropenias (53.1% in the olaratumab + doxorubicin arm vs. 33.9% in the single-agent doxorubicin arm), and

alopecias (51.6% in the olaratumab + doxorubicin arm vs. 41.5% in the single-agent doxorubicin arm).

Table 48 Most Common Treatment Emergent Adverse Events by MedDRA High-Level Term, Trial JGDG

High Level Term	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Doxorubicin N=65 n(%)
Nausea and vomiting symptoms	51 (79.7)	35 (53.9)
Asthenic conditions	45 (70.3)	45 (69.2)
Neutropenias	34 (53.1)	22 (33.9)
Alopecias	33 (51.6)	27 (41.5)
Musculoskeletal and connective tissue pain and discomfort	29 (45.3)	12 (18.5)
Anemias NEC	26 (40.6)	24 (36.9)
Gastrointestinal atonic and hypomotility disorders NEC	25 (39.1)	23 (35.4)
Diarrhea (excl infective)	21 (32.8)	15 (23.1)
Appetite disorders	20 (31.3)	14 (21.5)
Leukopenias NEC	18 (28.1)	5 (7.7)
White blood cell analyses	18 (28.1)	12 (18.5)
Coughing and associated symptoms	17 (26.6)	13(9.2)
Mucosal findings abnormal	17 (26.6)	12 (18.5)
Upper respiratory tract signs and symptoms	16 (25.0)	6 (9.2)
Febrile disorders	15 (23.4)	12 (18.5)
Gastrointestinal and abdominal pains (excl oral and throat)	14 (21.9)	10 (15.4)
Thrombocytopenias	14 (21.9)	12 (18.5)
Headaches NEC	13 (20.3)	7 (10.8)
Upper respiratory tract infections	13 (20.3)	8 (12.3)
Pain and discomfort NEC	12 (18.8)	7 (10.8)
Breathing abnormalities	11 (17.2)	13 (20.0)
Lacrimation disorders	11 (17.2)	3 (4.6)
Peripheral neuropathies NEC	11 (17.2)	6 (9.2)
Stomatitis and ulceration	11 (17.2)	12 (18.5)
Muscle related signs and symptoms NEC	10 (15.6)	2 (3.1)
Edema NEC	10 (15.6)	8 (12.3)
Bladder and urethral symptoms	9 (14.1)	3 (4.6)
Joint related signs and symptoms	9 (14.1)	3 (4.6)
Physical examination procedures and organ system status	9 (14.1)	8 (12.3)
Potassium imbalance	9 (14.1)	7 (10.8)
Flatulence, bloating and distension	8 (12.5)	2 (3.1)
Anxiety symptoms	7 (10.9)	2 (3.1)
Magnesium metabolism disorders	7 (10.9)	1 (1.5)
Nail and nail bed conditions (excl infections and infestations)	7 (10.9)	5 (7.7)
Oral dryness and saliva altered	7 (10.9)	5 (7.7)
Total fluid volume decreased	7 (10.9)	6 (9.2)

(Reviewer generated table based on: ADSL.xpt, AE.xpt, MAED)

N = number of treated patients; n = number of patients with given event; NEC = not elsewhere classified

Treatment Emergent Adverse Events from the ISS database

In the ISS database, a total of 466 of 485 (96.1%) patients had at least one TEAE. TEAEs varied in the randomized studies due to the different chemotherapy agents used. In patients who received at least one dose of olaratumab in the eight supportive studies, the most common TEAEs were similar to what was observed in Trial JGDG. These were fatigue (169 [43.2%] patients), musculoskeletal pain (150 [38.3%] patients), nausea (122 [31.2%] patients), and neutropenia (113 [28.9%] patients).

Laboratory Findings

Trial JGDG required laboratory testing at baseline, at regularly scheduled intervals, and at the discretion of the investigator. Laboratory abnormalities were analyzed using the laboratory datasets. Tables were constructed of treatment-emergent laboratory abnormalities, i.e., a laboratory abnormality that represents an increase in toxicity grade from baseline and occurs within 30 days following last dose of assigned protocol treatment (or until next anti-cancer therapy if initiated earlier than 30 days after last dose of protocol treatment). For patients that did not have a post-baseline laboratory reported, the Applicant counted them as missing but included them in the denominator of their calculation of the incidence. This reviewer calculated the incidence of laboratory abnormalities based on a denominator consisting of patients with a baseline and at least one on-study test for each laboratory test, which are represented in Table 49.

Table 49 Common Laboratory Test Result Abnormalities¹, Trial JGDG

Laboratory Abnormality	Olaratumab + Doxorubicin ¹ n(%)			Single-agent Doxorubicin ¹ n(%)		
	N	All Grades (%)	Grades 3-4 (%)	N	All Grades (%)	Grades 3-4 (%)
Chemistry						
Hyperglycemia	62	51.6	1.6	61	27.8	3.2
Increased aPTT	60	33.3	5.0	39	12.8	0
Hyponatremia	63	28.5	0	62	32.3	0
Hypokalemia	63	20.6	7.9	62	14.5	3.2
Hypophosphatemia	61	21.3	4.7	62	6.5	3.2
Elevated ALT	63	17.5	0	62	16.1	0
Increased Alkaline Phosphatase	63	15.8	0	60	6.7	0
Hypomagnesemia	64	15.6	0	63	7.9	0
Hypocalcemia	63	12.7	0	62	12.9	0
Hematology						
Leukopenia	64	89.6	46.8	63	77.7	44.4
Lymphopenia	62	77.4	43.5	59	72.8	37.2
Neutropenia	63	65.1	47.6	60	63.3	38.3
Thrombocytopenia	63	63.4	6.3	62	43.5	11.3

(Reviewer generated table based on: LB.xpt, EX.xpt, and ADSL.xpt)

N = number in denominator

1. Laboratory incidence is based on a denominator consisting of patients with a baseline and at least one on-study test for each of the test.

Results reported in this table represent laboratory abnormalities that occurred in $\geq 10\%$ of patients

Vital Signs

In Trial JGDG, vital sign measurements included temperature, pulse rate, respiration rate, and blood pressure. Measurements were obtained at baseline, prior to each cycle, at the end of therapy, and 30-days post-therapy. In addition, vital signs were measured prior to and at the completion of all olaratumab infusions, and prior to and 1 hour following infusion of doxorubicin per protocol.

A total of 11 patients in Trial JGDG developed a temperature of $\geq 38^\circ\text{C}$ (seven [10.9%] patients in the olaratumab + doxorubicin arm and four [6.2%] patients in the single-agent doxorubicin arm). Two patients in the olaratumab + doxorubicin arm had a temperature of $\geq 39^\circ\text{C}$.

In Trial JGDG, hypotension occurred with equal frequency in the two treatment groups. Eleven (17.2%) patients in the olaratumab + doxorubicin arm and 12 (18.5%) patients in the single-agent doxorubicin arm experienced a systolic blood pressure less than 90mm Hg. Despite the equal presentation of hypotension in the vital signs analysis noted by the reviewer, hypotension was reported as an AE in more patients in the single-agent doxorubicin arm (7.7%) than in the olaratumab + doxorubicin arm (4.7%). In addition, pyrexia was reported as an AE at a higher rate in the olaratumab + doxorubicin arm vs. single-agent doxorubicin arm, 18.5% vs. 23.4%, respectively.

No patient in either treatment arm had a heart rate less than 60 beats per minute (bpm). For heart rates >100 bpm, there were 39 (60.9%) patients in the olaratumab + doxorubicin arm and 35 (54.7%) patients in the doxorubicin arm. The AE of tachycardia was similar between treatment arms: three (4.6%) patients in the single-agent doxorubicin arm experienced tachycardia as compared to four (6.3%) patients in the olaratumab + doxorubicin arm. Bradycardia occurred in one (1.6%) patient in the olaratumab arm and none in the single-agent doxorubicin arm.

Electrocardiograms (ECGs)

In Trial JGDG, ECG and ECHO evaluations were required at baseline, prior to Cycles 5 and 7, at the end of therapy, and when clinically indicated by the Investigator. Cardiac dysfunction is a well-characterized adverse reaction to doxorubicin. Abnormal ECG findings were rare in both treatment arms. The key finding on ECHO was a decrease in LVEF. (Refer to Sections 7.3.7 and 7.3.8 for details related to cardiac arrhythmias and cardiac dysfunction.)

The reviewer noted that the majority of patients had the pre-specified ECG and ECHO evaluations. A total of 126 of 129 (97.7%) patients had baseline ECG and ECHOs.

QT

In all cases, QT was evaluated by the investigator and reported in the CRF. There was 1 (6.4%) Grade 1 prolongation of QT that occurred in the olaratumab + doxorubicin arm. No patients in the single-agent doxorubicin arm experienced prolongation of the QT.

Immunogenicity

The effect of anti-olaratumab antibodies on efficacy, safety, and exposure could not be assessed due to the limited number of patients with treatment-emergent anti-olaratumab antibodies. (Refer to Section 5.4 for further details)

7.3.5 Analysis of Submission-Specific Safety Issues

Adverse Events of Special Interest

The Applicant defined adverse events of special interest as events (AESIs) that are associated with other agents in a similar class of drugs or that were observed in preclinical evaluation or earlier clinical studies of olaratumab. Across all nine studies, IRRs are considered to be an AESI for olaratumab and/or olaratumab plus doxorubicin. In Trial JGDG, cardiac arrhythmias and cardiac dysfunction are considered to be AESIs for doxorubicin and/or olaratumab plus doxorubicin. Each AESI is defined by PTs based on SMQs (MedDRA v.17.1). The AESI of IRR includes a list of PTs, the AESI of cardiac dysfunction was defined by the cardiac failure SMQ, and the AESI of cardiac arrhythmias was defined by the cardiac arrhythmias SMQ. The list of PTs used to identify patients with AESIs is provided in Appendix 14.1. Table 65 and Table 66

Infusion Related Reaction (IRR)

IRRs are an associated risk for monoclonal antibody therapy and were assessed by the Applicant in Trial JGDG for olaratumab. In Trial JGDG, 8 of 64 patients (12.5%) in the olaratumab + doxorubicin arm experienced any-grade IRR; 2 (3.1%) patients experienced a Grade ≥ 3 IRR. Six of the 30 patients (20.0%) in the single-agent doxorubicin arm who received single-agent olaratumab after discontinuation of doxorubicin experienced any-grade IRR; 2 (6.7%) patients had a Grade ≥ 3 IRR. An additional patient who received single-agent olaratumab had a Grade 5 IRR. All IRRs occurred in Cycle 1 or Cycle 2. All Grade ≥ 3 IRRs occurred during the first olaratumab dose. Per protocol, patients were not required to get premedication prior to olaratumab; however, the majority of patients received premedication with dexamethasone, diphenhydramine, or another drug. All patients who experienced a Grade ≥ 3 IRR were permanently discontinued from therapy.

Initially, the Applicant assessed rates of IRR using 48 pre-specified PTs (Refer to Appendix 14.1 Table 65) for their analysis of the safety population (patients identified using the 48 PTs are referred to as the core safety population). All events that occurred within 24 hours were reviewed. A total of 12 of the 94 (12.8%) patients in Trial JGDG who received at least one dose

of olaratumab (64 patients in the olaratumab + doxorubicin arm and 30 patients who received single-agent olaratumab after discontinuation of single-agent doxorubicin patients) were found to have an IRR in the core phase (eight in the olaratumab + doxorubicin arm and four who received single-agent olaratumab arm). After further review by the Applicant, two of the patients who had an IRR in the olaratumab + doxorubicin arm were not considered to be an IRR. The FDA requested the Applicant include nine additional PTs and conduct a post-hoc analysis using all 67 PTs. The additional terms include pyrexia, chills, flushing, hypotension, dyspnea, back pain, and abdominal pain, abdominal pain lower, and abdominal pain upper. After the Applicant performed this analysis, two additional patients in the olaratumab + doxorubicin arm and two patients who received single-agent olaratumab were assessed as having had an IRR. These patients were added to the core phase patients and are referred to as the post-hoc group. The incidence of IRRs in the post-hoc analysis was 14 of 94 (14.9%) of patients. Table 50 shows the results for IRRs from the core and post-hoc analysis.

