Protocol I5B-MC-JGDJ

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Doxorubicin plus Olaratumab versus Doxorubicin plus Placebo in Patients with Advanced or Metastatic Soft Tissue Sarcoma

NCT02451943

Approval Date: 29-Jan-2015

1. Protocol I5B-MC-JGDJ

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Doxorubicin plus Olaratumab versus Doxorubicin plus Placebo in Patients with Advanced or Metastatic Soft Tissue Sarcoma

Olaratumab (LY3012207)

I5B-MC-JGDJ is a global, multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial that will compare the safety and efficacy in patients with advanced or metastatic STS after treatment with doxorubicin (75 mg/m^2 on Day 1) plus olaratumab (15 mg/kg on Days 1 and 8) versus doxorubicin (75 mg/m^2 on Day 1) plus placebo (on Days 1 and 8) in a 21-day cycle. Patients will receive combination treatment for 8 cycles, followed by monotherapy olaratumab or placebo until evidence of progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria are met.

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Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 29-Jan-2015 GMT

2. Synopsis

Study Rationale

This Phase 3 study is a multicenter, randomized, double-blind study in which patients with metastatic or locally advanced soft tissue sarcoma (STS) who are not amenable to treatment with surgery or radiotherapy with curative intent will be treated with doxorubicin plus olaratumab versus doxorubicin plus placebo intravenously for 8 cycles. Patients without disease progression will be allowed to continue olaratumab or placebo monotherapy for Cycles >8.

Clinical Protocol Synopsis: Study I5B-MC-JGDJ

<table>
<tr><td colspan="2">Name of Investigational Product: Olaratumab (LY3012207)</td></tr>
<tr><td colspan="2">Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Doxorubicin plus Olaratumab versus Doxorubicin plus Placebo in Patients with Advanced or Metastatic Soft Tissue Sarcoma</td></tr>
<tr><td>Number of Planned Patients:
Entered/Screened: Approximately 500
Enrolled/Randomized: Approximately 460
Completed (number of patients who will complete the overall survival [OS] endpoint): Approximately 322</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="2">Length of Study: Approximately 48 months
Planned first patient visit: June 2015
Planned last patient visit (excluding the continued access period): October 2019
Planned interim analysis: 37% (at least 120 OS events) and 60% (at least 194 OS events)</td></tr>
<tr><td colspan="2">Objectives: The primary objective is to compare doxorubicin plus olaratumab versus doxorubicin plus placebo with respect to OS in patients with advanced or metastatic soft tissue sarcoma (STS) which is not amenable to treatment with surgery or radiotherapy with curative intent.

The secondary objectives of the study are to compare doxorubicin plus olaratumab versus doxorubicin plus placebo with respect to:
• Progression-free survival (PFS)
• Objective response rate (ORR) (complete response [CR] + partial response [PR])
• Disease control rate (DCR; CR + PR + stable disease [SD])
• Duration of response (DoR)
• Duration of disease control
• Patient-reported outcomes (PROs): Pain, Health-related Quality of Life (HRQoL), and health status
• Safety and tolerability
• Pharmacokinetics (PK) and immunogenicity

Additional prespecified objectives include, but are not limited to:
• Assessment of the association between biomarkers and clinical outcomes
• Assessment of the association between clinical variables, such as histological subtypes, and clinical outcomes</td></tr>
<tr><td colspan="2">Study Design: Study I5B-MC-JGDJ is a global, multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial that will compare the efficacy and safety in patients with advanced or metastatic STS treated with doxorubicin (75 mg/m^2 on Day 1) plus olaratumab (15 mg/kg on Days 1 and 8) versus doxorubicin (75 mg/m^2 on Day 1) plus placebo (on Days 1 and 8) in a 21-day cycle. Eligible patients will be randomized 1:1 into the 2 treatment options and stratified as follows:
• Number of prior systemic therapies for advanced/metastatic disease (0 versus ≥1)
• Histological tumor type (leiomyosarcoma versus liposarcoma versus other STS type)
• ECOG PS (0 versus 1)
• Region (North America versus Europe versus Rest of World [ROW])

Patients will receive combination treatment for 8 cycles followed by monotherapy olaratumab or placebo until evidence of progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria are met. No crossover will be permitted.</td></tr>
</table>

Diagnosis and Main Criteria for Inclusion and Exclusions: Patients at least 18 years of age, ECOG PS 0 to 1, anthracycline naïve, with histologically confirmed, advanced or metastatic STS, and not amenable to treatment with surgical resection or radiotherapy with curative intent. Patients with gastrointestinal stromal tumor (GIST) or Kaposi's sarcoma will be excluded.

Test Product, Dosage, and Mode of Administration: Olaratumab: injection for intravenous (IV) use, supplied in single-use 500 mg/50 mL vials containing 10 mg/mL of product in histidine buffer, administered to patients as an IV infusion at 15 mg/kg on Days 1 and 8. Cycles are 21 days in length.

Reference Therapy, Dose, and Mode of Administration: Placebo: injection for IV use, supplied in single-use vials, administered to patients as an IV infusion on Days 1 and 8. Doxorubicin: commercial formulations will be used and administered intravenously. Doxorubicin (75 mg/m^2) is to be administered on Day 1 of each 21-day cycle, for 8 cycles. Dexrazoxane: Commercially available dexrazoxane may be administered at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion, prior to each doxorubicin infusion for the prevention of cardiotoxicity and its use is recommended in patients receiving 5 or more cycles of doxorubicin. Dexrazoxane should be administered after completion of the olaratumab/placebo infusion, prior to administration of doxorubicin. Doxorubicin should be administered within 30 minutes of receiving dexrazoxane.

Planned Duration of Treatment: Treatment continues until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met. Doxorubicin plus olaratumab/placebo will be administered for 8 cycles, or until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met. Patients who discontinue doxorubicin due to unacceptable toxicity prior to the completion of the planned 8 cycles, may continue receiving single-agent olaratumab/placebo until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met. Patients who complete 8 cycles of combination treatment will continue to receive olaratumab/placebo monotherapy at the same dose and schedule until there is documentation of disease progression, death, intolerable toxicity, or other discontinuation criteria are met.

Short-term follow-up (postdiscontinuation): 30 days (±7 days)

Long-term follow-up (postdiscontinuation): every 6 weeks [±7 days] until PD, thereafter every 2 months [±7 days] for the first 2 years, then every 6 months [±14 days] until the patient's death or overall study completion

Continued access: After study completion, patients on study treatment who continue to experience clinical benefit and no undue risks, in the opinion of the investigator, may continue to receive study treatment until one of the criteria for discontinuation is met. A continued access follow-up visit will occur 30 days (±7 days) after discontinuation.

Criteria for Evaluation:
Efficacy: Overall survival (time from randomization to death) is the primary per-patient measure for efficacy.

Radiographic assessments will be performed according to Response Evaluation Criteria in Solid Tumors (Response Evaluation Criteria in Solid Tumors [RECIST], Version 1.1) criteria, will be performed every 6 weeks (±7 days) until radiographic documentation of PD.

The following additional efficacy measures will be determined for each patient, with planned statistical analyses specified in Section 12 and in the Statistical Analysis Plan (a separate document). Specific definitions of each of these measures (such as defining events and censoring for each time to event endpoint) will be provided in the Statistical Analysis Plan.

- Progression-free survival (PFS)
- Objective Response Rate (ORR)
- Disease Control Rate (DCR)
- Duration of response (DoR)
- Duration of disease control
- Time to any progression (death without progression censored)
- Time to any new metastases (censoring for death and for other type of PD)
- New-metastases-free survival (nMFS)
- Time to any progression based solely on increased sum of target lesions
- Time to first worsening of pain and HRQoL

- Time to first worsening of ECOG performance status

Safety: Safety will be evaluated based on reported adverse events (AEs), physical examinations, vital signs, laboratory tests, electrocardiograms (ECGs), and results from echocardiograms (ECHOs) or multigated acquisition (MUGA) scans. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) and graded using the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0. Clinical laboratory toxicity will be graded using NCI-CTCAE criteria, Version 4.0.

Patient-Reported Outcomes (PROs): Pain will be assessed with the Brief Pain Inventory Short Form Modified [mBPI-sf], HRQoL will be assessed with The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 version 3.0 [EORTC QLQ-C30] and health state will be assessed with the EuroQol 5-Dimension 5-Level [EQ-5D-5L]. Patients will complete the instruments on Day 1 of every cycle and at the 30-day short-term follow-up visit. A full due diligence will be taken to collect PRO measures during long-term follow-up (every 6 weeks [±7 days] until PD, thereafter every 2 months [±7 days] for the first 2 years, then every 6 months [±14 days] until the patient's death or overall study completion).

Immunogenicity: Blood samples will be collected to determine olaratumab antibodies in serum at baseline, during the study, and in the event of an olaratumab infusion-related reaction (IRR) serum will be collected as soon as possible after the onset, at the resolution, and 30 days after the IRR.

Pharmacokinetics: Blood samples will be collected to assess the serum concentrations of olaratumab and the plasma concentration of doxorubicin. Serum concentrations of olaratumab will be assayed using a validated enzyme-linked immunosorbent assay (ELISA) method. Doxorubicin concentrations in plasma will be analyzed using a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay.

Biomarkers: Samples will be collected and analyses will be performed on biomarkers relevant to pathways associated with STS, the mechanism of action of olaratumab or doxorubicin, and/or cancer-related conditions, and may also be used for related research methods. The evaluation of the samples may involve analysis of DNA, RNA, and/or proteins.

Statistical Methods:

The primary objective of this study is to compare olaratumab plus doxorubicin (experimental arm) versus placebo plus doxorubicin (control arm) in terms of OS in patients with advanced, metastatic STS. The study will screen approximately 500 patients to enroll 460 patients in 1:1 randomization (230 patients in the experimental arm and 230 patients in the control arm). The intent-to-treat sample size of 460 was selected assuming the final analysis of OS will occur when at least 322 OS events have been observed; therefore, the sample size of 460 ensures a maximum of 30% censoring at the final OS analysis.

The final total of 322 OS events (deaths) is an appropriate minimum for the final analysis of OS, providing 80% statistical power for a two-sided log-rank test at a 0.05 significance level (assuming the true OS HR is 0.73). An OS HR of 0.73 corresponds approximately to an increased median survival from 15 months (estimated from published clinical data in various types of patients with advanced or metastatic STS as well as based on the JGDG trial results) in doxorubicin alone to 20.5 months for olaratumab combined with doxorubicin.

Two interim efficacy analyses for OS are planned after 120 (37% of the targeted final number of 322 OS events) and 194 OS events (60% of the final OS events) have been observed. An O'Brien-Fleming alpha spending function will be used to determine the efficacy boundary. Approximate O'Brien-Fleming alpha levels and OS HR boundaries for the two interims and the final analysis are as follows (using EAST® 6.3):

- First interim: 120 events, alpha = 0.0005, HR < 0.525
- Second interim: 194 events, alpha = 0.0075, HR < 0.680
- Final: 322 events, alpha = 0.0476, HR < 0.801

An overall two-sided alpha level of 0.05 is maintained across interim and final analyses of OS through the use of this O'Brien-Fleming method. In addition, a scheme (e.g. Glimm et al. 2010) for maintaining a 0.05 study-wise alpha error rate across OS and the following secondary endpoints will be pre-specified in the Statistical Analysis Plan:

- PFS
- ORR
- DCR

- Duration of response
- Duration of disease control

Time to event analyses at both the interim and final analysis time points will be based on the stratified log-rank test, stratified by randomization strata (case report form [CRF] data). The testing boundaries (approximate values can be found in Section 12.1) will be determined using an O'Brien-Fleming alpha spending function. OS survival curves, the median with 95% CI and survival rates at various time points for each treatment group will be estimated using Kaplan-Meier method (Kaplan and Meier 1958). The HR will be estimated using a stratified Cox regression model, stratified by randomization strata (CRF data). All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint.

The interim analyses will be performed by an independent Data Monitoring Committee (iDMC). The iDMC Charter (a separate document) will provide detailed guidance for the conduct of the interim analyses and describe the process for recommending changes to the trial in the event that interim OS results are statistically significant. In the event of a statistically significant interim result for OS, investigative sites will be informed that the study has met its primary objective and thus confirmed the efficacy of olaratumab in combination with doxorubicin. It is recommended that any patients currently receiving study treatment at the time of a positive interim result should continue his/her study treatment as originally planned. This recommendation is appropriate given that any positive interim result will not support the use of olaratumab in patients who have (currently or previously) received treatment with single-agent doxorubicin.