Table 50 Adverse Events of Special Interest, Infusion-Related Reaction, Trial JGDG

	Olaratumab + Doxorubicin N=64 n(%)		Single-agent Doxorubicin N=65 n(%)		Single-agent Olaratumab after Single-agent Doxorubicin N = 30 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Core IRR Analysis ¹	6 (9.4)	2 (3.1)	0	0	4 (13.3)	2 (6.7)
Post-hoc Analysis ²	2 (3.1)	0	2 (3.1)	0	2 (3.1)	0
TOTAL	8 (12.5)	2(3.1)	2 (3.1)	0	6 (20.0)	2 (6.7)

(Reviewer generated table based on: ADSL.xpt, AE.xpt, narratives)

Abbreviations: IRR = infusion-related reaction; N = number of treated patients; n = number of patients in specified category.

1.Core patients include patients defined as having in from the initial 48 PT

2. Post-hoc analysis include patients defined as having an IRR the additional 9 PT

For patients that experienced an IRR, several different interventions were employed with details provided in Table 51. Other treatment included supplemental oxygen, breathing treatments, and epinephrine.

Table 51 Infusion-Related Reactions Interventions, Trial JGDG

Study	Olaratumab Treated Patients with IRR N	Olaratumab Infusion Interruption n (%)	Olaratumab Infusion Rate Decreased n(%)	Anti-histamine n(%)	Corticosteroid n(%)	Other Treatment n (%)
Olaratumab + doxorubicin	8	6 (75.0)	2 (25.0)	4 (50.0)	1 (12.5)	5 (62.5)
Single-agent Olaratumab ¹	6	4 (33.3)	0	1 (6.7)	2 (33.3)	4 (66.7)
Total Patients	14	10 (71.4)	3 (21.4)	7 (50.0)	3 (21.4)	10 (71.4)

(Reviewer generated table based on: CM.xpt, EX.xpt, ADSL.xpt, narratives, Applicant IR)

1. Patients initially randomized to the Control Arm who received single-agent olaratumab subsequent to discontinuation of single-agent doxorubicin.

A total of 10 (62.5%) patients who had a Grade 1 or 2 IRR underwent subsequent administration of olaratumab. Three patients experienced an IRR upon rechallenge; all were Grade 1 or 2.

Table 52 Infusion-related reactions (IRR) and Rate of IRR Recurrence in Olaratumab-treated Patients, Trial JGDG

Study	Patients with an IRR to olaratumab N	Patients who were re-dosed after first IRR ¹ n (%)	IRR observed upon rechallenge n (%)	Recurrent IRR by Grade ²	
				Grade 1 or Grade 2 n (%)	Grade ≥ 3 n (%)
Olaratumab + doxorubicin	8	6 (75.0)	2 (33.3)	2 (33.3)	0
Single-agent Olaratumab ³	6	4 (66.7)	1 (25.0)	1 (25.0)	0
Total Patients, n (%)	14	10 (71.4)	3 (30.0)	3 (30.0)	0

(Reviewer generated table based one: Module 5: 5.3.5.3: Significant and Notable Patients, narratives)

Abbreviations: IRR = infusion-related reaction; N = number of treated patients; n = number of patients in category.

1. Patients with a documented IRR were analyzed to determine if they experienced AEs that were consistent with an IRR in a subsequent cycle.

2. Patients are only counted once, so if they have multiple recurrences of IRR or they have multiple AE adjudicated to be involved in a single occurrence of an IRR, they are only counted once and counted under their highest grade term adjudicated to be indicative of an IRR.

3. Patients initially randomized to the Control Arm who received single-agent olaratumab subsequent to discontinuation of Single-agent doxorubicin.

Narratives were provided for all patients who experienced an IRR and were evaluated by the reviewer. There was a 100% concordance with the Applicant's assessment of IRRs in both the core and post-hoc analysis. One patient that received single-agent olaratumab after discontinuation of single-agent doxorubicin had a Grade 5 IRR. This occurred in 75 year-old man who had several baseline cardiac comorbidities (ischemic cardiomyopathy, myocardial infarction, ventricular tachycardia, stent placement, heart valve replacement, as well as an implantable defibrillator) who discontinued single-agent doxorubicin after two doses due to a decrease in ejection fraction (43%). The patient subsequently received olaratumab. Ten minutes into the first infusion of olaratumab, the patient developed loss of consciousness and was found to be unresponsive and pulseless; ECG showed ventricular fibrillation and CPR was unsuccessful. The reported event of cardiac arrest was deemed by the investigator and the Applicant to be possibly related to olaratumab. The Applicant determined this to be an IRR given the temporal administration of olaratumab.

This reviewer sent information requests to the Applicant for additional information in regards to premedication administration for all patients so a determination could be made as to the preventative nature of medication intervention on IRRs. Although not required per protocol, premedications were given to the majority of patients that received olaratumab. The reviewer noted that corticosteroids were used more often than antihistamines as a premedication. Although administration of premedication prior to the infusion of olaratumab was up to the discretion of the Investigator (except in the case of a patient experiencing a prior IRR then premedication was mandatory with subsequent infusions), the majority of patients received premedication(s). Overall, 93.7% (59 of 63) of patients received a premedication on Cycle 1 Day

1 and 100% received it on Cycle 2 Day 1, in contrast to 13% of patients receiving premeditations on Cycle 1 Day 8 and 16% on Cycle 2 Day 8. In the olaratumab + doxorubicin arm, 6 of 8 (75%) patients who experienced an IRR received premedication, and 2 of 6 (33%) patients in the single-agent doxorubicin arm who received single-agent olaratumab and experienced an IRR had received premedication.

Table 53 provides details on premedication administered to all patients who had an IRR.

Table 53 Premedication Administered to Patients who Experienced an IRR

Subject	Age/Sex	Cycle	Preferred Term	Grade	Premedication	Brief Description of Event
Olaratumab + Doxorubicin						
001-1030	76/F	C1D1	Hypersensitivity	4	None	Unresponsive 5 minutes during infusion. Chest compression, diphenhydramine, pseudoephedrine.
002-1002	55/F	C1D1	Infusion related reaction	2	None	Dyspnea, chest wall pain, and flushing. Infusion interrupted. Oxygen and diphenhydramine given
004-1006	58/F	C2D1	Infusion related reaction	2	Dexamethasone	Headache, chest pain, anxiety, and shortness of breath during infusion. Interrupted and restarted at decreased rate. Received lorazepam.
012-1024	64/M	C1D1	Hypersensitivity	2	Diphenhydramine	Itchy hives, numbness in lips, eye swelling which resolved that day without treatment. Dose was interrupted.
012-1026	68/M	C1D1	Hypersensitivity	4	Diphenhydramine Dexamethasone	Loss of consciousness. Infusion stopped. Received hydrocortisone.
012-1027	69/M	C1D1	Hypersensitivity	2	Diphenhydramine Dexamethasone	Flushing and itching of extremities. Received hydrocortisone.
015-1024	37/F	C1D1	Pyrexia	1	Dexamethasone	Fever during infusion.
001-1003	43/M	C2D1	Infusion related reaction	2	Dexamethasone	Neuropathic pain in the lower back during the infusion. Given diphenhydramine.
Single-agent olaratumab after discontinuation of single-agent doxorubicin						
002-1007	76/M	C1D1	Hypersensitivity		None	Chills and rigors during infusion. Infusion interrupted. Received
002-1009	63/M	C1D1	Chills	1	None	Chills resolved the same day without
008-1006	74/M	C1D1	Cardiac Arrest	5	None	During the infusion, not feeling well, difficulty breathing, collapsed and was pulseless. CPR initiated but patients died.
010-1004	62/F	C1D1	Infusion related reaction	2	None	Flu-like symptoms during infusions. No interruption or modification.
012-1010	54/M	C2D1	Flushing	1	Diphenhydramine Dexamethasone	Infusion interrupted. Flushing resolved same day. No modifications.

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Subject	Age/Sex	Cycle	Preferred Term	Grade	Premedication	Brief Description of Event
012-1015	45/F	C1D1	Infusion related reaction	4	Diphenhydramine Dexamethasone	Eight minutes into infusion had tingling in hands, nausea, flushing, shortness of breath, and emesis. Infusion stopped. Treated with hydrocortisone, fluids, famotidine, oxygen.

(Reviewer generated table based on: Narratives)

Abbreviations: M = male, F = female, C = cycle; D = day

From the analysis of the use of premedication in mitigating IRRs, there is uncertainty regarding whether use of premedication reduces the risk or lessens the severity of IRRs when given as primary prevention. IRRs occur in the first two cycles in the vast majority of cases and it is possible their administration could lessen the severity of an IRR. The Applicant will provide justification for the use of requiring premedication prior to administration of olaratumab. Updates to the proposed label may be made based on this data. The reviewer also analyzed the IRR data across the eight supportive studies and concluded the overall incidence and timing of IRRs appeared consistent with that observed in Trial JGDG. The reviewer agreed with the Applicant's inclusion of IRRs in the Warnings and Precautions section of the label.

IRRs from the ISS Database

In the ISS database, a total of 70 of 485 (14.4%) patients who had at least one dose of olaratumab experienced any grade IRR. The rate of IRRs across the eight supportive studies (14.3% [56 of 391 patients]) was consistent with what was observed in Trial JGDG (14.9%). IRRs occurred most commonly in Cycles 1 and 2 except for one event in Cycle 5 Day1 in Trial JGDH. This patient experienced a Grade 1 event of red flashes. In Trials JGDI and the Phase 1b portion of Trial JGDG, IRRs occurred in five patients (12.5%). There were no Grade 4 events and one patient experienced a Grade 3 event. Three patients with Grade 1 or 2 underwent rechallenge, no patients experienced a subsequent IRR. In the four non-randomized studies, 14 (14.6%) patients experienced an IRR; all were Grade 1 or 2 events. After rechallenge, 5 of 14 patients (37%) experienced a Grade 1 or 2 IRR. In the three randomized studies, IRRs occurred in 29 (15.2%) patients in the olaratumab-containing arms vs. eight (4.3%) patients in the control arms. Grade ≥ 3 IRR occurred in four (2.1%) patients in the olaratumab-containing arms vs. two (1.1%) patients in the control arms. Twenty-five patients underwent rechallenge in the olaratumab arm. Four had a subsequent IRR; all were Grade 1 or 2.

Table 54 summarizes the IRRs for the ISS database.

Table 54 Infusion-Related Reactions, ISS¹

Study	Single-agent Olaratumab or Olaratumab-containing Arm			Control Arm		
	N	n(%)		N	n(%)	
	N	Any Grade	Grade 3	N	Any Grade	Grade 4
Safety Trial						

Study	Single-agent Olaratumab or Olaratumab-containing Arm N n(%)			Control Arm N n(%)		
	N	Any Grade	Grade 3	N	Any Grade	Grade 4
JGDG Phase 2	64	8 (12.5)	2 (3.1)	65	6 (20.0)	2 (6.7)
Randomized Trials						
JGDA	62	6 (9.7)	0	61	3 (10.7)	0
JGDB	67	17 (25.4)	1 (1.5)	64	2 (11.1)	1 (5.6)
JGDD	62	6 (9.7)	3 (4.8)	59	3 (15.8)	1 (5.3)
Non-randomized Trials						
JGDC	19	5 (26.3)	0	0	n/a	n/a
JGDE	40	4 (10.0)	0	0	n/a	n/a
JGDF	16	0	0	0	n/a	n/a
JGDH	21	5 (23.8)	0	0	n/a	n/a
Secondary Trials						
JGDI	25	3 (12.5)	1 (4.2)	0	n/a	n/a
JGDG Phase 1b	15	2 (13.3)	0	0	n/a	n/a

(Reviewer generated table based on: ADSL.xpt, AE.xpt, narratives)

Abbreviations: N= number of patients

1. Includes patients in the core and post-hoc analysis

Cardiac Dysfunction

Cardiac dysfunction occurred in 15 (23.4%) patients in the olaratumab + doxorubicin arm vs. 11 (16.9%) patients in the single-agent doxorubicin arm. One patient in the olaratumab + doxorubicin arm experienced a Grade 3 event of cardiac congestive cardiac failure and decrease in LVEF. Patients in the olaratumab + doxorubicin arm received more infusions of doxorubicin (seven vs. four in the single-agent doxorubicin arm). The cumulative dose of doxorubicin was higher in the olaratumab + doxorubicin arm (488 mg/m² vs. 300 mg/m² in the single-agent doxorubicin arm). Dexrazoxane was administered to all patients during Cycles 5 to 8 in both arms.