Safety: Safety analyses will be performed on the safety population (that is, all randomized patients who received at least 1 dose, including a partial dose, of any study treatment, and will include summaries of incidences of treatment-emergent adverse events (TEAEs) by maximum CTCAE grade that occurred during the study treatment period or within approximately 30 days after the decision is made to discontinue of study treatment. Additionally, the following (but not limited to) safety-related outcomes will be summarized: study treatment discontinuation due to TEAEs, deaths during the study treatment period or within 30 days after the decision is made to discontinue of study treatment, treatment-emergent serious adverse events (SAEs) during the study treatment period or within 30 days after the decision is made to discontinue study treatment, hospitalizations, and transfusions during the study treatment period or within 30 days after the decision is made to discontinue study treatment.

Adverse events (AEs), including TEAEs, will be listed and summarized in frequency tables using MedDRA. Severity of AEs will be classified using CTCAE version 4.0. Other safety data, such as laboratory tests, echocardiography, and vital signs, will be listed and summarized, if appropriate.

Patient-Reported Outcomes (PROs): For each instrument (mBPI-sf, EORTC QLQ-C30, and EQ-5D-5L), percentage compliance will be calculated as the number of completed assessments divided by the number of expected assessments (that is, patients still on study and alive). Data will be separately summarized by treatment and time point using descriptive statistics. Analyses of time to first worsening of pain as well as HRQoL domains and sub-domains will be conducted.

Immunogenicity: Incidence of anti-olaratumab antibodies will be tabulated. Correlation to olaratumab drug level, activity, and safety will be assessed, as appropriate.

Pharmacokinetics: The PK parameters of olaratumab will be computed by nonlinear mixed effect modelling using [redacted] PK data collected for doxorubicin will be analyzed using descriptive methods.

Biomarkers: Analyses will be performed on biomarkers relevant to pathways associated with STS, the mechanism of action of olaratumab or doxorubicin, and/or cancer-related conditions. Assay results will be summarized and correlated with clinical outcomes.

3. Table of Contents

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Doxorubicin plus olaratumab versus Doxorubicin plus Placebo in Patients with Advanced or Metastatic Soft Tissue Sarcoma

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4. Abbreviations and Definitions

Term	Definition
AC	Assessment Committee
AE	adverse event Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
blinding	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BSA	body surface area
BSC	best supportive care
CBR	clinical benefit rate
CI	confidence interval
CNS	central nervous system
collection database	A computer database where clinical trial data are entered and validated.

companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
continued access period	The period between study completion and end of trial during which patients on olaratumab who continue to experience clinical benefit and no undue risks may continue to receive olaratumab until one of the criteria for discontinuation is met.
CR	complete response
CrCl	creatinine clearance
CRF/eCRF	case report form/electronic case report form Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CSFs	colony-stimulating factors
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTS	change in tumor size A measure of tumor dynamics from which tumor response is derived. Tumor size is the sum of tumor measurements across all target tumors at a given evaluation (RECIST criteria).
DCR	disease control rate
DoR	duration of response
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.

enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
EORTC QLQ-C30	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ 5D-5L	EuroQol 5-Dimension 5-Level
ERB/IRB	ethical review board/institutional review board A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
ESAs	erythropoiesis-stimulating agents
evaluable patients	Patients must have received at least 1 dose of study therapy and have either started treatment in Cycle 3 or discontinued all study treatment prior to Cycle 3 due to any reasons. This population applies only to the safety interim analyses.
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FSH	follicle-stimulating hormone
GCP	good clinical practice
GIST	gastrointestinal stromal tumors
GnRH	gonadotropin-releasing hormone
H_0	null hypothesis
H_a	alternative hypothesis
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IG/IK	immunogenicity

IgG1	immunoglobulin G, subclass 1
IND	Investigational New Drug application
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	International Normalized Ratio
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient substance or placebo being tested, or used as a reference, in a clinical trial. Investigational product (IP) includes a product with a marketing authorization when: 1. used or assembled (formulated or packaged) in a way different from the authorized form, 2. used for an unauthorized indication, or 3. used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intention-to-treat The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive web-response system
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
LLN	Lower Level of Normal
mBPI-SF	Brief Pain Inventory Short Form Modified

MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	progressive disease
PDA	personal data assistant
PDGF	platelet-derived growth factor
PDGFRα	platelet-derived growth factor receptor alpha
PDGFRβ	platelet-derived growth factor receptor beta
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PPS	per protocol set The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	Preferred Term or prothrombin time
PTT	partial thromboplastin time
QTc	corrected QT interval
randomize	the process of assigning patients to an experimental group on a random basis
RECIST	Response Evaluation Criteria in Solid Tumors

reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
ROW	rest of the world
SAE	serious adverse event
SAP	Statistical Analysis Plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SOC	System Organ Class
STS	soft tissue sarcoma
Study completion	This study will be considered complete after the final analysis/evaluation of overall survival is performed.
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TPO	third-party organization
TTP	time to progression
ULN	upper limits of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR2	vascular endothelial growth factor receptor-2

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Doxorubicin plus olaratumab versus doxorubicin plus placebo in Patients with Advanced or Metastatic Soft Tissue Sarcoma

5. Introduction

5.1. Soft Tissue Sarcoma

Soft tissue sarcoma (STS) is a heterogeneous group of tumors that arise mainly from embryonic mesoderm, with some neuroectodermal contribution and differentiation to non-epithelial extraskeletal tissue including muscle, fat, and fibrous tissue (D'Angelo et al. 2014). There are approximately 50 tumor subtypes of STS (Sharma et al. 2013) and they can be located anywhere in the body. This is a rare tumor group that comprises approximately 1% of adult cancers with an annual incidence of the disease in the UK and USA, respectively, of 3,300 (ESMO 2014) and 10,000 (ACS 2014). STS is best treated by multidisciplinary teams specialized in the management of these tumors (Linch et al. 2014). When the disease is localized, it is usually treated with curative intent using surgical resection with or without radiotherapy and chemotherapy. Unfortunately, STS recurs frequently as locally inoperable or metastatic disease, at which point systemic therapy plays a prominent role in the multidisciplinary management of this tumor.

Cytotoxic chemotherapy has been the mainstay therapy for treating advanced stage STS, providing overall response rates of about 25% in the first-line setting (Linch et al. 2014). Despite the use of chemotherapy, advanced-stage STS is almost invariably fatal and there is a clear need to find novel and effective therapies.

For many decades, anthracycline based chemotherapy has been the standard first-line option for patients with metastatic soft tissue sarcoma. A recent Phase 3 trial performed by the European Organization for the Research and Treatment of Cancer (EORTC) randomized soft tissue sarcoma patients to receive doxorubicin with or without ifosfamide (Judson et al. 2014). Patients treated with the combination achieved a significantly higher response rate and progression-free survival compared to those randomized to single agent doxorubicin. However, there was no significant difference in overall survival between the two treatment arms. In view of these findings, single agent doxorubicin is considered the standard treatment option for many patients with metastatic soft tissue sarcoma (NCCN 2011; ESMO 2012; Schöffski et al. 2014). Doxorubicin and ifosfamide is often reserved for patients with symptomatic disease or those in which down staging could result in surgical resection.

A number of randomized Phase 3 trials have demonstrated that dexrazoxane significantly reduces the risk of anthracycline-associated cardiotoxicity, with no effect on progression-free and overall survival (Jones 2008).

5.2. Olaratumab Background

Olaratumab is a recombinant human immunoglobulin G subclass 1 (IgG1)-type monoclonal antibody that binds to platelet-derived growth factor receptor (PDGFR)α. This antibody possesses high affinity binding for PDGFRα and blocks platelet-derived growth factor (PDGF)-AA, -BB, and -CC from binding to the receptor. In addition to blocking ligand-induced cell mitogenesis and receptor autophosphorylation, olaratumab inhibits ligand-induced phosphorylation of the downstream signaling molecules Akt and mitogen-activated protein kinase (MAPK).

PDGF/PDGFRα signaling plays a role in both organ and tissue development, as well as in pathogenesis of nonmalignant diseases (for example, pulmonary fibrosis) and malignant cancers. Many cancer types have been shown to consistently express PDGFRα on tumor tissues, including osteosarcoma, chondrosarcoma, prostate cancer, breast cancer, ovarian cancer, and others. In malignant disease, the PDGF/PDGFRα axis is effective in promoting tumor growth and proliferation through both autocrine and paracrine mechanisms. PDGFRα is expressed on stromal cells, as well as the cancer cells themselves, within certain tumors. Furthermore, studies have shown that PDGF/PDGFRα signaling affects tumor vasculature through paracrine mediation of vascular endothelial growth factor (VEGF) production (Shah et al. 2010).

5.3. Study Rationale

Previously reported data support the molecule being advanced in human trials, including the Sponsor's Phase 1b/2 trial, titled 'A Phase 1b/2 Randomized Phase 2 Study Evaluating the Efficacy of Doxorubicin With or Without a Human Anti-PDGFRα Monoclonal Antibody (IMC-3G3) in the Treatment of Advanced Soft Tissue Sarcoma.' The experimental Arm A received olaratumab (15 mg/kg) on Day 1 and Day 8 plus doxorubicin (75 mg/m²) on Day 1 of each 21-day cycle for up to 8 cycles. The control Arm B received Doxorubicin (75 mg/m2) on Day 1 of each 21-day cycle for up to 8 cycles. The primary analysis of this trial (based on 103 PFS events observed as of the 15 August 2014 cutoff date) showed a statistically significant improvement in PFS over doxorubicin alone, with a stratified PFS HR of 0.67 (p=0.0615 relative to the protocol-defined two-sided significance level of alpha=0.1999]). The median PFS was 28.6 weeks (6.6 months) for the investigational arm and 18.0 weeks (4.1 months) for the control arm. At the time of the primary analysis, an interim analysis of OS (based on 83 events) showed an improvement (HR=0.44; p = 0.0005) with a median of 64.0 weeks (14.7 months) on the control arm compared to 108.7 weeks (25 months) for the combination. The following Grade ≥3 adverse events (AEs) occurred in ≥ 5% of the population: Arm A > Arm B, neutropenia (51.5% vs 33.8%), anemia (12.5% vs 7.7%), fatigue (9.4 vs 3.1%), and thrombocytopenia (9.4% vs 7.7 %); Arm A < Arm B, febrile neutropenia (12.5% vs 13.8%) and infections (6.3% vs 10.8%). There was no significant difference in post-therapy LVEF (Eli Lilly and Company 2014).

The proposed study is a Phase 3 trial of the efficacy and safety of olaratumab in combination with doxorubicin for the treatment of advanced or metastatic soft tissue sarcoma (STS) that is not amenable to treatment with surgical resection or radiotherapy with curative intent.

More information about the known and expected benefits, risks and reasonably anticipated adverse events (AEs) of olaratumab may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to olaratumab may be found in Section 7 (Development Core Safety Information) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

6. Objectives

6.1. Primary Objective

The primary objective is to compare doxorubicin plus olaratumab versus doxorubicin plus placebo with respect to overall survival (OS) in patients with advanced or metastatic soft tissue sarcoma (STS) which is not amenable to treatment with surgery or radiotherapy with curative intent.

6.2. Secondary Objectives

The secondary objectives of the study are to compare doxorubicin plus olaratumab versus doxorubicin plus placebo as follows:

- Progression-free survival (PFS)
- Objective response rate (ORR) (complete response [CR] + partial response [PR])
- Disease control rate (DCR) (CR + PR + stable disease [SD])
- Duration of response (DoR)
- Duration of disease control
- Patient-reported Outcomes (PROs): Pain, Health-related Quality of Life (HRQoL), and health status
- Safety and tolerability
- PK and immunogenicity

6.3. Additional Prespecified Objectives

- Assessment of the association between biomarkers and clinical outcomes
- Assessment of clinical variables, such as histological subtypes, and clinical outcomes

7. Study Population

Eligible patients will have a histological diagnosis of advanced or metastatic STS, not amenable to treatment with surgical resection or radiotherapy with curative intent.

All patients meeting the eligibility requirements will be considered for enrollment regardless of race, religion, or gender. The investigator or the Sponsor will not grant exceptions to eligibility criteria. Individuals who do not meet the criteria for participation in this study within the 21-day screening period (screen failure) may be re-screened. Note that repeating laboratory tests during the 21-day screening period does not constitute re-screening. Screening laboratory tests may not be repeated more than once in order to meet eligibility during the 21-day screening period. If a repeat screening laboratory value meets eligibility, it is recommended that the test is rechecked to confirm stability.