The Applicant performed an additional analysis for the PT peripheral edema and determined that there was no evidence suggesting these patients had cardiac dysfunction or deterioration of cardiac function. When peripheral edema was excluded from the consolidated term cardiac dysfunction, the incidence of cardiac dysfunction was similar between groups, 7.8% in olaratumab + doxorubicin arm vs. 6.2% in the single-agent doxorubicin arm.

In the patients who received single-agent olaratumab after discontinuation of single-agent doxorubicin, four (13.3%) of patients had cardiac dysfunction; there were no Grade 3 or 4 events. All four patients had peripheral edema.

Table 55 Adverse Events of Special Interest, Cardiac Dysfunction, Trial JGDG

Consolidated Preferred Term Cardiac Dysfunction	Olaratumab + Doxorubicin N=64 n(%)		Single-agent Doxorubicin N=65 n(%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac Dysfunction	12 (23.4)	1 (1.6)	11 (16.9)	0
Peripheral Edema	10 (15.6)	0	7 (10.8)	0
Ejection Fraction Decreased	5 (7.8)	1 (1.6)	4 (6.2)	0
Cardiac Failure Congestive	1 (1.6)	1 (1.6)	0	0
Hepatojugular Reflux	1 (1.6)	0	0	0
Jugular Vein Distention	1 (1.6)	0	0	0
Left Ventricular Dysfunction	1 (1.6)	0	0	0

(Reviewer generated table based on: ADSL.xpt, AE.xpt)

Abbreviations: N = number of treated patients; n = number of patients in category.

The incidence of patients with LVEF less than 50% was comparable between the two treatment arms as shown in Table 56. There was a trend for a higher percentage of patients with LVEF decrease of ≥10% on the olaratumab + doxorubicin arm vs. the single-agent doxorubicin arm. The Applicant stated that although fewer patients on the single-agent doxorubicin arm received doxorubicin treatment in these later cycles, and thus did not have cardiac evaluations at these time points.

Table 56 Summary of Abnormal LVEF Results, Trial JGDG

	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Doxorubicin N=65 n(%)
Pre-treatment (Baseline)		
N	64	65
<50%, n(%)	0	0
Prior to Cycle 5 ¹		
N	38	27
<50%, n(%)	2 (5.3)	1 (3.7)
Prior to Cycle 7 ¹		
N	35	18
<50%, n(%)	2 (5.7)	0
Lowest Post-Baseline		
N	51	32
<50%, n(%)	6 (11.8)	3 (9.4)

(Reviewer generated table based on: Y1.xpt, ADSL.xpt)

Abbreviations: LVEF = left ventricular ejection fraction; N = number of patients with assessment at baseline and at time point; n = number of patients in given category.

1. Within 3 days prior to treatment on Day 1 of the indicated cycle.

The reviewer evaluated all narratives for patients with cardiac dysfunction. All events were Grade 1 or 2 except one patient in the olaratumab + doxorubicin arm with the Grade 3 events of cardiac failure congestive and ejection fraction decreased. In this case, doxorubicin therapy was discontinued and the patient went onto received four cycles of single-agent olaratumab

before discontinuing due to disease progression. In all cases where a patient reported peripheral edema in the olaratumab + doxorubicin arm, the reviewer agrees with the Applicant's assessment that there was no indication of cardiac dysfunction that accompanied the event of peripheral edema. In the olaratumab + doxorubicin arm, the reviewer noted that there were several cases of unilateral limb swelling that resolved the same day, peripheral edema that was noted prior to initiation of study therapy, and one case that was associated with a DVT. There were no cases of concomitant decrease in LVEF when peripheral edema was noted in the olaratumab + doxorubicin arm. One patient in the single-agent doxorubicin arm that had peripheral edema experienced a decrease in LVEF. All four patients that received single-agent olaratumab after discontinuation of doxorubicin arm had peripheral edema and none were associated with other signs or symptoms of cardiac dysfunction. The background rate of cardiac dysfunction did not increase with the administration of olaratumab with doxorubicin. No safety signals related to cardiac dysfunction was observed in reviewing this consolidated PT across the eight supportive studies.

Cardiac Arrhythmias

The incidence of cardiac arrhythmias was similar in both treatment arms (15.6% in the olaratumab + doxorubicin arm vs. 15.4% in the single-agent doxorubicin arm) and all events were Grade 1 and 2 except for one Grade 3 event of syncope in the doxorubicin arm. The most common event was tachycardia which occurred in 6.3% of patients in the olaratumab + doxorubicin arm vs. 4.6% of patients in the single-agent doxorubicin arm. In patients that received single-agent olaratumab after discontinuation of single-agent doxorubicin, the incidence of cardiac arrhythmias was 13.3%.

The reviewer evaluated all the patient narratives of cardiac arrhythmia and agrees with the Applicant's assessment. In addition, all eight supportive studies were reviewed, and a cardiac arrhythmia no safety signal was not identified. Like cardiac dysfunction, the background rate of cardiac arrhythmias did not increase with the administration of olaratumab with doxorubicin.

Cardiac Toxicity in the ISS Database

There were no safety signals identified for cardiac toxicity to suggest that cardiac dysfunction or cardiac arrhythmias are adverse drug reactions of olaratumab in the ISS database.

Musculoskeletal Pain

Musculoskeletal pain was an unexpected adverse event per the Applicant. Musculoskeletal pain occurred more frequently in patients in the olaratumab + doxorubicin arm (64.1% vs. 24.6% of patients in the single-agent doxorubicin arm) as shown in Table 57. The majority of patients had a Grade 1 or 2 event. Grade 3 musculoskeletal pain occurred in five (7.8%) patients in the

olaratumab + doxorubicin arm vs. one (1.5%) patient in the single-agent doxorubicin arm. The most common PT reported was pain in the extremity in 15 (23.4%) patients in olaratumab + doxorubicin arm vs. one (1.5%) patient in the single-agent doxorubicin arm. Musculoskeletal pain led to discontinuation of olaratumab in one patient who experienced Grade 3 pain in extremity. (Refer to Section 7.4.4 Dropouts and Discontinuations).

The Applicant evaluated the narratives for each patient to determine possible causation and confounding factors that may have led to the imbalance of musculoskeletal pain in the olaratumab + doxorubicin arm vs. the single-agent doxorubicin arm. The Applicant stated that the increased use of G-CSF in the olaratumab + doxorubicin arm (55%) vs. the single-agent doxorubicin arm (37%) may have been a contributing factor, as well as sites of metastatic disease (causing radiculopathy), and sites primary tumors. Pain in the extremity was the most common reported TEAE under the consolidated PT musculoskeletal pain. An analysis of pain in the extremity by the Applicant demonstrated that the majority of AEs attributed to pain in extremity did not appear to be directly related to olaratumab but were related to underlying disease (8 of 15 patients in the olaratumab + doxorubicin arm). Four of the remaining seven patients had pain in the extremity that was related to another AE: cellulitis, DVT of the leg, peripheral neuropathy, and generalized muscle spasms and pain.

Table 57 Summary of Treatment-Emergent Musculoskeletal Pain (Consolidated Term), Trial JGDG

Preferred Term Consolidated TEAE Category	Olaratumab + Doxorubicin N=64 n(%)		Single-agent Doxorubicin N=65 n(%)		Single-agent Olaratumab after Single-agent Doxorubicin Treatment N=30 n(%)	
	Any Grade	Grade 3	Any Grade	Grade 3	Any Grade	Grade 3
Musculoskeletal Pain	41 (64.1)	5 (7.8)	16 (24.6)	1 (1.5)	11 (36.6)	3 (10.0)
Pain in Extremity	15 (23.4)	2 (3.1)	1 (1.5)	0	2 (6.7)	1 (3.3)
Back Pain	12 (18.8)	2 (3.1)	6 (9.2)	0	3 (10.0)	2 (6.7)
Muscle Spasms	10 (15.6)	0	1 (1.5)	0	0	0
Arthralgia	8 (12.5)	0	2 (3.1)	0	3 (10.0)	0
Musculoskeletal Chest Pain	8 (12.5)	1 (1.6)	2 (3.1)	0	1 (3.3)	0
Myalgia	6 (9.4)	0	2 (3.1)	0	1 (3.3)	0
Bone Pain	5 (7.8)	0	1 (1.5)	0	0	0
Musculoskeletal Pain	4 (6.3)	0	2 (3.1)	1 (1.5)	1 (3.3)	0
Flank Pain	2 (3.1)	0	1 (1.5)	0	0	0
Groin Pain	2 (3.1)	0	0	0	0	0
Neck Pain	1 (1.6)	0	0	0	0	0

(Reviewer generated table base on: ADSL.xpt, AE.xpt)

There were no Grade 4 or 5 events

Abbreviations: TEAE = treatment-emergent adverse events; N = number of treated patients (one PT per patient); n = number of patients in category

This reviewer analyzed all the data provided by the Applicant in addition to data requested through information requests to identify or confirm a causal relationship for the increase in musculoskeletal pain in the olaratumab + doxorubicin arm and in patients who received single-agent olaratumab vs. the single-agent doxorubicin arm. It is interesting to note that although the rate of musculoskeletal pain is higher in the patients that received single-agent olaratumab after discontinuation of single-agent doxorubicin vs. the single-agent doxorubicin arm, the rate is not as high as in the olaratumab + doxorubicin arm. The Applicant states the increased rate of musculoskeletal pain seen in the olaratumab + doxorubicin arm may be due to sites of metastatic disease and site of primary tumor; however, randomization should have remedied this. Although G-CSF was used more frequently in the olaratumab + doxorubicin arm, one might expect the report of bone pain (often associated with the use of G-CSF) to be more frequent in later cycles. The reviewer requested additional information in regards to recurrence of musculoskeletal pain and opioid use in patients with Grade 3 events to evaluate the impact on patients experiencing this AE. The recurrence rate of musculoskeletal pain was low and occurred more frequently with PTs muscle spasms (two patients) and pain in the extremity (four patients). The use of opioids was not unexpected. For the seven patients in the olaratumab + doxorubicin arm and those who received single-agent olaratumab after discontinuation single-agent doxorubicin who had a Grade 3 event, six (85.7%) were on opioids at the time of the AE. Five of the seven were hospitalized and received a combination of intravenous and oral pain medications. Upon discharge, two (28.6%) patients had an additional opioid added to their home regimen (morphine was given for one month after discharge to one patient and fentanyl to the other patient).

This reviewer's overall assessment of musculoskeletal pain is that there is no clear etiology or mechanistic explanation for the increased rate seen in the olaratumab + doxorubicin arm. The reviewer noted that although the incidence of musculoskeletal pain was higher in the olaratumab + doxorubicin arm and in those who received single-agent olaratumab, the majority of events are Grade 1 or 2, it did not cause dose modifications, discontinuation of olaratumab was reported in one case, and it was managed through standard of care measures with analgesics. Of the five patients who experienced a Grade 3 event in the olaratumab + doxorubicin arm, four of the five patients had preexisting pain that worsened and one patient had an infection at the site of pain. Based on the totality of the data, musculoskeletal pain is considered an adverse drug reaction of olaratumab and is included in olaratumab labeling.

Musculoskeletal pain in the ISS Database

Across the ISS database, a total of 240 of 485(49.5%) patients experienced an AE of consolidated term musculoskeletal pain. Musculoskeletal pain occurred in 12 of 40 (50%)

patients in Trials JDGI and the Phase 1b portion of Trial JGDG; there were two (5%) Grade 3 events. In the four non-randomized trials (JGDC, JGDE, JGDF, JGDH), musculoskeletal pain occurred in 25 patients (26.0%); there was one (1.1%) Grade 3 event. In the three randomized trials (JGDA, JGDB, JGDD), the incidence of musculoskeletal pain was 108 of 191 patients (56.5%) in the olaratumab-containing arms vs. 92 of 184 (50%) in the control arms. Trial JGDB was the only trial in which musculoskeletal pain occurred at a higher incidence in the control arm as compared to the olaratumab-containing arm (71.9% vs. 64.2%, respectively). There were eight (41.9%) Grade 3 events in the olaratumab-containing arms and seven (38%) in the control arms. In patients who received single-agent olaratumab after discontinuation of the control arm, 21 (32.3%) patients had any Grade musculoskeletal pain; three were Grade 3. Significant variation occurred in the incidence of consolidated term musculoskeletal pain across the ISS database. Overall, the incidence was the higher in the olaratumab-containing arms 49.5% vs. 43.4%). It is difficult to make direct comparisons given the nature of the various tumor types and chemotherapy agents used. Table 58 summarizes the consolidated term musculoskeletal pain across the ISS database.