Patients may be considered for re-screening after discussion with the Lilly study physician or designee. Patients may be re-screened up to 1 time. The interval between re-screenings should be at least 28 days. Patients who will be re-screened must sign a new informed consent form (ICF) and will be assigned a new identification number.

Prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions) is not permitted.

7.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

[1] The patient signed an ICF and authorization for release of health information for research prior to any study-specific procedures being performed

[2] The patient is aged ≥ 18 years at study entry

[3] The patient has histologically confirmed diagnosis of locally advanced unresectable or metastatic disease not amenable to curative treatment with surgery or radiotherapy. Patients with Kaposi's sarcoma and gastrointestinal stromal tumors (GIST) will be excluded.

[4] The patient has measurable or nonmeasurable but evaluable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1, Eisenhauer et al. 2009; refer to Attachment 6). Tumors within a previously irradiated field will be designated as "nontarget" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiotherapy.

[5] The patient has a performance status 0-1 on the Eastern Cooperative Oncology Group (ECOG) scale (refer to Attachment 4)

[6] The patient has not received any previous treatment with anthracyclines

[7] The patient may have had any number of prior systemic cytotoxic therapies for advanced/metastatic disease.

[8] The patient has resolution of adverse events to ≤ Grade 1, by National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 criteria, of all clinically significant toxic effects of prior locoregional therapy, surgery, , or systemic anti-cancer therapy

[9] The patient has consented to provide adequate archived formalin-fixed paraffin embedded (FFPE) tumor tissue or be subject to a pre-treatment biopsy of primary or metastatic tumor tissue for research (if adequate archived tissue is unavailable) (refer to Section 10.4.2.3). Availability of an adequate tumor tissue sample is required for study eligibility.

[10] The patient has adequate hematologic, organ, coagulation, and cardiac function within 2 weeks (14 days) prior to randomization:

- Absolute neutrophil count (ANC) ≥1.5 x 10^9/L. G-CSF cannot be administered within 2 weeks (14 days) prior to randomization
- Platelet count ≥100 x 10^9/L
- Hemoglobin ≥8.0 g/dL. No transfusions are allowed within 2 weeks (14 days) prior to randomization.
- The creatinine clearance is ≥ 45 mL/min (refer to Attachment 5 for the Cockroft-Gault formula).
- Total bilirubin within normal limits (except for patients with Gilbert's Syndrome, who must have a total bilirubin <3 mg/dL)
- Alanine aminotransferase/aspartate aminotransferase (AST/ALT) ≤ 3.0 × ULN; if the liver has tumor involvement, AST and ALT ≤5.0 × ULN are acceptable
- The patient has an adequate coagulation function as defined by International Normalized Ratio (INR) ≤1.5 or prothrombin time (PT) ≤1.5 x ULN, and partial thromboplastin time (PTT/aPTT) ≤1.5 x ULN.

[11] The patient has left ventricular ejection fraction (LVEF) ≥50% assessed within 21 days prior to randomization

[12] Females of child-bearing potential must have a negative serum pregnancy test within 7 days prior to randomization

(a) Females not of child-bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause.

A "postmenopausal woman" is a woman meeting either of the following criteria:

- spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea that induced the amenorrhea (for example, oral contraceptives,

hormones, gonadotropin releasing hormone, antiestrogens, selective estrogen receptor modulators (SERMs), or chemotherapy

- spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone (FSH) level >40 mIU/mL

[13] Females of child-bearing potential and males and must agree to use highly effective contraceptive precautions during the trial and up to 3 months following the last dose of study drug. A highly effective method of birth control is defined as one that results in a low failure rate (that is, <1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUDs), sexual abstinence, or a vasectomized partner. For patients using a hormonal contraceptive method, information regarding the product under evaluation and its potential effect on the contraceptive should be addressed.

[14] The patient has, in the opinion of the investigator, a life expectancy of at least 3 months

7.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[15] The patient is diagnosed with GIST or Kaposi sarcoma

[16] The patient has active central nervous system (CNS) or leptomeningeal metastasis (brain metastasis) at the time of randomization. Patients with a history of a CNS metastasis previously treated with curative intent (for example, stereotactic radiation or surgery) that have not progressed on follow-up imaging, have been asymptomatic for at least 60 days and are not receiving systemic corticosteroids and or/anticonvulsants, are eligible. Patients with signs or symptoms of neurological compromise should have appropriate radiographic imaging performed before randomization to rule out brain metastasis.

[17] The patient has received prior treatment with doxorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones (for example, mitoxantrone).

[18] The patient had prior radiotherapy of the mediastinal/pericardial area or whole pelvis radiation.

[19] The patient has history of another primary cancer, with the exception of a) curatively treated non-melanomatous skin cancer, b) curatively treated cervical carcinoma in situ, c) other primary non-hematologic malignancies or solid tumor treated with curative intent, no known active disease and no treatment administered during the last 3 years prior to randomization

[20] The patient has electively planned or will require major surgery during the course of the study

[21] The patient has uncontrolled intercurrent illness including, but not limited to, an ongoing/active infection requiring parenteral antibiotics, symptomatic congestive heart failure (CHF), left ventricular dysfunction (LVEF < 50%), severe myocardial

insufficiency, cardiac arrhythmia, cardiomyopathy, or a psychiatric illness/social situation that would limit compliance with study requirements

[22] The patient has unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction within 6 months of randomization

[23] The patient has a resting heart rate of >100 bpm

[24] The patient has a QTc interval of >450 msec and >470 msec for males and females, respectively, on screening ECG

[25] Females who are pregnant or breastfeeding

[26] The patient has a known allergy to any of the treatment components including a history of allergic reactions attributed to compounds of chemical or biological composition similar to olaratumab

[27] The patient is enrolled in, or discontinued within 28 days of randomization from, another trial involving an investigational agent or use of non-approved drug or device, or concurrent enrollment in any other type of medical research judged scientifically or medically incompatible with this trial. Patients participating in surveys or observational studies are eligible to participate in this study.

[28] The patient has current hematologic malignancies

[29] The patient has an active fungal, bacterial, and/or known viral infection including human immunodeficiency virus (HIV) or viral (A, B, or C) hepatitis (screening is not required)

7.2.1. Rationale for Exclusion of Certain Study Candidates

The exclusion criteria have been carefully selected by the Sponsor to ensure their ethical and scientific acceptability, and to help establish specificity of the patient population for both efficacy and safety analyses.

7.3. Discontinuation

The reason for discontinuation and the date of discontinuation will be collected for all patients. All randomized patients who discontinue, regardless of whether or not they received study treatment, will have procedures performed as shown in the Study Schedule (Attachment 1).

Patients who are discontinued from the study treatment early will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

If a patient withdraws informed consent, he or she must not be contacted unless he or she has explicitly provided permission and consent. Lilly may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorization.

7.3.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the Lilly CRP and the investigator to determine whether the patient may continue in the study, with or without study treatment.

The patient may continue to receive study drugs if all of the following conditions are met:

- In the opinion of the investigator, the patient is receiving benefit
- The Lilly CRP or clinical research scientist (CRS) and the investigator determines that no effective alternative therapy exists
- The Lilly CRP/CRS and the investigator agree there is no safety concern meriting discontinuation of study drugs

The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without study treatment.

7.3.2. Discontinuation of Patients

In addition, patients will be discontinued from the study drug and/or from the study in the following circumstances:

- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- investigator/physician decision
    - the investigator/physician decides that the patient should be discontinued from the study or study drugs
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drugs occurs prior to introduction of the other agent
- patient decision
    - the patient requests to be discontinued from the study or study drug
- sponsor decision
    - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- evidence of progressive disease

- unacceptable toxicity
- significant noncompliance with study procedures and/or treatment

The discontinuation reason and date will be collected for all patients. The date of discontinuation (for any of the above reasons) from study treatment is to be reported on the case report form (CRF). Patients who discontinue will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

7.3.3. Patients who are Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow.

Site personnel, or an independent third party, will attempt to collect the vital status (that is, alive or dead) for all enrolled patients who are lost to follow-up, including enrolled patients who do not receive study treatment, within legal and ethical boundaries. Site personnel, or an independent third party, may search public sources for vital status information. If the patient's vital status is determined, the vital status will be documented and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

7.3.4. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) or institutional review board (IRB) of the study site judges discontinuation of study site participation necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7.3.5. Discontinuation of the Study

The study will be discontinued if Lilly judges discontinuation of the study necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

8. Investigational Plan

8.1. Summary of Study Design

Study I5B-MC-JGDJ is a global, multicenter, randomized, double-blind, parallel, placebo-controlled Phase 3 trial in patients with advanced or metastatic STS who is doxorubicin naïve but may have had any number of prior systemic cytotoxic and/or non-PDGF/PDGFR-directed therapies. Previous therapy must be completed ≥ 4 weeks (28 days) prior to randomization.

Eligible patients will be randomized 1:1 into 1 of 2 treatment options (olaratumab plus doxorubicin or placebo plus doxorubicin). Randomization will be stratified by:

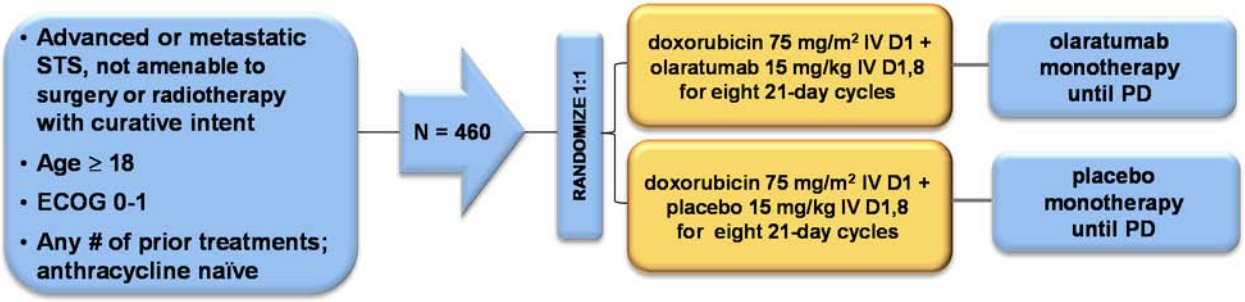
- Number of prior systemic therapies for advanced/metastatic disease (0 versus ≥1)
  NOTE: any neoadjuvant and adjuvant therapy administered for advanced/metastatic disease will not be considered as a prior line of therapy
- Histological tumor type (leiomyosarcoma versus liposarcoma versus other STS type)
- ECOG performance status (0 versus 1)
- Region (North America versus Europe versus Rest of World [ROW])

Patients assigned to the experimental arm will receive olaratumab 15mg/kg IV on Days 1 and 8 followed by doxorubicin 75 mg/m^2 IV on Day 1 of a 21-day cycle. Patients assigned to the control arm will receive placebo 15 mg/kg IV on Days 1 and 8 followed by doxorubicin 75 mg/m^2 IV on Day 1 of a 21-day cycle.

Patients will receive combination treatment for 8 cycles, followed by monotherapy olaratumab or placebo until evidence of progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria are met. No crossover will be permitted.

Use of dexrazoxane (in a 10:1 ratio versus doxorubicin dose) to mitigate cardiotoxicity during treatment with doxorubicin is allowed at the investigator's discretion and is recommended for all patients receiving 5 or more cycles of doxorubicin.

Figure JGDJ.1 illustrates the study design.



Abbreviations: D = day; ECOG PS = Eastern Cancer Oncology Group performance status; IV = intravenous, PD = progressive disease

Figure JGDJ.1. Illustration of study design.

Terms used to describe the periods during the study are defined below:

- **Baseline:** begins when the ICF is signed and ends at the first study treatment (or at discontinuation, if no treatment is given).
- **Study Period:** begins at the first study treatment and ends at study completion.
  - **Study Treatment Period:** begins at the first study treatment and ends when the patient and the investigator agree that the patient will no longer continue study treatment. The date of this agreement is to be reported on the case report form (CRF) as the Date of Discontinuation from study treatment.
  - **Post discontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.
    - ***Short-term follow-up*** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (±7 days). The short-term follow-up visit occurs at or near the end of the short-term follow-up period (±7 days).
    - ***Long-term follow-up*** begins the day after short-term follow-up is completed.
      - ***Follow-up for progression*** - Patients that discontinue study treatment for reasons other than progression will be follow every 6 weeks (±7 days) until PD.
      - ***Follow-up for survival*** - Patients will be followed every 2 months (±7 days) for the first 2 years, then every 6 months (±14 days) until the patient's death or overall study completion.
- **Continued Access Period:** begins after study completion and ends at the end of trial. During the continued access period, patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met. The continued access period includes continued access follow-up. Refer to Section 8.1.4 for more details.
  - Continued access follow-up: begins the day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days (±7 days). The continued access follow-up visit occurs at or near the end of the continued access follow-up period.

8.1.1. Baseline and Study Treatment Period Assessments

Baseline radiographic assessment of disease will be performed within 28 days prior to randomization; scans performed prior to the date of consent may be used provided they are within 28 days of Cycle 1 Day 1 (C1D1).

Imaging and tumor assessment will be performed every 6 weeks (±7 days), irrespective of treatment cycles. Imaging requirements include CT scan or magnetic resonance imaging (MRI) of chest, abdomen, and pelvis and other areas, as clinically indicated. It is recommended that CT imaging of the abdomen/pelvis be performed with IV contrast, whenever possible. If this is not feasible/advisable secondary to hypersensitivity or other conditions, then gadolinium-enhanced MRI is preferred. For patients with known serious allergic reactions to CT contrast material, a CT of the chest without contrast and contrast-enhanced MRI of the abdomen/pelvis are encouraged.

The patient's first treatment will be administered within 7 days following randomization. Patients in both arms will receive any necessary premedication if needed (see Section 9.1.1) prior to the infusion of study therapy at each treatment cycle.

A treatment cycle will be defined as 3 weeks (21 days ± 3 days). The start of study treatment will be considered C1D1.

Patients in the experimental **Arm A** will receive:

- Olaratumab on Day 1 and Day 8 of every 3-week cycle as an IV infusion over approximately 60 minutes, followed by a 1-hour observation period for the first 2 cycles. If there is no evidence of an IRR after the D1 and D8infusions of olaratumab in the first 2 cycles, no observation period is required for subsequent treatment cycles (in the event an IRR occurs thereafter, then the 1-hour observation should be reinstituted).
- Doxorubicin (after the olaratumab administration and 1-hour observation period, if instituted) on Day 1 of every 3-week cycle as an IV infusion over approximately 60 minutes for 8 cycles. Dexrazoxane may be administered at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion, within 30 minutes prior to each doxorubicin infusion for the prevention of cardiotoxicity. It is recommended that all patients receiving 5 or more cycles of doxorubicin receive dexrazoxane.

Patients in the control **Arm B** will receive:

- Placebo on Day 1 and Day 8 of every 3-week cycle as an IV infusion over approximately 60 minutes, followed by a 1-hour observation period for the first 2 cycles. If there is no evidence of an IRR after the D1 and D8 infusions of olaratumab during the first 2 cycles, no observation period is required for subsequent treatment cycles (in the event an IRR occurs thereafter, then the 1-hour observation should be reinstituted).

- Doxorubicin (after the olaratumab administration and 1-hour observation period, if instituted) on Day 1 of every 3-week cycle as an IV infusion over approximately 60 minutes for 8 cycles. Dexrazoxane may be administered at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion, within 30 minutes prior to each doxorubicin infusion for the prevention of cardiotoxicity. It is recommended that all patients receiving 5 or more cycles of doxorubicin receive dexrazoxane.

Administration and dosing of all therapeutic products will occur as described in Section 9.1.

Criteria for starting the next cycle are defined in Section 9.4.1.1. Dose reductions for olaratumab/placebo will be made in the event of specific treatment-related AEs, as described in Section 9.4.1.1.1. Supportive care guidelines are detailed in Section 9.6.1. No dose escalations or re-escalations are permitted.

Patients will undergo radiographic assessment of disease status (CT or MRI) according to RECIST v. 1.1), every 6 weeks (±7 days), as calculated from randomization, until there is radiographic documentation of PD.

Patients in both arms will be treated until there is documented PD, toxicity requiring cessation of treatment, withdrawal of consent, or until other withdrawal criteria are met. In the event there is symptomatic deterioration resulting in treatment discontinuation, radiographic confirmation should be performed. For patients who discontinue treatment for any reason other than radiographically documented PD (for example, symptomatic deterioration), radiographic assessments should continue as scheduled every 6 weeks (±7 days) following the first dose of study therapy until objective radiographic evidence of PD. Following treatment discontinuation, follow-up information regarding further anticancer treatment and survival status will be collected every 2 months (±7 days) for the first 2 years, then every 6 months (±14 days) until the patient's death or overall study completion. Follow-up will continue as long as the patient is alive, withdraws consent from treatment, or until study completion as defined in Section 8.1.3.

8.1.2. Postdiscontinuation Follow-Up Period Assessments

Adverse event (AE) information will be collected until at least 30 days after the decision is made to discontinue study treatment. After the 30-day short-term follow-up visit, only new and ongoing SAEs deemed related to study treatment will be collected.

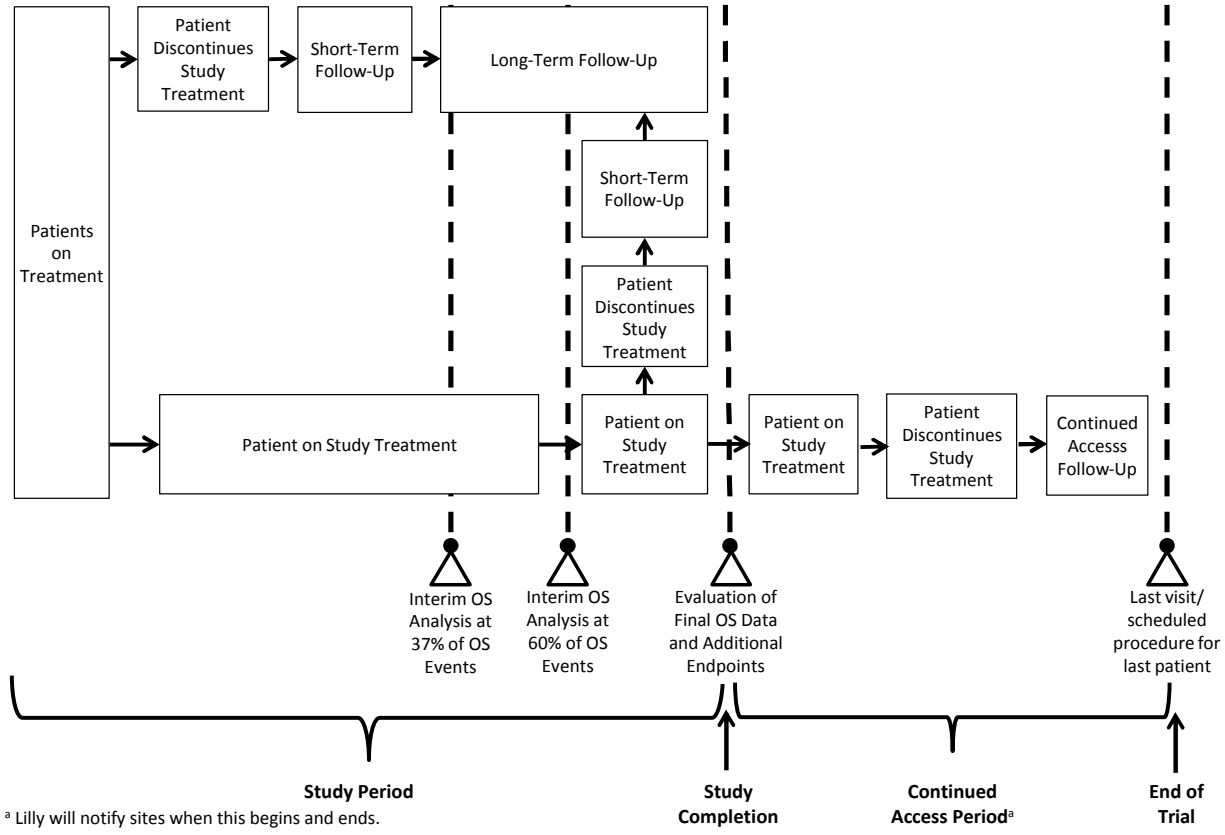
8.1.3. Study Completion and End of Trial

The primary objective is OS, and when there are at least 322 OS events among the study population there will be a database lock to report the final study results.

Figure JGDJ.2 is a diagram of the study period and continued access period. This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final evaluation of OS, as determined by Lilly. Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient.

Upon study completion, investigators and patients may be unblinded to study treatment assignment.

The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed any applicable continued access follow-up.



Abbreviation: OS = overall survival.

Figure JGDJ.2. Study period and continued access diagram.

8.1.4. Continued Access Period

Olaratumab may be made available after all study outcomes have been met (excluding exploratory) to patients who are still receiving and benefitting from study treatment in countries where the drug cannot be lawfully prescribed.

The continued access period will apply to this study only if at least 1 patient is still on study treatment when study completion occurs.

After study completion, all patients who are on study treatment and who are eligible for continued access will be unblinded. Patients receiving olaratumab and experiencing ongoing clinical benefit and no undue risks may continue to receive olaratumab in the continued access

period until one of the criteria for discontinuation is met (see Section 7.3). Patients receiving placebo will be discontinued from study treatment. Lilly will notify investigators when the continued access period begins.

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

During the continued access period, all AEs, SAEs, and olaratumab exposure will be reported on the CRF. Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 10.3.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE. Blood samples for PK and immunogenicity analysis will be collected only in the event of an infusion-related reaction.

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

8.1.5. Committees

The following committees will be established to evaluate patients' safety and/or efficacy of the study treatment. There will be charters for these committees to follow.

Independent Data Monitoring Committee (iDMC)

The independent Data Monitoring Committee (iDMC) will be established to conduct interim efficacy and safety analyses as specified in Section 12.2.13 and will follow an approved iDMC charter. The iDMC will communicate back to Lilly Senior Management Designee (SMD) about their assessment.

The iDMC will also review adverse events of special interest (AESI), including:

- myocardial failure, dysfunction
- myocardial ischemia or infarction
- arrhythmias
- cardiovascular insufficiency

The iDMC meetings to review interim data will occur approximately twice per year prior to the final analysis of the study. See Section 12.2.13 for additional details.

Independent Review Committee (IRC)

An Independent Review Committee (IRC) may review the CT scans and MRI scans for tumor assessments from selected patients if necessary (for example, based on inquiries from regulatory authorities).

8.1.6. Study Duration

Study treatment will continue until documented PD, death, intolerable toxicity, or other discontinuation criteria are met.

From first patient visit to last patient visit, the estimated study duration is 4 years.

8.2. Discussion of Design and Control

A randomized, controlled design is being used in this study. Randomization minimizes systematic bias in the selection and assignment of patients to study treatment and provides justification for inferential statistical methods to be used on data from this study. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study treatment and minimizes bias in the assessment and interpretation of observed treatment effects. Patients will be stratified for differences in factors thought to be associated with clinical outcomes to further reduce the potential for bias and improve the power of the analyses. Assessment of bias is further minimized by the use of a double blind and placebo control.

Investigational treatment administration in this study is double-blind; that is, patients, investigational sites, and the sponsor study team do not have immediate access to treatment assignments for any patients. This design feature minimizes potential bias due to knowledge of patient's treatment during evaluation of study endpoints, at the patient level or aggregated across patients.

9. Treatment

9.1. Treatments Administered

The following treatments will be administered in this study every 3-week (21-day) ± 3 day cycle:

- Experimental Arm A: doxorubicin (75 mg/m^2 IV infusion on Day 1) plus olaratumab (15 mg/kg IV infusion on Days 1 and 8)
- Control Arm B: doxorubicin (75 mg/m^2 IV infusion on Day 1) plus placebo (equivalent volume IV infusion on Days 1 and 8)

Table JGDJ.1 shows the treatment regimens.