Table 58 Musculoskeletal Pain (Consolidated Term), ISS Database

Study	Single-agent Olaratumab or Olaratumab-containing Arm			Control Arm		
	N	Any Grade n(%)	Grade 3	N	Any Grade n(%)	Grade 4
Safety Trial						
JGDG Phase 2	64	41 (64.1)	5 (7.8)	65	16 (24.6)	1 (1.5)
Randomized Studies						
JGDA	62	36 (58.1)	2 (3.2)	61	26 (42.6)	2 (3.3)
JGDB	67	43 (64.2)	5 (7.5)	64	46 (71.9)	4 (6.3)
JGDD	62	29 (46.8)	1 (1.6)	59	20 (33.9)	1 (1.7)
Non-randomized Trials						
JGDC	19	9 (47.7)	1 (5.3)	0	n/a	n/a
JGDE	40	11 (27.5)	0	0	n/a	n/a
JGDF	16	1 (6.3)	0	0	n/a	n/a
JGDH	21	4 (19.0)	0	0	n/a	n/a
Secondary Trials						
JGDI	25	5 (20.0)	0	0	n/a	n/a
JGDG Phase 1b	15	7 (46.7)	2 (13.1)	0	n/a	n/a

(Reviewer generated table based on: ADSL.xpt, AE.xpt)

Abbreviations: N= number of patients

Neutropenia

The Applicant analyzed the data for both investigator reported neutropenia and laboratory resulted values. There was a difference in the rates of neutropenia for all Grades and for Grade 4 between the two the Investigator reported and laboratory results. Neutropenia occurred at a

similar rate between arms in the laboratory-based assessment (64.1% in the olaratumab + doxorubicin arm vs. 60.3% in the single-agent doxorubicin arm) but occurred at a much higher frequency in the olaratumab + doxorubicin arm vs. single-agent doxorubicin arm when analyzed based on adverse events reported by the investigator (57.8% vs. 35.4%, respectively). Incidence of infections was similar between arms. Table 59

Table 59 Treatment-Emergent Severe Infections and Neutropenic Infection, Trial JGDG

	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Doxorubicin N=65 n(%)	Single-agent Olaratumab after single-agent Doxorubicin Treatment N=30 n(%)
Severe Infection ¹	13 (20.3)	14 (21.5)	0
Neutropenic Infection ²	8 (12.5)	11(16.9)	0
Non-neutropenic Infection	5 (7.8)	3 (4.6)	0

(Reviewer generated table based on: ADSL.xpt, AE.xpt)

1. Severe infection is defined as Grade ≥ 3 infection or any grade sepsis/septic shock/febrile neutropenia/neutropenic sepsis

2. Neutropenia infection is defined as (1) Any grade febrile neutropenia or (2) Severe infection with a coinciding event of Grade ≥ 4 neutropenia.

A coinciding Grade ≥ 4 neutropenia is defined as (1)a Grade ≥ 4 TEAE of neutropenia with start or end date within 2 weeks prior to or within 1 week after the onset of the severe infection, or (2) a Grade ≥ 4 absolute neutrophil count (ANC) laboratory value decrease with sampling date within 2 weeks prior to or within 1 week after the onset of the severe infection.

Abbreviations: N = number of treated patients; n = number of patients in category.

Neutropenia as Assessed by Reported Adverse Events

Neutropenia as reported by the Investigator occurred in 37 (57.8%) of patients in the olaratumab + doxorubicin arm and 23 (35.4%) of patients in the single-agent doxorubicin arm. Grade 3 or 4 neutropenia occurred at a higher rate in the olaratumab + doxorubicin arm vs. the single-agent doxorubicin arm (53.2% vs. 32.3%, respectively). The rate of febrile neutropenia was similar between arms (12.5% in the olaratumab + doxorubicin arm vs. 13.8% in the single-agent doxorubicin arm). No neutropenia related infection led to death in either arm. Neutropenia led to dose modifications in 20.3% of patients in the olaratumab + doxorubicin arm and 9.2% of patients in the single-agent doxorubicin arm.

Neutropenia as Assessed by Laboratory Testing

The incidence of neutropenia as assessed by laboratory testing was comparable between arms for all grades (64.1% in the olaratumab + doxorubicin arm vs. 60.3% in the single-agent doxorubicin arm). The incidence of Grade 4 neutropenia was higher in the olaratumab + doxorubicin arm (31.3%) vs. the single-agent doxorubicin arm (19.0%).

This reviewer agrees with the Applicant's assessment that although neutropenia was higher in the olaratumab arm + doxorubicin as reported by the Investigator and higher incidence in Grade 4 by laboratory values, this did not translate into increased rates of febrile neutropenia,

infections, discontinuations, or deaths. The higher rate of Grade 4 neutropenia seen in the assessment of neutropenia based on laboratory data in the olaratumab + doxorubicin arm could be due to patients receiving higher cumulative doses of doxorubicin and for more cycles than the patients in the single-agent doxorubicin arm. There is a cumulative effect of myelosuppression that occurs with repeated administration and bone marrow recovery time is longer. This reviewer noted that neutropenia did not occur as a TEAE in patients who received single-agent olaratumab after discontinuation of single-agent doxorubicin.

Neutropenia by Laboratory Assessment in the ISS Database

In the ISS database, a total of 135 of 480 (28.1%) had any grade neutropenia by laboratory assessment. In Trial JGDI and the Phase 1b portion of Trial JGDG, neutropenia by laboratory assessment occurred in 14 patients (35.0%), Grade 3 was higher than Grade 4 (four [10.0%] patients had Grade 3 vs. one [2.5%] patient with Grade 4). In the four non-randomized trials, neutropenia according to laboratory values occurred in 15 (15.6%) patients. Grade 3 and 4 neutropenia occurred in one patient each. In the three randomized studies, the incidence of neutropenia was slightly higher in the olaratumab-containing arms vs. the control arms, 34.0% vs. 27.2%; Grade 3 to 4 were 15.2% vs. 9.8%, respectively. The reviewer noted that neutropenia rates were different in both phases of Trial JGDG and JGDI although patients received both olaratumab and doxorubicin; however, rates of neutropenia coincide with longer duration of exposure to both olaratumab and doxorubicin in the Phase 2 portion of Trial JGDG.

Table 60 Neutropenia by Laboratory Testing, ISS Database

Study	Single-agent Olaratumab or Olaratumab-containing Arm				Control Arm			
	N	Any Grade	Grade 3	Grade 4	N	Any Grade	Grade 3	Grade 4
JGDG Phase 2	64	41 (64.1)	10 (15.6)	20 (31.3)	63	38 (60.3)	10 (15.9)	12 (19.0)
Randomized Trials ¹	191	65 (34.0)	20 (10.5)	9 (4.7)	184	50 (27.2)	14 (7.6)	4 (2.2)
Non-randomized Trials ²	96	15 (15.6)	1 (1.0)	1 (1.0)	0	n/a	n/a	n/a
JGDI	25	7 (28.0)	1 (4.0)	1 (4.0)	0	n/a	n/a	n/a
JGDG Phase 1b	15	7 (46.8)	3 (20.0)	0	0	n/a	n/a	n/a

(Reviewer generated table based on: ADSL.xpt, LB.xpt)

Abbreviations: N= number of patients

1. Randomized Trials: JGDA, JGDB, JGDD

2. Non-randomized Trials: JGDC, JGDE, JGDF, JGDH

7.3.6 Safety Analyses by Demographic Subgroups

Age

In Trial JGDG, 17 (26.6%) patients who received olaratumab plus doxorubicin and 24 (36.9%) who received doxorubicin were ≥ 65 years of age. Table 61 shows the incidences of TEAEs by

age and treatment group. The incidence of all Grade, and Grade 3 or 4 AEs in patients ≥ 65 years was generally consistent with the incidence rate of AEs experienced in patients < 65 years in the same treatment group and between treatment arms. There was an insufficient number of patients aged ≥ 65 years to assess differences in response based on this demographic.

Table 61 Comparison of Treatment-Emergent Adverse Events by Age, Trial JGDG

	Olaratumab + Doxorubicin N=64		Single-agent Doxorubicin N=65	
	<65 N=47 n (%)	≥ 65 N=17 n (%)	<65 N=41 n (%)	≥ 65 N=24 n (%)
Any TEAE	47 (100)	16 (94.1)	40 (97.6)	24 (100)
Grade 3-4 TEAEs	36 (76.6)	15 (88.2)	27 (65.9)	18 (70.0)
Grade 5 TEAEs	0	0	3 (73.1)	6 (25.0)
Any SAE	20 (42.6)	7 (41.2)	15 (36.6)	10 (41.7)
TEAEs leading to discontinuation	4 (8.5)	4 (23.5)	4 (9.8)	8 (33.3)

(Reviewer generated table based on: ADSL.xpt, AE.xpt and verified: ISS Table 2.7.4.22)

Abbreviations: N = number of treated patients; n = number of patients in category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Sex

In Trial JGDG, female patients represented of 38 (59.4%) patients in the olaratumab + doxorubicin arm vs. 33 (50.8%) in the single-agent doxorubicin arm. Table 62 shows the incidence of TEAEs by treatment and gender. Overall there is no consistent pattern of TEAE difference between genders and no evidence that gender affects tolerability of olaratumab plus doxorubicin.

Table 62 Comparison of Treatment-Emergent Adverse Events by Gender, Trial JGDG

	Olaratumab + Doxorubicin N=64		Single-agent Doxorubicin N=65	
	Male N=26 n (%)	Female N=38 n (%)	Male N=32 n (%)	Female N=33 n (%)
Any TEAE	22 (96.2)	38 (100)	32 (100)	32 (97.0)
Grade 3-4 TEAEs	19 (73.1)	32 (84.2)	21 (65.6)	24 (72.7)
Grade 5 TEAEs	0	0	8 (12.5)	1 (3.0)
Any SAE	8 (30.8)	19 (50.0)	12 (37.5)	13 (39.4)
TEAEs leading to discontinuation	4 (15.4)	4 (10.5)	10 (31.3)	2 (6.1)

(Reviewer generated table based on: ADSL.xpt, AE.xpt and verified: ISS Table 2.7.4.24)

Abbreviations: N = number of treated patients; n = number of patients in category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Race

In the safety population of Trial JGDG, the majority of patients in both arms were White. There were no differences among racial subgroups except in the patients experiencing Grade 3 to 4 TEAEs both Whites and non-whites in which the incidence was higher in the olaratumab + doxorubicin arm as compared to the single-agent doxorubicin arm. In addition, Grade 5 events were more common in the single-agent doxorubicin arm.

Table 63 Comparison of Treatment-Emergent Adverse Events by Race, Trial JGDG

	Olaratumab + Doxorubicin N=64		Single-agent Doxorubicin N=65	
	White N=53 n (%)	Non-White N=11 n (%)	White N=59 n (%)	Non-White N=6 n (%)
Any TEAE	52 (98.1)	11 (100)	58 (98.3)	6 (100)
Grade 3-4 TEAEs	43 (81.1)	8 (72.7)	42 (71.2)	3 (50.0)
Grade 5 TEAEs	0	0	8 (13.6)	1 (16.7)
Any SAE	2 (41.5)	5 (45.5)	23 (39.0)	2 (33.3)
TEAEs leading to discontinuation	8 (15.1)	0	11 (18.6)	1 (16.7)

(Reviewer generated table based on: ADSL.xpt, AE.xpt and verified: ISS Table 2.7.4.25)

Abbreviations: N = number of treated patients; n = number of patients in category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

7.3.7 Specific Safety Studies/Clinical Trials

There were no additional studies performed to evaluate any specific safety concerns.