Table JGDJ.1. Treatment Regimens/Dosing Schedule

	Study Drug	Dose	Route	Timing
ARM A	Olaratumab[a]	15 mg/kg	IV	approximately 1 hour infusion Day 1 and Day 8 of each 21-day cycle
	1-hour observation period[b] followed by			
	Doxorubicin[c]	75 mg/m^2	IV	IV injection on Day 1 of each 21-day cycle
	OR			
ARM B	Placebo[a]	equivalent volume	IV	approximately 1 hour infusion Day 1 and Day 8 of each 21-day cycle
	1-hour observation period[b] followed by			
	Doxorubicin[c]	75 mg/m^2	IV	IV injection on Day 1 of each 21-day cycle

Abbreviations: IV = intravenous; PO = orally.

a Premedication is recommended prior to infusion of olaratumab or placebo. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at the investigator's discretion. Premedication must be provided in the setting of a prior Grade 1-2 infusion-related reaction, as detailed in Section 9.4.1.1.2.1. All premedication administered must be adequately documented in the eCRF.

b A 1-hour observation period is required after the administration of the first and second doses of olaratumab/placebo. If there is no evidence of an infusion-related reaction during the initial 2 cycles of olaratumab/placebo, then no observation period is required for subsequent treatment cycles. In the event an infusion-related reaction occurs thereafter, then the 1-hour observation period should be reinstituted, see Section 9.2.1.

c Administer doxorubicin intravenously over 3 to 10 minutes. Decrease the rate of doxorubicin administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur. Dexrazoxane may be administered at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion, within 30 minutes prior to each doxorubicin infusion for prevention of cardiotoxicity. It is recommended that all patients receiving 5 or more cycles of doxorubicin receive dexrazoxane.

Any measurements used to determine dose should be taken at each cycle, and dose should be recalculated for each cycle.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drugs and planned duration of each individual's treatment to the patient/site personnel/legal representative,
- verifying that instructions are followed properly,
- maintaining accurate records of study drug dispensing and collection,
- and returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be assessed.

9.1.1. Premedication

Premedication is recommended prior to infusion of olaratumab or placebo. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Given the emetogenic potential of doxorubicin, premedication with antiemetics per institutional guidelines is recommended. Additional premedication may be provided at investigator discretion.

Premedication must be provided in the setting of a prior Grade 1 or 2 IRRs, as detailed in Section 9.4.1.1.2.1. All premedication administered must be adequately documented in the eCRF.

If doxorubicin premedication is required prior to the doxorubicin infusion, this must be done after the completion of olaratumab infusion, not before the olaratumab infusion. This premedication may be administered within the hour that follows completion of the olaratumab infusion.

9.2. Materials and Supplies

Olaratumab and placebo will be provided to the sites by Lilly.

Study drug will be supplied as a sterile preservative-free solution for IV infusion in single-use vials containing 500 mg/50 mL of olaratumab (10 mg/mL) or placebo.

Olaratumab/placebo is formulated in 10 mM histidine, 100 mM glycine, 50 mM sodium chloride, 75 mM mannitol, and 0.02% polysorbate-20, pH 5.5. All excipients used in the formulation of olaratumab/placebo drug product are of pharmacopeia grade. Each single-use vial of olaratumab/placebo is packaged in a 50-mL nominal volume USP type I glass vial, stoppered with a FluroTec® coated latex-free stopper and sealed with an aluminum seal and a flip-off cap.

Where commercially available, doxorubicin hydrochloride will be purchased by the sites. In the event that there are regional restrictions or supply limitations, doxorubicin may be provided to the sites by Lilly.

Where commercially available, dexrazoxane will be purchased by the sites. In the event that there are regional restrictions or supply limitations, dexrazoxane may be provided to the sites by Lilly.

Clinical study materials will be labeled according to the country's regulatory requirements.

9.2.1. Olaratumab/Placebo

Aseptic technique is to be used when preparing and handling olaratumab/placebo. Patients are to receive 15 mg/kg of olaratumab/placebo on Days 1 and 8 of each 21-day treatment cycle administered as an IV infusion. On the days that both olaratumab/placebo and doxorubicin (or doxorubicin with dexrazoxane) are administered, olaratumab/placebo will be administered prior to doxorubicin (or dexrazoxane with doxorubicin). The dose of olaratumab/placebo is dependent upon the patient's baseline body weight. Actual body weight will be used for dose calculation. Subsequent doses of olaratumab/placebo must be recalculated if there is a ≥10% change (increase or decrease) in body weight from baseline; subsequent doses may be recalculated if there is a <10% change (increase or decrease) in body weight from baseline and considered clinically relevant by the treating investigator.

Olaratumab/placebo is compatible with commonly used infusion containers. Refer to the IB or pharmacy manual for detailed information.

The dose of olaratumab/placebo will be aseptically withdrawn from the vial and transferred to a sterile infusion bag or an evacuated glass container. Different drug product lots must not be mixed in a single infusion. For doses other than 250 mL, a sufficient quantity of sterile normal saline (0.9% weight/volume) solution should be added (or removed in the case of a prefilled container such as AVIVA) to make the total volume 250 mL. The container should be gently inverted to ensure adequate mixing.

The dose should be infused over approximately 60 minutes. The infusion rate should not exceed 25 mg/min. Infusion durations longer than 60 minutes are permitted in specific circumstances (that is, for larger patients in order to maintain an infusion rate that does not exceed 25 mg/min or in the setting of olaratumab/placebo prior infusion-related reaction); the infusion duration must always be accurately recorded.

The infusion set must be flushed immediately postinfusion of dose with sterile normal saline to ensure complete delivery of the calculated dose.

Infusion reactions may occur during or following olaratumab/placebo administration (see Section 9.4.1.1.1 for definitions of Grade 3 and 4 infusion reactions).

CAUTION: Infusion-related reactions may occur during or following olaratumab administration (see Section 9.4.1.1.1.1 for a definition of Grade 3 and 4 infusion-related reactions). During the administration of olaratumab, patients should be in an area with resuscitation equipment and treatments necessary for advanced life support and cardiopulmonary resuscitation (CPR), such as bronchodilators, vasopressor agents (e.g., epinephrine), oxygen, glucocorticoids, antihistamines, IV fluids, and so forth. A 1-hour observation period is required after the administration of the

first and second doses of olaratumab/placebo. If there is no evidence of an infusion-related reaction during the initial 2 cycles of olaratumab/placebo, then no observation period is required for subsequent treatment cycles. In the event an infusion related reaction occurs thereafter, then the 1-hour observation should be reinstituted.

9.2.2. Doxorubicin

Investigators should consult the approved doxorubicin hydrochloride package insert for complete prescribing information (including warnings, precautions, contraindications, adverse reactions, and dose modifications) and follow institutional procedures for the administration of doxorubicin. If a patient should have an infusion-related reaction to doxorubicin, the investigator should follow the manufacturer's recommendations and clinical guidelines in the management of the patient.

Doxorubicin 75 mg/m^2 is administered IV. The dose of doxorubicin should be reconstituted in 100 mL of normal saline. Administer doxorubicin intravenously over 3 to 10 minutes. Decrease the rate of doxorubicin administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur.

Doxorubicin must be reconstituted prior to infusion. The reconstituted solution is stable for 7 days at room temperature and under normal room light and 15 days under refrigeration (2ºC to 8ºC). It should be protected from exposure to sunlight.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

See Section 9.6.1.1 for dexrazoxane administration. Doxorubicin should be given within 30 minutes after completing the infusion with dexrazoxane.

9.3. Method of Assignment to Treatment

Upon completion of all screening evaluations to confirm a patient's eligibility, the site will register the patient by the Interactive Web Response System (IWRS), which is web-based and accessible 24 hours a day. The IWRS registration consists of assigning the patient a unique study identification number for all patients will be randomized into 1 of the 2 treatment arms on a 1:1 basis.

The IWRS will assign patients to treatment arms according to a stratified method of randomization (that is, independent randomization within each of 36 strata or cells), defined by the following 4 prognostic factors:

- Number of prior systemic therapies for advanced/metastatic disease (0 versus ≥1)
  NOTE: any neoadjuvant and adjuvant therapy administered for advanced/metastatic disease will not be considered as a prior line of therapy
- Histological tumor type (leiomyosarcoma versus liposarcoma versus other STS type)
- ECOG performance status (0 versus 1)
- Region (North America versus Europe versus ROW)

Once the patient is registered through the IWRS, he/she is considered to be enrolled in the study.

9.4. Selection and Timing of Doses

A cycle is defined as an interval of 21 days (a delay of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 3 days and not counted as a protocol deviation).

The actual doses of olaratumab administered will be determined by measuring the patient's weight in kilograms at the beginning of each cycle. If the patient's weight does not fluctuate by more than ±10% from the weight used to calculate the prior dose, the dose will not need to be recalculated. A ±5% variance in the calculated total dose will be allowed for ease of dose administration.

The actual doses of doxorubicin administered will be determined by calculating the patient's body surface area (BSA) at the beginning of each cycle. If the patient's weight does not fluctuate by more than ±10% from the weight used to calculate the prior dose, the BSA will not need to be recalculated. A ±5% variance in the calculated total dose will be allowed for ease of dose administration.

Patients will receive combination treatment for 8 cycles, followed by monotherapy olaratumab or placebo until evidence of progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria are met.

9.4.1. Special Treatment Considerations

9.4.1.1. Dose Adjustment and Delays

Treatment may be delayed for up to 21 days to allow a patient sufficient time for recovery from study drug-related toxicity. If a patient does not recover from the toxicity within 42 days from D1 of the previous cycle, the patient must be discontinued from study therapy.

Any patient who requires a dose reduction will continue to receive the reduced dose for the remainder of the study. Any patient who has had 2 dose reductions and who experiences a toxicity that would cause a third dose reduction must be discontinued from study treatment.

Since all investigators are blinded to treatment arms, they will treat all patients as if the patient received study drug versus placebo and will adjust doses accordingly.

In general, discontinuation of 1 study drug (olaratumab/placebo or doxorubicin) will not necessitate discontinuation of the other study drug. In the event of alteration or discontinuation of olaratumab/placebo therapy due to an olaratumab/placebo-related toxicity, doxorubicin need not be altered, and the planned doxorubicin schedule should be maintained. In the event that olaratumab/placebo treatment is discontinued for reason of toxicity, the patient may continue treatment with doxorubicin through Cycle 8 at the discretion of the investigator. Similarly, olaratumab/placebo therapy should not be altered or discontinued for doxorubicin-related toxicity. Alteration or discontinuation of doxorubicin will always necessitate a corresponding change to dexrazoxane, if administered, in order to maintain a dosage ratio of 10:1

(dexrazoxane:doxorubicin). In the event that doxorubicin is discontinued for reason of toxicity, the patient may continue treatment with olaratumab/placebo until one or more discontinuation criteria are met, at the discretion of the investigator.

9.4.1.1.1. Olaratumab/Placebo

9.4.1.1.1.1. Infusion-Related Reactions

As with other monoclonal antibodies, hypersensitivity reactions may occur during or following olaratumab administration.

Patients treated with olaratumab/placebo should be closely monitored for signs and symptoms indicative of an infusion reaction by the medical staff from the start of the infusion until at least 1 hour after the end of the infusion in an area where emergency medical resuscitation equipment and other agents (epinephrine, prednisolone equivalents, etc.) are available.

Olaratumab/placebo infusion reactions will be defined according to either the NCI-CTCAE NCI-CTCAE version 4.0 definition of infusion-related reactions.

Definitions of Infusion-Related Reactions for Protocols Utilizing NCI-CTCAE version 4.0

The NCI-CTCAE version 4.0 definition of infusion-related reactions (NCI-CTCAE version 4.0 section "General disorders and administration site conditions") is provided in Table JGDJ.2.

Symptoms occurring during or following infusion of investigational therapy may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome (NCI-CTCAE version 4.0 section "Immune system disorders"). In the setting of symptoms occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE term "infusion-related reaction" and any additional terms (including those not listed here) that best describe the event. Those described above should be graded as described in Table JGDJ.2.

Table JGDJ.2. NCI-CTCAE version 4.0 Infusion-Related Reactions

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hr	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Allergic reaction	Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24 hr	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.					
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hr	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilator support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					

Abbreviations: IV = intravenous; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs = nonsteroidal antiinflammatory drugs.

In general, if a patient experiences a Grade 1 or 2 infusion-related reaction, the infusion rate should be decreased for the duration of the infusion and all subsequent infusions, as directed in the protocol. In addition, patients with Grade 1 and 2 infusion reactions should be treated according to standard medical practices. After a Grade 1 or 2 infusion reaction, patients should be premedicated with antihistamines, steroids, acetaminophen, etc., as appropriate for subsequent infusions.

A Grade 3 or 4 infusion-related reaction will require immediate treatment, including the use of epinephrine, bronchodilators, and/or glucocorticoids for symptomatic bronchospasm, IV fluids and/or pressors for hypotension, and immediate and permanent discontinuation of olaratumab with appropriate supportive care.

Consistent with usual medical practice, selected parenteral medications may be utilized for Grade 2 infusion-related reaction as detailed below. The Lilly Study Physician should be contacted immediately if questions arise concerning the grade of the reaction.

The following are general treatment guidelines for olaratumab infusion-related reactions. Please refer to each protocol for specific instruction.

Grade 1

- Slow the infusion rate by 50%
- Monitor the patient for worsening of condition
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion

Grade 2

- Stop the infusion
- Administer diphenhydramine hydrochloride 50 mg IV (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
- Monitor for worsening of condition
- For subsequent infusions, premedicate the patient with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion

For a second occurrence of a Grade 1 or 2 infusion-related reaction, administer dexamethasone 8 to 10 mg IV (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally, and dexamethasone 8 to 10 mg IV (or equivalent).

Grade 3

- Stop the infusion and disconnect the infusion tubing from the patient
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 8 to 10 mg IV (or equivalent), bronchodilators for bronchospasm, and other medications/treatment as medically indicated
- Patients who have a Grade 3 infusion reaction should not receive further olaratumab treatment

Grade 4

- Stop the infusion and disconnect the infusion tubing from the patient
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 8 to 10 mg IV (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 should not receive further olaratumab treatment

If a patient should have an infusion-related reaction to olaratumab, all attempts should be made to obtain an anti-olaratumab antibody blood sample as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. In addition, these same samples may be assessed for levels of olaratumab and for pharmacodynamic markers to provide information on the nature of the infusion-related reaction. The procedure for sample collection and handling is described in a separate procedural manual.

9.4.1.1.1.2. Hematologic Toxicity

For Grades 1 to 2 hematologic toxicity, no dose modification of olaratumab/placebo is required. For olaratumab/placebo-related Grade 3 toxicity not adequately controlled with appropriate supportive care (including hematopoietic growth factors, if indicated), withhold dose until toxicity ≤Grade 2 or has returned to pretreatment baseline; at this time, dose should be reduced to 12 mg/kg of olaratumab/placebo and treatment resumed. In the case of Grade 4 hematologic toxicity associated with olaratumab/placebo, withhold the dose until toxicity is ≤Grade 1, then reduce dose to 10 mg/kg and resume treatment.

9.4.1.1.1.3. Nonhematologic Toxicity

Specific guidelines for dose adjustments in patients who experience olaratumab infusion-related reactions may be found in Section 9.4.1.1.1.

General guidelines for dose modification for other nonhematologic toxicities related to olaratumab are shown in Table JGDJ.3.

Table JGDJ.3. General Guidelines for Dose Modification Due to Nonhematologic Toxicities Related to Olaratumab

Reaction Grade	Required Dose Modification
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 2 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 ≤ 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 with this agent will be permanently discontinued.
Grade 4	The dose must be withheld until dose toxicity is ≤ 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, olaratumab treatment will be discontinued.

9.4.1.1.2. Doxorubicin

9.4.1.1.2.1. Hematologic Toxicity

Doxorubicin will not be administered if the patient's ANC is <1000 cells/µL or if the platelet count is <100,000 cells/µL. When necessary, the next treatment cycle should be delayed until the ANC is ≥1000 cells/µL and the platelet count is ≥100,000 cells/µL and nonhematologic toxicities have resolved. For patients who experience ≥Grade 3 neutropenic fever or infection or Grade 4 neutropenia without fever lasting more than 1 week, doxorubicin should be reduced to 75% of the starting dose (that is, to approximately 60 mg/m^2). If a patient experiences a second incidence of neutropenic fever/infection or has another episode of Grade 4 neutropenia lasting >1 week, then a second dose reduction to 45 mg/m^2 will be necessary. Therapeutic and secondary prophylactic use of Neulasta® (pegfilgrastim) or other G-CSFs will be allowed per current ASCO guidelines or patients with Grade 4 ANC without fever/infection lasting less than 1 week, retreatment will be allowed at the investigator's discretion with the full dose of doxorubicin (75 mg/m^2)with recommended use of G-CSFs per current ASCO guidelines (Smith et al, 2006). See Table JGDJ.4 for doxorubicin dose modification for neutropenia.

Table JGDJ.4. General Guidelines for Doxorubicin Dose Modification Due to Neutropenia

Toxicity	Required Dose Modification
ANC <1000 cells/µL	No doxorubicin administered; treatment cycle delayed.
At retreatment:	
If ≥Grade 3 neutropenic fever/infection has occurred	Approximately 60 mg/m^2 doxorubicin.
If Grade 4 neutropenia lasting longer than 1 week has occurred	Approximately 60 mg/m^2 doxorubicin.
Grade 4 absolute neutrophil count (ANC)without fever/infection	Retreatment with doxorubicin at full dose at investigator's discretion with recommended use of prophylactic G-CSFs.
Second incidence of either: 1) ≥Grade 3 neutropenic fever/infection 2) Grade 4 neutropenia lasting longer than 1 week	Second dose reduction to 45 mg/m^2.

9.4.1.1.2.2. Cardiovascular

The diagnostic method used at baseline for cardiovascular assessments (for example ECHO or MUGA scans) should be the same method used throughout the study, unless the assessment indicates the need for further intervention.

ECG changes, arrhythmias, tachycardia, and/or chest pain should be managed based on the specific findings.

Patients will undergo baseline LVEF determination by ECHO or MUGA scan. This evaluation may be repeated at any time during the study if clinically indicated. If an ECHO/MUGA scan conducted on study indicates a resting LVEF is <50%, then the ECHO or MUGA scan should be repeated. A decrease in LVEF of 10% below the lower limit of normal or an absolute decrease of 20%, or if the absolute LVEF decreases to or below 40%, then doxorubicin will be discontinued. Doxorubicin should also be discontinued if the patient develops Grade 3 or 4 left ventricular systolic dysfunction (symptomatic congestive heart failure). If doxorubicin is discontinued for the above changes in LVEF, the patient may continue on study with olaratumab, provided that the patient meets all other entry criteria.

If a patient does not recover from the toxicity within 42 days from D1 of the previous cycle, doxorubicin must be discontinued.

9.4.1.1.2.3. Hepatic Impairment

Doxorubicin is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C or serum bilirubin >5.0 mg/dL).

Decrease the dose of doxorubicin in patients with elevated serum total bilirubin concentrations as noted in Table JGDJ.5:

Table JGDJ.5. General Guidelines for Doxorubicin Dose Modification Due to Elevated Serum Total Bilirubin Concentrations

Serum bilirubin concentration	Doxorubicin Dose reduction
1.2 to 3 mg/dL	50%
3.1 to 5 mg/dL	75%
Greater than 5 mg/dL	Do not initiate doxorubicin Discontinue doxorubicin

9.5. Blinding

This is a double-blind study.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. Individuals (IWRS, clinical trials materials management, Global Patient Safety, iDMC, and data management personnel) validating the database will not have access to aggregate summary reports or statistics. PK data that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Upon overall study completion (see Section 8.1.1), investigators may unblind patients to study treatment assignment.

Efficacy information (as outlined in Section 10.1) will not be shared with sites until the study is completed (see Section 8.1.3). Treatment assignment will be scrambled in the reporting database until the database lock for data analysis. This will ensure unblinded aggregate efficacy results are not available until the time of final data analysis.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient may be discontinued from study treatment. In cases where there are ethical reasons to have the patient remain on study treatment, the investigator must obtain specific approval from a Sponsor physician or designee for the patient to continue on study treatment.

9.5.1. Emergency Unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

All events resulting in an unblinding event must be recorded and reported through the IWRS. If the investigator or patient becomes unblinded in the IWRS, that patient may be discontinued from study treatment.

9.5.2. Inadvertent Unblinding

Every effort will be made to blind both the patient and the investigator to the identity of the treatment, but the inadvertent unblinding of a patient may occur. A double-blind study design is known to be imperfect in the oncolytic setting because the potential for individual unblinding exists due to treatment-related signs and symptoms. If an investigator, site personnel performing assessments, or patient is unblinded, the unblinding will not be sufficient cause (in and of itself) for that patient to be discontinued from study treatment or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasons to have the patient remain on the study treatment. For patients to continue on study treatment in the event of unblinding, the investigator must obtain specific approval from a Lilly CRP for the patient to continue in the study.

9.6. Concomitant Therapy

All concomitant medications should be recorded throughout the patient's participation in the study.

Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the 30-day short-term follow-up visit.

With the exceptions listed in the sections below, no other chemotherapy, experimental medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, surgery for cancer, or experimental medications will be permitted while patients are on study treatment.

Appropriate documentation for all forms of premedications, supportive care, and concomitant medications (eg, medications such as sedatives, antibiotics, analgesics, antihistamines, corticosteroids, erythropoietin; procedures such as paracentesis, thoracentesis; or blood products such as blood cells, platelets, fresh frozen plasma transfusions) must be captured on the eCRF.

If doxorubicin premedication is required prior to the doxorubicin infusion, this must be done after the completion of olaratumab infusion, not before the olaratumab infusion.

9.6.1. Supportive Care

Patients should receive full supportive care, if necessary. Patients will receive supportive care as judged by their treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the Lilly CRP. Use of any supportive care therapy should be reported on the eCRFs.

9.6.1.1. Dexrazoxane

Dexrazoxane use to reduce the risk of doxorubicin-induced cardiotoxicity is recommended for patients receiving 5 or more cycles of doxorubicin, at the discretion of the investigator. Investigators should consult the dexrazoxane package insert for administration information (including warnings, precautions, contraindications, adverse reactions, and dose modifications).

Note that as the dose of dexrazoxane administered is proportionally dependent on the dose of doxorubicin administered, any dose modifications to doxorubicin will require a corresponding dose modification to dexrazoxane in order to maintain a dosage ratio of 10:1 (dexrazoxane:doxorubicin).

9.6.1.2. Granulocyte-colony Stimulating Factors and Erythroid Growth Factors

Following the first dose of doxorubicin treatment, the use of G-CSFs such as Neulasta® (pegfilgrastim) and erythroid stimulating factors (eg, erythropoietin) are permitted, including prophylactic use, during investigational therapy at the discretion of the investigator, according to American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2006).

9.6.1.3. Transfusion of Blood Products

Transfusions of red blood cells, platelets, or other blood products are permitted at the investigator's discretion, but may not be used to meet hematologic criteria for inclusion in the study (refer to Section 7.1, inclusion #10).

9.6.1.4. Anti-emetic Therapy

Both prophylactic and symptom-directed anti-emetic therapy are recommended and should be used in accordance with institutional guidelines (when existent) and/or at investigator's discretion.

9.6.2. Prohibited Therapies

Additional concurrent chemotherapy, radiation therapy, biologic response modifiers, or other investigational anticancer agents may not be administered to patients on this study. Palliative radiation to symptomatic sites of disease will not be permitted while on study.

9.6.2.1. Effect of CYP3A4, CYP2D6, and P-gp Inhibitors and Inducers on Doxorubicin

Doxorubicin is a major substrate of cytochrome P450 CYP3A4 and CYP2D6, and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4, CYP2D6, and/or P-gp (for example, verapamil), resulting in increased concentration and clinical effect of doxorubicin. Inducers of CYP3A4 (for example, phenobarbital, phenytoin, St. John's Wort) and P-gp inducers may decrease the concentration of doxorubicin. Avoid concurrent use of doxorubicin with inhibitors and inducers of CYP3A4, CYP2D6, or P-gp. Refer to Attachment 8 for a list.

9.7. Treatment Compliance

The study medication will be administered only at the investigational sites by the authorized study personnel. As a result, treatment compliance is ensured.

10. Efficacy, Patient Reported Outcomes, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Written informed consent must be obtained prior to any study-specific pretreatment evaluations.

Study procedures related to efficacy, safety, pain, health-related quality of life measures, sample collection and testing assessments and their timing are described in the sections below and shown in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Radiographic Assessments at Baseline and during Study Treatment

Within 28 days before the first dose of study treatments, baseline tumor measurements will be performed on each patient. Computed tomography (CT), including spiral CT, scans and magnetic resonance imaging (MRI) are the preferred methods of measurement.

The CT portion of a PET-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST.

The method of assessment used at baseline must be used consistently for tumor assessment and will be repeated every 6 weeks (±7 days), as calculated from the first dose of study therapy. Patients will be evaluated for response according to RECIST, v 1.1 guidelines (Eisenhauer et al. 2009), as outlined in Attachment 6.

After the primary analysis of OS and until study completion, Lilly will continue to collect survival data on all patients but may reduce data collection for other efficacy data. The frequency and types of efficacy assessments (other than collection of OS data) will be at the discretion of the investigator, based on the standard of care. Lilly will notify investigators when this reduced data collection begins and ends.

During the continued access period, efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator, based on the standard of care, and these data will not be collected or analyzed.