7.3.8 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No studies have been performed to assess the potential of olaratumab plus doxorubicin for carcinogenicity.

Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of olaratumab plus doxorubicin in pediatric patients has not been established.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no cases of overdose across all nine studies.

7.3.9 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There is no postmarketing experience of olaratumab.

Expectations on Safety in the Postmarket Setting

There are no recommended postmarketing requirements for safety related concerns with olaratumab at this time. Safety data from the ongoing confirmatory trial, JGDJ, will be analyzed for any new safety signals not presented in the label and any changes required in regard to known safety issues. Postmarketing safety will be assessed through routine pharmacovigilance.

7.3.10 Integrated Assessment of Safety

The evaluation of safety of olaratumab in patients with soft-tissue sarcomas (STS) was primarily based on the Phase 2 portion of Trial 15B-IE-JGDG, an open-label, randomized, multicenter, active-controlled trial. The clinical review of safety focused on the 129 patients randomized in the Phase 2 portion of the Trial of which 64 received at least one dose of olaratumab and an additional 30 patients received single-agent olaratumab after discontinuation of single-agent doxorubicin. Evaluation of eight additional trials supported the safety review; however, these studies were not pooled due to differences in trial design, drug regimen, and tumor type. The key safety concerns with olaratumab are IRRs, neutropenia, and musculoskeletal pain. No additional major safety concerns were identified in this Reviewer's analysis of Trial JGDG or in any of the eight supportive studies. Table 64 provides a high-level overview of safety in Trial JGDG. There were no deaths due to AEs in the olaratumab + doxorubicin arm, SAEs were higher in the olaratumab + doxorubicin arm with the most common being neutropenia. Neutropenia most commonly led to discontinuation in both arms.

Table 64 High-level summary of Adverse Events, Trial JGDG

	Olaratumab + Doxorubicin N=64 n(%)	Single-agent Doxorubicin N=65 n(%)
Death due to adverse event	0	4 (6.2)
Serious adverse events	27 (42.2)	25 (38.5)
Discontinued due to adverse event	8 (12.5)	12 (18.5)
Grade 3-4 adverse events	51 (79.7)	45 (69.3)
All grade adverse events	63 (98.4)	64 (98.5)

(Reviewer generated table base on (Source: ADSL.xpt, AE.xpt, EX.xpt)
N = number of treated patients; n = number of patients in category

IRRs are a known adverse reaction to monoclonal antibodies. The incidence and timing of IRRs was similar across all nine studies. For the eight supportive studies the IRR rate was 14.4%, and 14.9% for Trial JGDG. IRRs most commonly occurred in Cycles 1 and 2 except in one case, were

mainly Grade 1 or 2, and all Grade ≥ 3 occurred with the first infusion of olaratumab. There was one death due to an IRR in a patient with a significant cardiac history. Premedication was not required in the protocol but was administered to the majority of patients on Day 1 of each cycle in Trial JGDG. The reviewer considers IRRs to be the most significant adverse event related to olaratumab. The evidence that premedication mitigates or decreases the severity of IRRs is not clear. (b) (4)

Musculoskeletal pain occurred more frequently in patients in the olaratumab + doxorubicin arm (64.1% vs. 24.6% of patients in the single-agent doxorubicin arm). Grade 3 to 4 musculoskeletal pain occurred in 7.8% of patients in the olaratumab + doxorubicin arm vs. 1.5% in the single-agent doxorubicin arm. There was one musculoskeletal event that led to discontinuation in the olaratumab + doxorubicin arm. The majority of events were low grade, and mitigated with supportive care and analgesics.

Although cardiac toxicity was a potential concern in Trial JGDG because of the administration of doxorubicin, there was only a small difference in the rates of cardiac dysfunction between treatment arms, which was no longer present when the preferred term peripheral edema was removed from the analysis (7.8% vs. 6.2% in the single-agent doxorubicin arm). In addition, no safety signals for cardiac toxicity were discovered in the safety analysis of the eight studies. The reviewer does not recommend additional monitoring for cardiac toxicity outside of that which is considered standard of care for doxorubicin treatment.

Analysis of neutropenia by laboratory results was comparable between the two arms in Trial JGDG: 64.1% in the olaratumab + doxorubicin arm vs. 60.3% in the single-agent doxorubicin arm. There was a difference between Grade 4 neutropenia: 31.3% vs. 19.0%; however, that did not translate into higher rates of febrile neutropenia, infections, discontinuations or death. The incidence of neutropenia in the eight supportive studies varied; however, the incidence of neutropenia (any grade) in the three randomized studies was also higher in patients who received olaratumab plus chemotherapy than in patients who received chemotherapy without olaratumab.

The clinical review of safety for this BLA determined that the safety profile of olaratumab plus doxorubicin is acceptable in patients with anthracycline-naïve, relapsed or refractory STS not amenable to surgery or radiation. The most serious risks of olaratumab are infusion-related reactions, including risk of fatal infusion-related reactions, and severe and life-threatening neutropenia. Oncologists are experienced in the monitoring and management of these serious risks. This reviewer does not recommend a risk evaluation and mitigation strategy (REMS) based on the current safety profile of olaratumab. Recommendation for safe and effective use of olaratumab, including monitoring and management IRRs, will be addressed in labeling.

SUMMARY AND CONCLUSIONS

7.4 Statistical Issues

Trial JGDG was not originally designed for regulatory consideration. The significance level of 0.20 for the primary endpoint of PFS does not meet the regulatory standard for providing adequate evidence of effectiveness. Also, the original protocol did not have a statistical analysis plan for OS.

A Phase 2 study designed as a proof-of-concept study may not be conducted with the rigor of large Phase 3 clinical trials, including multiple looks at the data. A second concern with small trials is generalizability, as often Phase 2 trials are restricted to a limited number of sites and eligibility criteria.

The PFS analysis results [HR = 0.67 (95% CI: 0.44, 1.02); p-value = 0.06] met the protocol-specified criteria. This allowed for the evaluation OS data. The HR for OS was 0.46 (95% CI: 0.30, 0.71) with an estimated difference in median OS of 11.6 months. This was statistically significant, accounting for the interim looks and using a re-randomization test. In the FDA review of the conduct of Trial JGDG, no apparent deficiencies were observed. The observed effect of olaratumab on OS is substantially large and the probability of a chance finding is very small. In addition, if the true HR is indeed 0.46, using a two-sided alpha of 0.05, there is a 95% chance of observing a significant effect with 91 events based on FDA's simulation (10,000 iteration, EAST 6.2). Since the magnitude of the improvement of OS is large with respect to both the estimated HR and the difference in OS medians, the results suggest that findings purely due to chance are very small, after taking into consideration the small sample size and interim analysis.

7.5 Conclusions and Recommendations

STS are a rare and heterogeneous group of diseases. Patients who do not have curative local control options with surgery or radiation have an extremely poor prognosis and represent a patient population with a life-threatening illness and an unmet medical need.

Trial JGDG was a multi-center, open-label trial which randomized (1:1) patients with advanced STS who had not previously received an anthracycline to either olaratumab + doxorubicin or doxorubicin. Patients received either doxorubicin 75 mg/m² followed by olaratumab 15 mg/kg on day 1 and 8 of each 21-day cycle or doxorubicin 75 mg/m² on day 1 of each 21-day cycle. Treatment continued for up to eight cycles or until disease progression or unacceptable treatment-related toxicity. In the absence of disease progression, patients in the experimental arm who completed eight cycles of doxorubicin could receive olaratumab monotherapy at the same dose and schedule until progression or intolerable toxicity. Patients on the control arm were eligible to receive single-agent olaratumab upon disease progression.

Randomization was stratified by PDGFR- α expression (positive vs. negative), prior lines of treatment (0 vs. ≥ 1), histological tumor type (leiomyosarcoma vs. synovial sarcoma vs. other), and ECOG performance status (0-1 vs. 2) through a dynamic minimization method. The primary endpoint of Trial JGDG was PFS per investigator assessment and was designed with 80% power at a 2-sided alpha level of 20%. OS was a secondary endpoint and there were no statistical criteria, power analysis, or statistical procedure to adjust for multiplicity of the OS endpoint.

One hundred and thirty-three patients with metastatic STS were randomized (66 to olaratumab + doxorubicin and 67 to doxorubicin). Treatment with olaratumab + doxorubicin resulted in a clinically meaningful and statistically significant treatment effect with an improvement of 11.8 months in OS compared to treatment with doxorubicin alone. The median OS was 26.5 months (95% CI: 20.9, 31.7) compared to 14.7 months (95% CI: 9.2, 17.1); unstratified HR 0.52 (95% CI: 0.34, 0.79); p-value <0.05 given statistical considerations noted above. The median PFS as assessed by the investigator was 6.6 months (95% CI: 4.1, 8.3) vs. 4.1 months (95% CI: 2.8, 5.4), stratified HR 0.67 (95% CI: 0.44, 1.02), p=0.06. The confirmed ORR as assessed by BICR was low in both arms: 18.2% (95% CI: 9.8, 29.6) vs. 7.5% (95% CI: 2.5, 16.6).

Trial JGDG was designed as an activity-estimating trial of olaratumab + doxorubicin in patients with advanced STS. The statistical limitations of the trial design include less statistical rigor for the primary endpoint than is typical for a registration trial and lack of formal statistical considerations for the secondary OS endpoint. The limitations for clinical interpretation of the magnitude of treatment effect of olaratumab for this patient population include the small size of the trial given the heterogeneous patient population represented by more than 25 different STS histologies. Although this is typical of STS trials that are not limited by histology, the small numbers in this trial add to the uncertainty of clinical benefit for any one histology. Additional uncertainties are the discrepancy seen in the magnitudes of the PFS and OS benefits, and the potential impact of the imbalance between treatment arms in post-treatment therapies. These uncertainties can be further evaluated with additional data from the larger ongoing confirmatory trial JGDJ. Trial JGDG is considered an adequate and well-controlled trial that employed randomization between an experimental and standard of care arm, use of OS as the main efficacy endpoint for regulatory consideration, minimization of bias of the primary endpoint with use of an independent blinded central review of PFS, and reported a lack of substantial protocol deviations. In addition, the Applicant's analyses were able to be reproduced by FDA reviewers, and there were no concerns from OSI or EMA inspectors of three clinical sites, the Applicant site, and the contract radiology organization.

Despite the limitations in trial design, a substantial, statistically significant and clinically meaningful improvement in OS was observed in this trial for patients with STS treated with olaratumab + doxorubicin compared to doxorubicin alone, and the safety profile of olaratumab is considered to be acceptable in a patient population with a severe and life-threatening illness with a great unmet medical need. No other FDA-approved therapy for patients with advanced STS has demonstrated an advantage in OS. Therefore, we recommend the approval, under 21 CFR part 601, subpart E, of olaratumab, in combination with doxorubicin, for the treatment of patients with STS not amenable to curative treatment with radiotherapy or surgery and with a histologic subtype for which an anthracycline-containing regimen is appropriate, at a dose of 15

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

mg/kg on days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity. Accelerated approval is recommended given the uncertainty of the treatment effects of olaratumab in any one histologic subtype of STS, the magnitude of the OS benefit seen in this small clinical trial, and the need for further description of the clinical benefit of olaratumab for patients with STS in a larger clinical trial.

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Primary Statistical Reviewer

Statistical Team Leader

X Leslie Doros -A
(Affiliate)

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K. Chuk -S

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Primary Clinical Reviewer

Primary Clinical Reviewer

X Marc R.
Theoret -S

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Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

The Division did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) for this BLA. The Division plans to obtain the advice of two practicing oncologists and a patient advocate all with an interest or expertise in sarcoma. Details of the consults will be provided in an additional memo.

9 Pediatrics

Trials with safety or efficacy data pertaining to pediatric patients were not submitted with this BLA. The BLA is exempt from the requirement to assess the safety and effectiveness of the product for the claimed indication in all pediatric age categories under 21 CFR 314.55(d), Exemption for Orphan Drugs.