10.1.2. Radiographic Assessments during the Study Period Postdiscontinuation Follow-Up

Postdiscontinuation follow-up during the study period will be conducted as described in the Study Schedule (Attachment 1).

For those patients who discontinue study treatment without objectively measured progressive disease (PD), the investigative sites will continue to monitor patients and periodically evaluate

tumor response every 6 weeks (±7 days) by the same method used at baseline and throughout the study until the patient has objective disease progression, or until the final analysis of overall survival. After the patient has objective disease progression, radiologic tests are no longer required and the patient will be followed up approximately every 2 months (±7 days) for the first 2 years, then every 6 months (±14 days) until the patient's death or overall study completion.

After final analysis of OS, during the Continued Access Period, efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator, based on the standard of care.

Lilly will continue to collect survival data through study completion but may reduce data collection for other efficacy data. Lilly will notify investigators when this reduced data collection begins and ends..

10.1.3. Primary Efficacy Measure

Overall survival duration is measured from the date of randomization to the date of death due to any cause. For each patient, prior to each data analysis, a reasonable effort will be made to obtain the most up to date status of the patient (date of death or last date known to be alive). For each patient who is not known to have died as of the data-inclusion cutoff date for a particular analysis, OS will be censored for that analysis at the date the patient was last known to be alive. For any patient who has withdrawn consent for further follow-up of survival data, OS will be censored at the last date for which the patient consented to be followed for the study.

10.1.4. Additional Efficacy Measures

The following additional efficacy measures will be determined for each patient, with planned statistical analyses specified in Section 12 and in the Statistical Analysis Plan (a separate document). Specific definitions of each of these measures (such as defining events and censoring for each time to event endpoint) will be provided in the Statistical Analysis Plan.

- Progression-free survival (PFS)
- Objective Response Rate (ORR)
- Disease Control Rate (DCR)
- Duration of Response (DoR)
- Duration of Disease Control
- Time to any progression (censoring for death without progression)
- Time to any new metastases (censoring for death and for other type of PD)
- New-metastases-free survival (nMFS)
- Time to any progression based solely on increased sum of target lesions
- Time to first worsening of the mBPI-sf "worst pain" score
- Time to first worsening of the QLQ-C30 summary scores (for example, Global Health Status / Quality of Life score, Physical Functioning score, and Role Functioning score)
- Time to first worsening of ECOG performance status

10.2. Patient Reported Outcomes/Resource Utilization

Patient reported pain will be assessed using the mBPI-sf (Cleeland et al. 1991). Health related Quality of Life will be assessed with the EORTC QLQ-C30 (Aaronson et al. 1993). Health status will be assessed using the EQ-5D-5L (Janssen et al. 2008). The PRO measures will be collected on Day 1 of every cycle and at the 30-day short term follow-up visit. A full due diligence will be taken to collect PRO measures during long-term follow-up (every 6 weeks [±7 days] until PD, thereafter every 2 months [±7 days] for the first 2 years, then every 6 months [±14 days] until the patient's death or overall study completion).

Paper versions of the questionnaires will be used. It is recommended that the instruments be administered together and in sequence order, at the beginning of the visit prior to other study procedures, with the mBPI-sf presented first, followed by the EORTC QLQ-C30 and continuing with the EQ-5D-5L. Questionnaires should be administered to the patient prior to extensive interaction with site staff and study drug administration.

Patient-reported questionnaires should be completed by patients when a language translation is available in which the patient is fluent or literate.

10.2.1. mBPI-sf

The mBPI-sf (Cleeland et al. 1991) is an 11-item instrument used as a multiple-item measure of cancer pain intensity. In addition to pain intensity (4 items), the mBPI-sf is designed for patients to record the presence of pain in general, pain relief, and pain interference with function (general activity, mood, ability to walk, ability to perform normal work, relations with others, sleep, and enjoyment of life).

Responses for the mBPI-sf items are captured through the use of 11-point numeric rating scales anchored at 0 (*no pain* or *does not interfere*) and ranged through 10 (*pain as bad as you can imagine* or *completely interferes*). The focus of the analysis will be on the "worst pain". "Worst pain" intensity has been shown to meaningfully impact patients' lives as indicated by a strong correlation with functional interference scores in various types of cancer (Daut et al. 1983; Serlin et al. 1995; Ger et al. 1999; McMillan et al. 2000; Shi et al. 2009). Moreover, a study by Stone et al. (2004) suggested that patients' tendency to focus on the most severe level of pain during a recall period may bias average recalled pain. Therefore, the focus of the analysis will be on the "worst pain".

Analgesic use will be recorded on the eCRF. Data on each individual prescription and over-the-counter analgesic medication will be recorded on the Concomitant Medications eCRF including but not limited to drug name and mode of administration. The use of analgesics should be reviewed with the patient during each visit. Any changes to analgesic use (new or stopped analgesics) will be recorded on the eCRF. Analgesics will be classified into 1 of 6 categories, using an analgesic ladder approach with medication category based on a World Health Organization scale outlined in table below. A therapy category will be assigned according to the maximum category of therapy routinely administered based on analgesic data for that cycle.

The mBPI-sf population will include all patients who completed at least 1 baseline (Cycle 1 Day 1) followed by at least 1 mBPI-sf "worst pain" assessment after 1 cycle of study drug (Cycle 2 Day 1 or later). Patients with a mBPI-sf "worst-pain baseline score of 8 or more will not be included in the analysis.

Table JGDJ.6. World Health Organization Pain Scale

Code	Description
0	No analgesia
1	Aspirin (for pain, not cardiovascular prophylaxis), acetaminophen, nonsteroidal anti-inflammatory drugs
2	Codeine, hydrocodone, pentazocine, oxycodone
3	Oral morphine, hydromorphone, methadone, transdermal fentanyl
4	Parenteral opiates
5	Neurosurgical procedures (blocks)

10.2.2. EORTC QLQ-C30

Broadly used in cancer trials, validated, and available in over 80 different languages, the EORTC QLQ-C30 (Aaronson et al. 1993) is a reliable and validated tool. The EORTC QLQ-C30 v3.0 is a self-administered, cancer-specific questionnaire with multidimensional scales. The EORTC QLQ-C30 self-reported general cancer instrument consists of 30 items covered by 1 of 3 dimensions:

- global health status/quality of life (2 items)
- functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning)
- symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact)

The EORTC QLQ-C30 questionnaire is administered per the Study Schedule (Attachment 1). The recall period is the past week, completion time is typically 5 to 7 minutes, and the questionnaire will be scored as described by the EORTC scoring manual (Fayers et al. 2001). The EORTC population will include all patients who completed at least 1 baseline (Cycle 1 Day 1) followed by at least 1 EORTC assessment after 1 dose of study drug (Cycle 2 Day 1 or later).

10.2.3. EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of self-reported health status (Herdman et al. 2011). Specifically, this questionnaire is included in this trial to evaluate health-state utilities associated with advanced STS. These utility measures are an important input for economic evaluations concerning the value of treatment interventions.

The EQ-5D 5L is designed to be used in conjunction with other patient-reported measures. Patients will complete the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), 5-level (no problem, slight, moderate, severe, or extreme problem) assessment according to the Study Schedule (Attachment 1). A unique EQ-5D health state is

defined by combining 1 level from each of the 5 dimensions. Additionally, patients will indicate their current health status by marking on a visual analogue scale (VAS) ranging from 100 (best imaginable health state) to 0 (worst imaginable health state).

The recall period is "today." The EQ-5D-5L is designed for self-completion by respondents and is cognitively simple, taking only a few minutes to complete.

10.2.4. Resource Utilization

Investigators will be asked to document the use of best supportive care (BSC) measures, concomitant medications, transfusions, and treatment-related hospitalization days. Such assessments are to be taken throughout the study through the 30-day short-term post-discontinuation follow-up visit.

10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JGDJ.7 presents a summary of AE and SAE reporting guidelines. Table JGDJ.7 also shows which database or system is used to store AE and SAE data.

Table JGDJ.7. Adverse Event and Serious Adverse Event Reporting Guidelines

Period	Types of AEs/SAEs to be Reported	Collection Database	Lilly Safety System
Baseline (pretreatment)	Preexisting conditions	x	
	All AEs	x	
	SAEs related to protocol procedures	x	x
Study treatment period	All AEs	x	
	All SAEs	x	x
30-day short-term postdiscontinuation follow-up	All AEs	x	
	All SAEs	x	x
Long-term postdiscontinuation follow-up	All SAEs related to protocol procedures or study treatment	x	x
Continued access period	All AEs	x	
	All SAEs	x	x
Continued access follow-up	All AEs	x	
	All SAEs	x	x
After the patient is no longer participating in the study (that is, no longer receiving study treatment and no longer in follow-up)	All SAEs related to protocol procedures or study treatment that the investigator becomes aware of		x

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

10.3.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to that drug.

Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

Any clinically significant findings from ECGs, ECHOs/MUGAs, labs, or vital sign measurements that result in a diagnosis should be reported to Lilly or its designee.

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record the occurrence and nature of any AEs and any change in the preexisting condition(s). All AEs related to protocol procedures are reported to Lilly or its designee.

In addition, all AEs occurring after the patient receives the first dose of study treatment must be reported to Lilly or its designee via eCRF.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure or study drugs via eCRF.

Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits.

The National Cancer Institute (NCI)-CTCAE v 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the NCI-CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event.

In addition to collecting the AE verbatim and the CTCAE severity grade, AE verbatim text will also be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.3.1.1. Serious Adverse Events

An SAE is any adverse event from this study that results in one of the following outcomes:

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse event collection begins after the patient has signed informed consent and has received study treatments. If a patient experiences an SAE after signing informed consent, but prior to receiving study treatments, the event will not be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.

Study site personnel must alert Lilly or its designee of any **serious** adverse event (SAE) within 24 hours of investigator awareness of the event via a sponsor-approved method. If study site personnel contact Lilly or its designee by telephone regarding an SAE, study site personnel must also immediately provide official notification on study-specific SAE forms.

This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study treatment or other protocol-required procedure) should not be considered SAEs.

Serious adverse events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study treatments.

The investigator does not need to actively monitor patients for AEs once the trial has ended, unless provided otherwise in the protocol; however, if an investigator becomes aware of an SAE occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure or study treatments, the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.3.1.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Development Core Safety Information (DCSI) in the IB and that the investigator identifies as related to the study treatments or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

10.3.2. Other Safety Measures

10.3.2.1. Electrocardiograms

For each patient, 12-lead digital electrocardiograms (ECGs) will be collected according to the Study Schedule (Attachment 1) as single ECGs for overread. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high quality records.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/corrected QT (QTc) interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is present, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) and to determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

All digital ECGs will be electronically transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will then conduct a full overread on the ECG (including all intervals); a report based on data from this analysis will be issued to the investigative site. All data from the overreads will be placed in the Lilly database for analytical and study report purposes.

When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator (or qualified designee's) interpretation will be used for study entry and immediate patient management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

10.3.2.2. Echocardiograms/MUGA Scans

An echocardiogram or multi-gated acquisition (MUGA) scan is required within 28 days prior to randomization for all patients. Thereafter, echocardiograms or MUGA scans must be performed prior to treatment within 7 days prior to Day 1 of Cycles 5 and 7, at the end of Cycle 8, and when clinically indicated. After Cycle 9, perform echocardiograms or MUGA scans every 3 cycles until PD or treatment discontinuation, whichever comes first (refer to Attachment 1).

10.3.3. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review:

- trends in safety data
- laboratory analytes
- adverse events including monitoring of cardiac events such as:
    - myocardial failure, dysfunction

  - myocardial ischemia or infarction
  - arrhythmias
  - cardiovascular insufficiency
- If a patient experiences elevated alanine aminotransferase (ALT) >5× upper limit of normal (ULN) and elevated total bilirubin >2× ULN, clinical and laboratory monitoring should be initiated by the investigator. For patients entering the study with ALT >3× ULN, monitoring should be triggered at ALT >2× baseline.
- Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Attachment 3.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the data monitoring committee (an advisory group for this study formed to protect the integrity of data; refer to Section 12.2.13) can conduct additional analyses of the safety data.

For the purpose of this study, in which survival is a primary endpoint, all deaths and SAE reports will be reviewed in a blinded manner by Lilly during the clinical trial. These reports will be reviewed to assure completeness and accuracy but will not be unblinded to Lilly during the clinical trial. If a death or other clinical AE is deemed serious, unexpected, and possibly related to study treatments, only Lilly Global Patient Safety representatives external to the study team will be unblinded for regulatory reporting and safety monitoring purposes. These measures will preserve the integrity of the data collected during this trial and minimize any potential for bias while providing for appropriate safety monitoring.