10 Labeling Recommendations

10.1 Prescribing Information

Summary of Significant Labeling Changes (High-level changes and not direct quotations)		
Section	Proposed Labeling	FDA Revisions to Labeling
Highlights		
Indications and Usage	LARTRUVO™ is a platelet-derived growth factor receptor alpha (PDGFR-α) (b) (4)	FDA changed the established pharmaceutical class from PDGFR-α (b) (4) to PDGFR-α blocking antibody to be consistent with current labeling practices.
Warnings and Precautions	Infusion-Related Reactions: Monitor for signs and symptoms during infusion. Discontinue LARTRUVO for (b) (4) (2.2, 2.3, 5.1)	FDA added a warning for embryo-fetal toxicity based on literature reports describing the role of PDGFR-α in embryonic development and organogenesis and the embryo-fetal developmental toxicity study conducted in mice using an anti-murine PDGFR-α antibody.
Adverse Reactions	The most common adverse reactions (b) (4) LARTRUVO plus doxorubicin (b) (4) (b) (4) nausea, musculoskeletal pain, (b) (4), mucositis, vomiting, (b) (4) diarrhea. (6.1)	FDA revised the statement to include the most common adverse reactions occurring ≥20%. FDA added a statement about most common laboratory abnormalities occurring ≥20%.
Full Prescribing Information		
1 Indications and Usage	LARTRUVO™ is indicated, in combination with doxorubicin, for the treatment of patients with (b) (4) soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery.	FDA revised the indication to include patients with a histologic subtype for which an anthracycline-containing regimen is appropriate, from the clinical trial used as basis of FDA-approval.
2 Dosage and Administration 2.2 Premedication	- Premedicate (b) (4) (b) (4) intravenously, prior to the LARTRUVO (b) (4) (b) (4) (b) (4) (b) (4)	Given that infusion reactions were primarily restricted to first or second dose of antibody infusion, FDA requested that the Applicant provide justification for these instructions, or remove from labeling.

Summary of Significant Labeling Changes (High-level changes and not direct quotations)		
Section	Proposed Labeling	FDA Revisions to Labeling
	(b) (4)	
2 Dosage and Administration 2.3 Dose Modifications	(b) (4) <u>Neutropenia</u> (b) (4) neutropenic fever/infection or Grade 4 neutropenia lasting longer than 1 week (b) (4), discontinue administration of LARTRUVO until the absolute neutrophil count is 1,000 X (b) (4) and then reduce the dose to 12 mg/kg (b) (4)	Reviewer’s comment: These instructions are review issues and may be modified pending response from Applicant. (b) (4) (b) (4) FDA has asked the Applicant to determine (b) (4) (b) (4) For neutropenia, FDA has asked the Applicant to determine whether there is any evidence that this action mitigates the toxicity of severe neutropenia resulting in neutropenic fever or sepsis.
5 Warnings and Precautions 5.1 Infusion-Related Reactions	Infusion-related reactions (b) (4) (b) (4) clinical trials (b) (4) (b) (4) (b) (4) included flushing, shortness of breath, bronchospasm, or fever/chills, and in severe cases symptoms manifested as severe hypotension, anaphylactic shock, or cardiac arrest. (b) (4) (b) (4)	FDA revised to provide more detailed information about IRRs in the overall clinical trial experience and in the patients who received Lartruvo monotherapy following doxorubicin, e.g., incidence, interruption and discontinuation, treatment administered, and rechallenge.

Summary of Significant Labeling Changes (High-level changes and not direct quotations)		
Section	Proposed Labeling	FDA Revisions to Labeling
	(b) (4)	
5 Warnings and Precautions <i>5.2 Embryo-fetal Toxicity</i>	None.	FDA added a subsection to include a warning pertaining to embryo-fetal toxicity, based on literature reports describing the role of PDGFR- α in embryonic development and organogenesis and the embryo-fetal developmental toxicity study conducted in mice using an anti-murine PDGFR- α antibody.
6 Adverse Reactions <i>6.1 Clinical Trials Experience</i>	(b) (4) 485 patients received LARTRUVO (b) (4)	FDA expanded on this statement to describe that the data in Warnings and Precautions section were derived from nine studies: three randomized, open-label, active-controlled trials, four open-label, single-arm trials, and two trials which enrolled patients with STS who received Lartruvo at doses of 15 to 20 mg/kg in combination with doxorubicin.

Summary of Significant Labeling Changes (High-level changes and not direct quotations)		
Section	Proposed Labeling	FDA Revisions to Labeling
	Table 1: Adverse Reactions Occurring in ^{(b) (4)} Patients ^{(b) (4)} on LARTRUVO plus Doxorubicin for Soft ^{(b) (4)}	FDA revised the presentation of adverse reactions to include in Table 1: - Modified the cut-off for the list of adverse reactions, and retitled to, “Table 1: Adverse Reactions Occurring in ≥ 10% (All Grades) of Patients on the LARTRUVO and Doxorubicin Arm and at a Higher Incidence than in the Doxorubicin Arm (Between Arm Difference of ≥5% for All Grades or ≥2% for Grades 3 and 4) (Trial 1)” - Added adverse reactions alopecia, abdominal pain, decreased appetite, and neuropathy in Table 1. - Removed ^{(b) (4)} from Table 1 and placed in separate table as reporting by investigator of clinical laboratory data as adverse reactions results in under-reporting. - Added another table, “Table 2. Laboratory Abnormalities Occurring in >10% (all Grades) of Patients on the LARTRUVO and Doxorubicin Arm and at a Higher Incidence than in the Doxorubicin Arm (Between Arm Difference ≥ 5% for All Grades or ≥2% for Grades 3 and 4) (Trial 1)”, to list the laboratory test abnormalities.
7 Drug Interactions	^{(b) (4)}	FDA removed this section as there are no drug interactions, per 21 CFR 201.57(c)(8).
8 Use in Specific Populations 8.1 Pregnancy	<u>Risk Summary</u> Based on its mechanism of action [see <i>Clinical Pharmacology (12.1)</i>] ^{(b) (4)} ^{(b) (4)} LARTRUVO can cause fetal harm. No animal studies have been conducted	FDA added findings of cleft face and spina bifida in PDGFR-α knockout mice from literature reports, in addition to animal data from the embryo-fetal developmental toxicity

Summary of Significant Labeling Changes (High-level changes and not direct quotations)		
Section	Proposed Labeling	FDA Revisions to Labeling
	to evaluate (b) (4) effect (b) (4) on female reproduction and embryo-fetal development. Animal models link disruption of platelet-derived growth factor receptor alpha (PDGFR-α) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-α specific antibody to pregnant mice during organogenesis (b) (4)	study conducted in mice using an anti-murine PDGFR-α antibody.
8 Use in Specific Populations 8.2 <i>Lactation</i>	<u>Risk Summary</u> There is no (b) (4) presence of olaratumab in human milk, (b) (4) effects on the breastfed infant, or (b) (4) on milk production. (b) (4) (b) (4) Because of the potential risk for serious adverse reactions in (b) (4) infants from LARTRUVO, (b) (4) during treatment with LARTRUVO and for at least 3 months following the last dose.	FDA removed the statement about (b) (4) as it is not useful to prescribers.
8 Use in Specific Populations 8.3 <i>Females and Males of Reproductive Potential</i>	<u>Contraception</u> <i>Females</i> Based on its mechanism of action, LARTRUVO can cause fetal harm [see <i>Use in Specific Populations (8.1)</i>]. Advise females of reproductive potential to use effective contraception (b) (4) LARTRUVO and for (b) (4) 3 months after the last dose (b) (4)	Based on literature reports of animal knockout models, FDA added a statement that LARTRUVO may impair male fertility.
8 Use in Specific Populations 8.6 <i>Renal Impairment</i>	(b) (4)	FDA deleted sections because the information is not actionable and can be stated in Section 12.3, per Draft Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on

Summary of Significant Labeling Changes (High-level changes and not direct quotations)		
Section	Proposed Labeling	FDA Revisions to Labeling
		<u>Dosing and Labeling.</u>
8 Use in Specific Populations 8.7 Hepatic Impairment	(b) (4)	FDA deleted sections because the information is not actionable and can be stated in Section 12.3, per <u>Guidance for Industry: Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.</u>
12 Clinical Pharmacology 12.1 Mechanism of Action	Platelet-derived growth factor receptor alpha is expressed on cells (b) (4)	FDA added background information on PDGFR- α . Revised section to accurately reflect the pharmacology data submitted to the BLA. FDA removed (b) (4) (b) (4) (b) (4) that is more consistent with current labeling practices.
12 Clinical Pharmacology 12.2 Pharmacodynamics	(b) (4)	Based on FDA's determination that monoclonal antibodies do not carry risk of QT prolongation except in limited number of circumstances, this section is not required for this product.
12 Clinical Pharmacology 12.3	<u>Specific Populations</u> Age, sex, (b) (4) race (b) (4)	FDA revised the renal and hepatic impairment subsections as negative information may be combined for

Summary of Significant Labeling Changes (High-level changes and not direct quotations)		
Section	Proposed Labeling	FDA Revisions to Labeling
<i>Pharmacokinetics</i>	(b) (4)	succinctness per section 12 of <u>Draft Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format</u>
	(b) (4)	
13 Nonclinical	No studies have been performed to	Based on literature reports of animal

Summary of Significant Labeling Changes (High-level changes and not direct quotations)		
Section	Proposed Labeling	FDA Revisions to Labeling
Toxicology 13.1 <i>Carcinogenesis, Mutagenesis, Impairment of Fertility</i>	assess the potential of olaratumab for carcinogenicity or genotoxicity. Fertility studies have not been performed with olaratumab.	knockout models, FDA added a statement that LARTRUVO may impair male fertility.
14 Clinical Studies	Demographics and (b) (4) disease characteristics (b) (4) : median age 58 years (range 22 to 86); 44% men; 86% White; 8% Black; 3% Asian; (b) (4) (b) (4) 56% ECOG PS 0 and 39% ECOG PS 1; 65% no (b) (4) (b) (4) 38% leiomyosarcoma (b) (4) % (b) (4), (b) (4) % (b) (4) .	FDA added a description of the STS subgroups in Trial JGDG, given the heterogeneity of the patient population. FDA removed the statement (b) (4) . In accordance with standard practice, FDA will comment on imbalances where they appear to exist. FDA removed the statement (b) (4)
	(b) (4)	FDA removed (b) (4) (b) (4) For Table (b) (4) FDA revised the order of the efficacy results to present OS first followed by PFS and ORR based on OS as the more clinically important endpoint. In addition, FDA removed the (b) (4) (b) (4)

Summary of Significant Labeling Changes (High-level changes and not direct quotations)		
Section	Proposed Labeling	FDA Revisions to Labeling
	(b) (4)	

10.2 Patient Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

A risk evaluation and mitigation strategy (REMS) is not recommended based on the current safety profile of olaratumab.

12 Postmarketing Requirements and Commitments

21 CFR part 601, subpart E describes accelerated approval of biologic products for serious and life-threatening illnesses and is “subject to the requirement that the applicant study the biologic product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.” The recommendation for accelerated approval rather than regular approval is based on the uncertainty of the magnitude and breadth of the clinical benefit of overall survival and PFS given the small numbers of patients, heterogeneous patient population, and statistical considerations discussed in Section 7.4.

The following post-marketing trial to confirm clinical benefit is required: Conduct and submit the results of a multicenter, randomized clinical trial confirming the clinical benefit of olaratumab in combination with doxorubicin in patients with soft tissue sarcoma that is not amenable to surgery or radiation.

The Applicant is conducting an ongoing trial that is fully accrued and that should be capable, based on review of the trial design, of further defining the clinical benefit (b) (4)

[REDACTED]

13 Appendices

13.1 Preferred Terms

Infusion related Reaction

Table 65 Preferred Terms for Infusion-Related Reaction, Trial JGDG

Preferred Terms Infusion related reaction			
Allergic edema	Anaphylactic reaction	Anaphylactic shock	Anaphylactoid reaction
Anaphylactoid shock	Angioedema	Circulatory collapse	Circumoral edema
Conjunctival edema	Corneal edema	Cytokine release syndrome	Distributive shock
Drug hypersensitivity	Epiglottic edema	Eye edema	Eye swelling
Eyelid edema	Face edema	First use syndrome	Gingival edema
Gingival swelling	Gleich's syndrome	Hypersensitivity	Idiopathic urticaria
Infusion related reaction	Kounis syndrome	Laryngeal edema	Laryngotracheal edema
Limbal swelling	Lip edema	Lip swelling	Mouth edema
Oculorespiratory syndrome	Oropharyngeal swelling	Palatal edema	Periorbital edema
Pharyngeal edema	Scleral edema	Shock	Swelling face
Swollen tongue	Tongue edema	Tracheal edema	Type 1 hypersensitivity
Urticaria	Urticaria cholinergic	Urticaria chronic	Urticaria papular

Cardiac Dysfunction

Table 66 Preferred Terms Cardiac Dysfunction, Trial JGDG

Preferred Terms Cardiac Dysfunction			
Acute left ventricular failure	Acute pulmonary edema	Acute right ventricular failure	Cardiac asthma
Cardiac failure	Cardiac failure acute	Cardiac failure chronic	Cardiac failure congestive
Cardiac failure high output	Cardiogenic shock	Cardiopulmonary failure	Cardiorenal syndrome
Chronic left ventricular failure	Chronic right ventricular failure	Cor pulmonale	Cor pulmonale acute
Cor pulmonale chronic	Ejection fraction decreased	Hepatic congestion	Hepatojugular reflux
Left ventricular failure	Low cardiac output syndrome	Neonatal cardiac failure	Obstructive shock
Pulmonary edema	Pulmonary edema neonatal	Right ventricular failure	Ventricular failure

BLA 761038 Multi-disciplinary Review and Evaluation
LARTRUVO (Olaratumab)

Artificial heart implant	Atrial natriuretic peptide abnormal	Atrial natriuretic peptide increased	Brain natriuretic peptide abnormal
Brain natriuretic peptide increased	Cardiac cirrhosis	Cardiac index decreased	Cardiac output decreased
Cardiac resynchronization therapy	Cardiac ventriculogram abnormal	Cardiac ventriculogram left abnormal	Cardiac ventriculogram right abnormal
Cardiomegaly	Cardio-respiratory distress	Cardiothoracic ratio increased	Central venous pressure increased
Diastolic dysfunction	Dilatation ventricular	Dyspnea paroxysmal nocturnal	Heart transplant
Hepatic vein dilatation	Jugular vein distension	Left ventricular dysfunction	Myocardial depression
Nocturnal dyspnea	N-terminal prohormone brain natriuretic peptide abnormal	N-terminal prohormone brain natriuretic peptide increased	Edema due to cardiac disease
Neonatal edema	Orthopnea	Peripheral edema	Peripheral edema neonatal
Pulmonary congestion	Right ventricular dysfunction	Scan myocardial perfusion abnormal	Stroke volume decreased
Systolic dysfunction	Venous pressure increased	Venous pressure jugular abnormal	Venous pressure jugular increased
Ventricular assist device insertion	Ventricular dysfunction	Ventricular dyssynchrony	

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13.3 Financial Disclosure

Covered Clinical Study (Name and/or Number): JGDG

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>248</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S 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) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.4 Nonclinical Pharmacology/Toxicology

None

13.5 OCP Appendices (Technical documents supporting OCP recommendations)

PHARMACOMETRICS REVIEW

1 Population PK Analysis: Olaratumab

The applicant conducted population PK analysis using data from 4 studies: Studies JGDB, JGDE, JGDG, and JGDH.

Objectives: the population PK analysis has the following objectives:

- Characterize the PK of olaratumab in cancer patients
- Identify patient factors and laboratory parameters (for example, age, weight, hepatic and renal function) that may influence olaratumab disposition
- Characterize the effect of immunogenicity on the PK of olaratumab

Data: A total of 1501 olaratumab concentrations from 171 patients were included in the PK/PD analyses. Demographics at study entry for patients included in the population PK analysis are summarized in Table 67.

Table 67: Demographics at Study Entry for Patients Included in the Pharmacokinetic Analysis

	Age (year)				All 4 Studies
	JGDB	JGDE	JGDG	JGDH	
N	50	7	95	19	171
Arithmetic Mean	61.5	48.7	55.4	54.2	56.8
Arithmetic CV%	16	52	21	22	21
Minimum	43	24	22	33	22
Median	61.5	52	56.0	57.0	57
Maximum	82	63	77	74	82
Geometric Mean	60.7	46.8	53.9	52.8	55.4
Geometric CV%	16	34	25	24	24
Weight (kg)					
N	50	7	95	19	171
Arithmetic Mean	77.9	70.8	84.6	70.9	80.6
Arithmetic CV%	76	21	26	27.2	27
Minimum	49.1	53.4	49.9	37.3	37.3
Median	76.4	67.4	81.6	68.0	79.7
Maximum	151	89.7	148	115	151
Geometric Mean	75.4	69.5	81.9	68.4	77.8
Geometric CV%	26	22	26	28	27
Sex (M/F)					
N	29/21	3/4	41/54	11/8	84/87

Abbreviations: CV%= coefficient of variation; N = number of patients included in the pharmacokinetic analysis

Population PK Model Development

Base Model: The concentration-time data of olaratumab was best described with a two-compartment model. The model was parameterized with clearance (CL), central volume of distribution (V1), peripheral volume of distribution (V2), inter-compartmental clearance rate (Q). Exponential inter-subject variability was estimated with high precision for V1 and CL only.

Residual variability was best characterized by an additive/proportional error model. The base PK model estimates are summarized in Table 68.

Table 68: Pharmacokinetic Parameters in the Base Population Model

Parameter Description	Population Estimate (%SEE)	Inter-Patient Variability (%SEE)
Structural Model		
Clearance, CL (L/h)	0.0241 (4.02)	38.2% (15.7)
Central Volume of Distribution, V ₁ (L)	4.19 (4.32)	22.2% (18.8)
Peripheral Volume of Distribution, V ₂ (L)	3.58 (20.1)	-
Inter-compartmental clearance, Q (L/h)	0.0316 (25.6)	-
Residual Error (proportional)		
Additive (µg/mL)	9.78 (56.2)	
Proportional	22.6% (24.8)	

Abbreviation: SEE = standard error of the estimate.

Full Model

After establishment of the base model, the effects of patient factors were assessed for their influence on the disposition of olaratumab. Patient factors examined include age, gender race, body weight, body mass index, calculated creatinine clearance, ALT, AST, cancer indication, tumor size, etc. Forward selection of significant covariates and backward elimination of insignificant covariates were conducted to build the final model. After covariate selection, only patient body weight on CL and V₁, and tumor size on CL were retained in the final model. The parameter estimates of the final model were summarized below in Table 69. The model goodness-of-fit plots and VPC plots are shown in Figure 20 and Figure 21, respectively.

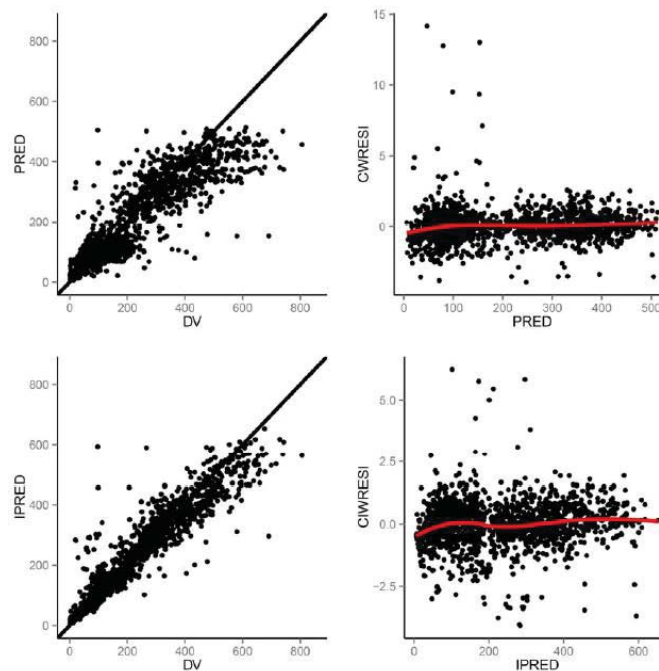
Table 69: Bootstrap Parameter Estimates for the Final Population Model

Parameter Description	Mean Parameter Estimate (95% CI)	Inter-Patient Variability (95% CI)
Structural Model		
CL (L/h)	0.0233 (0.0215 – 0.0253)	32.8% (27.7 – 38.0)
V ₁ (L)	4.15 (3.99 - 4.31)	15.4% (11.4 – 19.1)
V ₂ (L)	3.66 (2.69 – 4.90)	
Q (L/h)	0.0335 (0.0196 – 0.0524)	
Covariate Effects		
WTE _{CL} ^a	0.433 (0.216 – 0.654)	
WTE _{V1} ^b	0.611 (0.476 – 0.760)	
TUMR _{CL} ^a	0.00159 (0.000817 – 0.00252)	
Residual Error		
Additive (µg/mL)	11.4 (3.56 – 31.5)	
Proportional	22.2 (16.5– 27.2)	

Abbreviations: CI = confidence interval; CL = systemic clearance; Q = inter-compartmental clearance rate; TUMRCL = tumor size effect on clearance; V₁ = central volume of distribution; V₂ = peripheral volume of distribution; WTE_{CL} = body weight effect on clearance; WTE_{V1} = body weight effect on central volume of distribution.

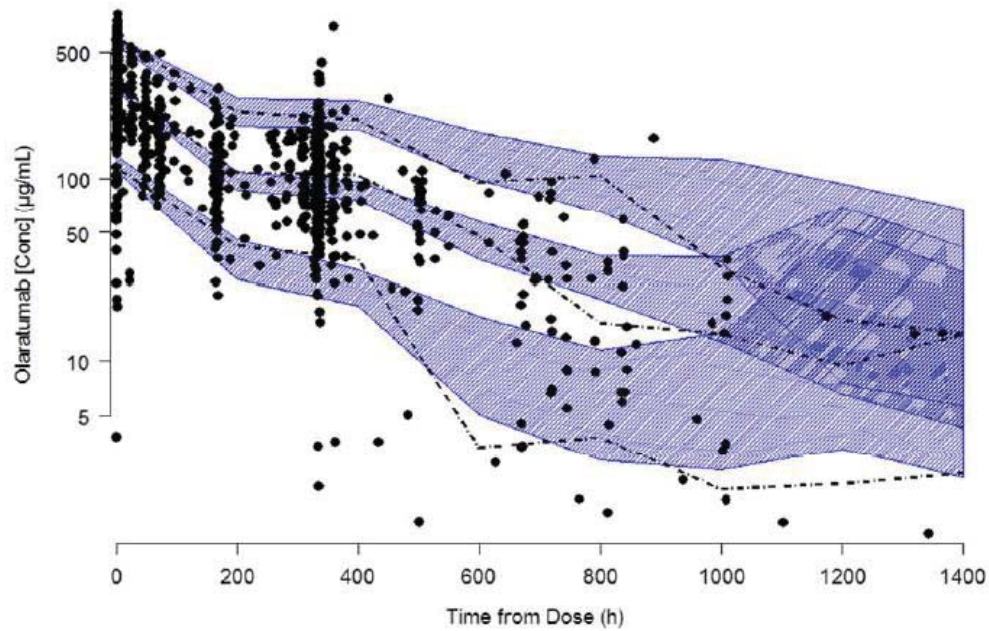
Source: Table 8.5 on page 40 of applicant’s population PK report

Figure 20: Goodness-of-fit Plot for the Olaratumab Final Model



Source: Figure ATT.9.2 on page 124 of applicant’s population PK report

Figure 21: Visual Predictive Check of the Final Olaratumab Population Pharmacokinetic Model



Source: Figure 8.4 on page 41 of applicant's population PK report

2 Exposure-Response Relationship for Efficacy in Study JGDG

Overall Survival Model:

Overall Survival (OS) in study JGDG was best described by a time-to-event model. The effect of olaratumab serum exposure on OS was explored using 2 PK endpoints: the trough serum level at the end of the first cycle of treatment (C_{min1}) and the average serum concentration throughout the patients' treatment duration (C_{avg}). For both PK endpoints, the effect of olaratumab on OS was best accounted for by an inhibitory E_{max} drug effect model with Hill coefficient on the hazard function. The full model can be described by the following equation. Parameter estimates for the overall survival model is shown in Table 70. Predicted overall-survival in study JGDG is shown in Figure 22. Predicted hazard ratio vs. olaratumab C_{min1} and C_{avg} is shown above (Figure 12).

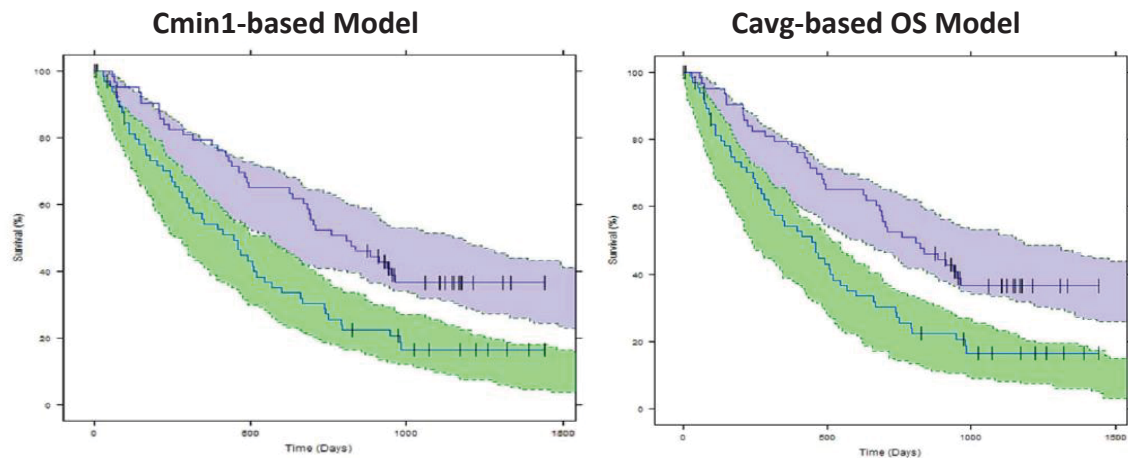
$$\frac{dHaz}{dt} = BASE\_HAZ \cdot \left(1 - \frac{E_{MAX} \cdot C^{Hill}}{EC_{50}^{Hill} + C^{Hill}} \right) \cdot (1 + EGRP_{BASE}) \cdot (1 + PRVTRT_{BASE})$$

Table 70: Parameter Estimates for the Overall Survival Model

Parameter Description	Population Estimate (%SEE)	
	Model Using C_{min1} as PK Endpoint	Model Using C_{avg} as PK Endpoint
Baseline Hazard		
$Base_{Hazard}$	0.00206 (0.00158 – 0.00280)	0.00204 (0.00156 – 0.00277)
Olaratumab Effect		
E_{MAX}	0.771 (0.625 – 0.884)	0.761 (0.607 – 0.876)
$EC_{min1\ 50}$ ($\mu\text{g/mL}$)	65.9 (50.9 – 80.3)	
$EC_{avg\ 50}$ ($\mu\text{g/mL}$)		135 (115 – 163)
Hill	8 (fixed)	8 (fixed)
Covariate Effects		
$EGRP_{Base}$	0.925 (0.273 – 1.83)	0.857 (0.220 – 1.72)
$PRVTRT_{Base}$	-0.57 (-0.740 – 0.345)	-0.528 (-0.706 – 0.282)

Abbreviations: C_{avg} = average concentration over patient’s entire treatment; C_{min1} = olaratumab trough serum concentration at the end of Cycle 1; $EC_{avg\ 50}$ = olaratumab C_{avg} yielding a 50% decrease in the baseline hazard; $EC_{min1\ 50}$ = olaratumab C_{min1} yielding a 50% decrease in the baseline hazard; E_{MAX} = maximum effect; Hill = Hill coefficient; $EGRP_{Base}$ = covariate effect of ECOG status on the Base hazard; $PRVTRT_{Base}$ = covariate effect of the number of prior treatment on the base hazard; SEE = standard error of the estimate.

Figure 22: Observed vs. Predicted Overall Survival in Study JGDG



Source: adapted from Figure 8.13 on page 58 of applicant’s population PK report

Progression-Free Survival Model:

Similar to the OS Model, PFS in study JGDG was best described by a time-to-event model with a simple exponential hazard function. The effect of olaratumab on PFS were also explored using C_{min1} and C_{avg} and best captured for both endpoints by an inhibitory E_{max} drug effect model with Hill coefficient on the hazard function.

The final PFS model can be described by the following equation:

$$\frac{dHaz}{dt} = BASE\_HAZ \cdot \left(1 - \frac{E_{MAX} \cdot C^{Hill}}{EC50^{Hill} + C^{Hill}} \right)$$

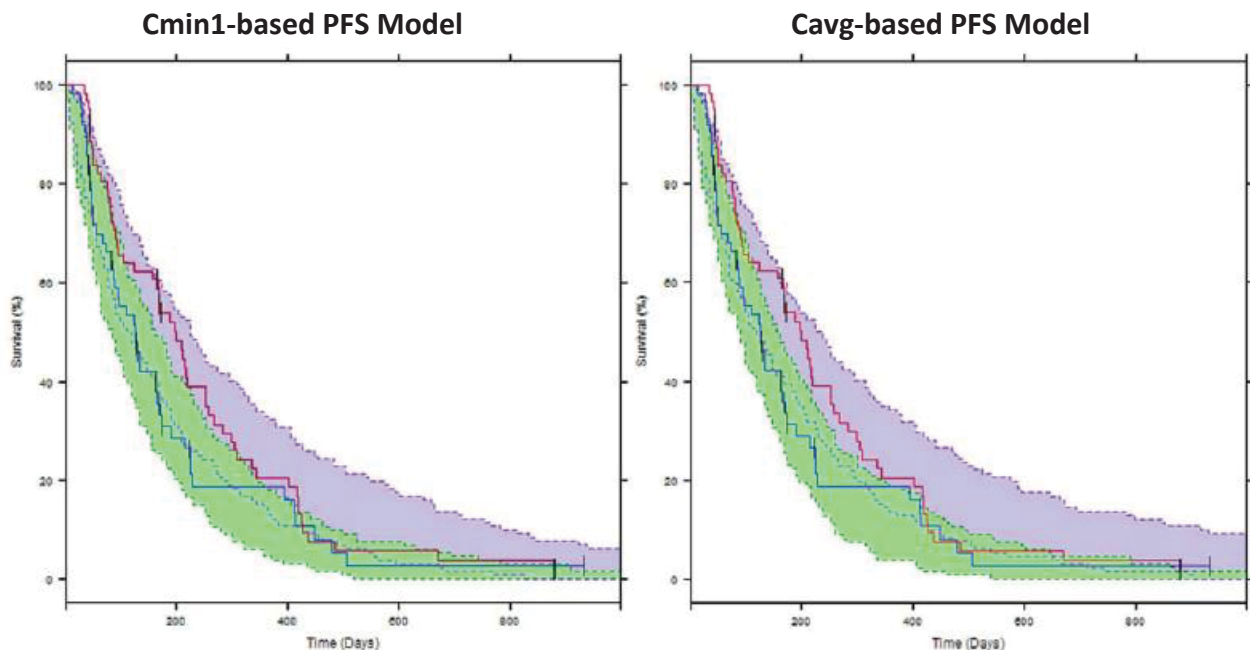
The parameter estimates for both PFS models are summarized in Table 71. Predicted PFS survival in study JGDG is shown in Figure 23.

Table 71: Parameter Estimates for the Progression Free Survival Model

Parameter Description	Population Estimate (%SEE)	
	Model Using C _{min1} as PK Endpoint	Model Using C _{avg} as PK Endpoint
Baseline Hazard		
Base _{Hazard}	0.00607 (0.00473 – 0.00786)	0.00619 (0.00476 – 0.00805)
Olaratumab Effect		
E _{MAX}	0.567 (0.363 – 0.723)	0.617 (0.435 – 0.770)
EC _{min1} 50 (µg/mL)	82.3 (69.3 – 95.4)	
EC _{avg} 50 (µg/mL)		182 (149 – 241)
Hill	8 (fixed)	8 (fixed)

Abbreviations: C_{avg} = average concentration over patient’s entire treatment; C_{min1} = olaratumab trough serum concentration at the end of Cycle 1; EC_{avg}50 = olaratumab C_{avg} yielding a 50% decrease in the baseline hazard; EC_{min1}50 = olaratumab C_{min1} yielding a 50% decrease in the baseline hazard; E_{MAX} = maximum effect; Hill = Hill coefficient; SEE = standard error of the estimate.

Figure 23: Observed vs. Predicted Progression-free Survival in Study JGDG



Source: Adapted from Figure 8.15 on page 62 of applicant’s population PK report

The applicant's final population PK model for olaratumab is acceptable. The model adequately characterized the PK profile of olaratumab after 15 mg/kg as indicated in the goodness-of-fit plot and the VPC plot. The inter-individual variability expressed as CV% was modest for clearance (33.3%) and the central volume compartment (15.6%) suggesting that key PK parameters were reasonably estimated from available data. The survival models that describe the relationship between olaratumab and OS and PFS are also acceptable. However, due to the limited sample size in Trial JGDG, these relationships will need further verification when more PK and efficacy data are available from the ongoing Trial JGDJ.

14 Division Director (DHOT)

John K.
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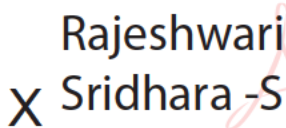
15 Division Director (OCP)

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16 Division Director (OB)

This application is based on an adequate, well-controlled and well-conducted randomized clinical trial. While the trial was initiated as a proof-of-concept trial with less restrictive operating characteristics and limited sample size, the observed data demonstrated a statistically significant, substantial improvement in overall survival. The smaller sample size resulted in wide confidence intervals around the estimates of the treatment effect as measured by hazard ratios for both overall survival and progression-free survival. Despite the wide confidence interval, the overall survival result was statistically significant with the upper confidence limit (0.71) of the hazard ratio well below 1. There was one unplanned interim analysis for overall survival and the level of significance was adjusted to account for this analysis. There were no apparent or detectable deficiencies in the conduct of the trial and no unplanned analyses of the data that would potentially bias the outcome of the clinical trial. A heterogeneous group of patients with multiple sub-types of sarcoma (Table 14) were enrolled in the clinical trial. Due to under representation of several sub-types with limited number of patients in the trial there remains uncertainty regarding the generalizability of the observed results to all the sub-types.

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17 Division Director (Clinical)

I concur with the review team's and consultants' recommendation that the BLA for olaratumab should be approved under the provisions of 21 CFR 601.41, due to the uncertainty of the observed effect on survival. My recommendation is based on the totality of the evidence, including treatment effects on secondary endpoints, safety issues, and the size and quality of the trial. The data supporting approval consist of the results of a single, small, randomized, multicenter clinical trial demonstrating a statistically significant treatment effect on the primary endpoint, progression-free survival at the pre-specified level of significance (0.2, two-sided); a highly statistically significant effect on overall survival that is clinically meaningful but uncertain in magnitude given large confidence intervals around the observed estimate; and incremental risks from the addition of olaratumab to doxorubicin, which do not outweigh the benefits of an improvement in overall survival. I note that the treatment effects on progression-free survival and overall response rate were not clinically meaningful and that the robustness of the effect on progression-free survival was influenced by the observer (investigator vs. independent review) and statistical test method (e.g., stratified vs. unstratified log-rank vs. re-randomization) employed. Additional limitations of the application, which require caution in interpretation of the results, are reliance on a single trial; the small sample size of the trial in which treatment effects may be overestimated; and enrollment of a heterogeneous patient population based on sarcoma subtype and histologic grade, in which balance for all known and unknown prognostic factors through randomization is particularly challenging given the small sample size.

As a condition of accelerated approval, clinical trials will be required to further verify and describe the clinical benefit of olaratumab by obtaining a more precise estimate of the treatment effect on survival.

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18 Office Director (or designated signatory authority)

Agree with regulatory action of Accelerated Approval. Please see prior reviews for discussion of risk-benefit and rationale for approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAMY E KIM
10/19/2016

RICHARD PAZDUR
10/19/2016