10.3.3.1. Cardiac Events of Special Interest

Patients exposed to doxorubicin are at risk for cardiovascular events. These events will be monitored throughout the JGDJ study as cardiac adverse events of special interest (AESI):

- left ventricular dysfunction as identified by echocardiogram or MUGA scan
- myocardial failure, dysfunction
- myocardial ischemia or infarction
- arrhythmias
- cardiovascular insufficiency

AESI data will be collected for all study treatment arms and monitored throughout the conduct of this study and across the development program. If cardiovascular events are reported, sites will be prompted to collect additional information.

10.3.4. Complaint Handling

Lilly collects product complaints on study treatments used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded doxorubicin and/or dexrazoxane are reported directly to the manufacturers of those drugs in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or its designee will be reported.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.4. Sample Collection and Testing

Attachment 1 and Attachment 7 list the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study and whether these will be performed at a central or local laboratory. In the event of a treatment-emergent hepatic abnormality, selected tests may be obtained as specified in Attachment 3.

10.4.1. Samples for Study Qualification and Health Monitoring

Blood and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health. Enrollment and treatment decisions may be based upon results of tests performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between local and central laboratory that may have an impact on eligibility or treatment decisions will not be considered protocol deviations.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.4.2. Samples for Translational Research

The following samples for biomarker and pharmacogenetics research are required to be collected from all patients in this study:

- plasma samples from whole blood (see Section 10.4.2.1)
- whole blood sample for DNA collection (see Section 10.4.2.2)
- archived tumor tissue or tumor tissue from biopsy (see Section 10.4.2.3)

Samples will be stored and analyses will be performed to assess biomarkers relevant for STS, the mechanism of action of olaratumab or doxorubicin and/or cancer-related conditions, and may also be used for related research methods. Samples will be stored until analyzed, as described below.

Plasma samples for biomarker research, whole blood samples for DNA, and tumor tissue samples will be collected at the times specified in the Study Schedule (Attachment 1 and Attachment 7). Translational research samples will be stored at a facility chosen by the Sponsor or designee.

Supplies required for the collection and shipment of the patients' stored samples will be supplied by the central laboratory vendor. Sample handling and shipment to the central laboratory will occur per instructions provided to the study site.

10.4.2.1. Blood Samples for Plasma Collection

Blood samples will be collected at specified time points (Attachment 7) for plasma collection. Potential pharmacodynamic and/or circulating markers may include, but are not limited to, PDGF, VEGF, PDGFRα, and PDGFRα ligand(s). The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor.

10.4.2.2. Whole Blood Samples for DNA Collection

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis. Sampling for such analysis will be a one-time collection, as noted in the Study Schedule (Attachment 1). Variable response to olaratumab and doxorubicin may be due to genetic determinants that impact drug absorption, distribution, metabolism and excretion, the mechanism of action of the drug, the availability of receptors, the disease etiology and/or the disease subtype itself.

Samples will be stored and analyses may be performed on genetic variants/copy number variations that are thought to play a role in soft tissue sarcoma, the mechanism of action of olaratumab or doxorubicin, and/or cancer-related conditions.

In the event of an unexpected AE or the observation of an unusual response, the samples may be genotyped and analysis may be performed to evaluate genetic association with response to olaratumab and/or doxorubicin. These investigations may include focused candidate gene studies or, if appropriate, genome-wide association studies may be performed to identify regions of the genome associated with the variability observed in drug response. Samples will only be used for investigations related to disease, cancer-related conditions, and drug under study in the context of this clinical program.

They will not be used for broad exploratory unspecified disease or population genetic analysis. Pharmacogenetic data will not be provided back to the investigator or the patient except where required by local law.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study treatment. Samples will be destroyed according to a process consistent with local regulation.

10.4.2.3. Mandatory Tumor Tissue Samples

Previously obtained archived FFPE tissue will be requested both for a central pathology review to confirm diagnosis and for exploratory biomarker research. In the event that archived tissue is not available at study entry, a tumor biopsy of primary or metastatic tissue will be required and must be collected prior to randomization (treatment can be initiated after tissue collection, without the need to wait for availability of tissue analysis results). A paraffin block (FFPE) is acceptable. Due diligence should be used to make sure that tumor specimen (not a normal adjacent or a tumor margin sample) is provided. De-identified and translated pathology notes accompanying archival tissue may also be requested.

Mutation profiling, copy number variability, gene expression, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations with these biomarkers relevant to pathways associated with STS, the mechanism of action of olaratumab, or doxorubicin, and/or cancer-related conditions, and may also be used for related research methods. The paraffin-embedded blocks will be sectioned and sent back to the site. Slides will not be returned.

Tissue samples will be stored for a maximum of 15 years after the last patient visit for the study; any samples remaining at that time will be destroyed.

10.4.3. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against olaratumab. To interpret the results of immunogenicity, blood samples will be collected at the same time points as the blood samples designated to measure the serum concentrations of olaratumab (as noted in Section 10.4.4).

In the event of an olaratumab/placebo infusion-related reaction (IRR), unscheduled blood samples will be collected for additional immunogenicity analysis. These additional samples will be collected as close as possible to the onset of the event, at the point of resolution from the event, and within 30 days after onset of the event (as noted in Attachment 7).

Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of the olaratumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of olaratumab. The serum samples collected for immunogenicity testing will be stored at a facility designated by the Sponsor.

Samples may be stored for a maximum of 15 years following last patient visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to olaratumab. The duration allows the sponsor to respond to regulatory requests related to olaratumab.

10.4.4. Samples for Drug Concentration Measurements Pharmacokinetics

At the visits and times specified in the Pharmacokinetic, Immunogenicity, and Pharmacodynamic Sampling Schedule (Attachment 7), venous blood samples will be collected for all patients randomized in the study. These samples will be used to determine the serum concentrations of olaratumab and plasma concentrations of doxorubicin.

Serum concentrations of olaratumab will be assayed using a validated enzyme-linked immunosorbent assay (ELISA) method. Doxorubicin concentrations in plasma will be analyzed using a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay.

Instructions for the collection and handling of blood samples will be provided by the sponsor. It is preferred that the blood samples be obtained from a peripheral location. Blood samples will be allowed from central access devices, but a sample drawn from a central catheter of any type for PK must take precautions to prevent obtaining a dilute sample. If multiple samples are obtained centrally, the PK sample should be the last specimen drawn to reduce the potential for a diluted or improperly drawn sample. The actual date and time (24-hour clock time) of each sampling will be recorded. Up to a maximum of 5 additional samples may be drawn at different time points during the study if warranted (for example, for safety assessment) and agreed upon between both the investigator and Lilly (refer to Attachment 7 for time points). In the event of an IRR, unscheduled blood samples will be collected to determine serum olaratumab concentrations, as described in Section 10.4.3.

These samples will be analyzed at a laboratory designated by the sponsor. The serum samples for PK will be stored at a facility designated by the Sponsor. The remaining sample materials collected for PK may be pooled and used for exploratory metabolism and other exploratory PK/pharmacodynamic work as deemed appropriate.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Bioanalytical samples collected to measure olaratumab and doxorubicin concentration will be retained for a maximum of 1 year following last patient visit for the study.

10.5. Appropriateness of Measurements

The measures used to assess safety and efficacy in this study are consistent with those used in most conventional oncology trials.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate
- Sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- Make periodic visits to the study site
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- Review and evaluate CRF data and use standard computer edits to detect errors in data collection
- Conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this trial. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome (PRO) measures (for example, a rating scale), a daily dosing schedule, or an event diary.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

The primary objective of this study is to compare olaratumab plus doxorubicin (experimental arm) versus placebo plus doxorubicin (control arm) in terms of OS in patients with advanced, metastatic STS. The study will screen approximately 500 patients to enroll 460 patients in 1:1 randomization (230 patients in the experimental arm and 230 patients in the control arm). The intent-to-treat sample size of 460 was selected assuming the final analysis of OS will occur when at least 322 OS events have been observed; therefore, the sample size of 460 ensures a maximum of 30% censoring at the final OS analysis.

The final total of 322 OS events (deaths) is an appropriate minimum for the final analysis of OS, providing 80% statistical power for a two-sided log-rank test at a 0.05 significance level (assuming the true OS HR is 0.73). An OS HR of 0.73 corresponds approximately to an increased median survival from 15 months (estimated from published clinical data in various types of patients with advanced or metastatic STS as well as based on the JGDG trial results) in doxorubicin alone to 20.5 months for olaratumab combined with doxorubicin.

Two interim efficacy analyses for OS are planned after 120 (37% of the targeted final number of 322 OS events) and 194 OS events (60% of the final OS events) have been observed. An O'Brien-Fleming alpha spending function will be used to determine the efficacy boundary. Approximate O'Brien-Fleming alpha levels and OS HR boundaries for the two interims and the final analysis are as follows (using EAST® 6.3):

- First interim: 120 events, alpha = 0.0005, HR < 0.525
- Second interim: 194 events, alpha = 0.0075, HR < 0.680
- Final: 322 events, alpha = 0.0476, HR < 0.801

An overall two-sided alpha level of 0.05 is maintained across interim and final analyses of OS through the use of this O'Brien-Fleming method. In addition, a scheme (e.g. Glimm et al. 2010) for maintaining a 0.05 study-wise alpha error rate across OS and the following secondary endpoints will be pre-specified in the Statistical Analysis Plan:

- PFS
- ORR
- DCR
- Duration of response
- Duration of disease control

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All CIs will be given at a 2-sided 95% level, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in the statistical analysis plan. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

If study data violate key statistical assumptions of an analysis method, alternative statistical methods may be used.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

12.2.1.1. Analysis Populations

The following populations will be defined for this study:

Intent-to-Treat population: will include all randomized patients. The ITT analysis of efficacy data will consider allocation of patients to treatment groups as randomized, and not by actual treatment received. This population will be used for all baseline, efficacy, and health outcome analyses.

Per-Protocol population: will include all patients who are randomized and received at least 1 cycle of study treatment, and do not have any major protocol violations that could potentially affect the efficacy conclusions of the study. This population will be defined in detail in the SAP prior to database lock, and will be used for sensitivity analyses of OS and PFS; other efficacy endpoints may also be analyzed.

Safety population: will include all randomized patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the actual study treatment a patient has received, regardless of the arm to which he or she was randomized. The safety population will be used for all dosing/exposure, adverse events, and resource utilization analyses.

12.2.2. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated as well as number and percentage of patients completing the study, or discontinuing (overall and by reason for discontinuation). A summary of all major protocol deviations will be provided.

12.2.3. Patient Characteristics

Description of patient characteristics at baseline, such as patient demographics, baseline disease characteristics, preexisting conditions, and prior therapies will be reported using descriptive statistics.

12.2.4. Concomitant Therapy

Concomitant medications will be summarized for the safety population.

12.2.4.1. Postdiscontinuation Therapy

The numbers and percentages of patients reporting postdiscontinuation therapies will be provided overall, by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug name, for the ITT population.

12.2.5. Treatment Compliance

The number of dose omissions, reductions, delays, number of cycles received, and dose intensity will be summarized for all treated patients per treatment arm.

12.2.6. Primary Outcome and Methodology

The analysis of OS at both the interim and final analysis time points will be based on the stratified log-rank test, stratified by randomization strata (CRF data). The testing boundaries (approximate values can be found in Section 12.1) will be determined using an O'Brien-Fleming alpha spending function. OS survival curves, the median with 95% CI and survival rates at various time points for each treatment group will be estimated using Kaplan-Meier method (Kaplan and Meier 1958). The HR will be estimated using a stratified Cox regression model, stratified by randomization strata (CRF data). All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint.

Two interim analyses are planned for efficacy as described in Section 12.1. The actual stopping boundaries and nominal alpha levels will be calculated at the time of conducting interim analyses and the final analysis, with efficacy boundaries and alpha values following an O'Brien-Fleming alpha spending function. The boundaries presented in Section 12.1 are approximate.

The following sensitivity analyses for OS will be performed:

- Unstratified log-rank test and Cox models
- Stratified log-rank test and Cox models, stratified by strata at randomization (IWRS data)
- Analysis for the per-protocol population
- Univariate and multivariate Cox regression model will be used to explore potential prognostic and/or predictive factors.

12.2.7. Other Analyses of Efficacy

12.2.7.1. Progression-Free Survival

A precise definition of events and censoring for progression-free survival will be defined in the SAP. Progression-free survival will be analyzed using the Kaplan-Meier method, and compared based on a log-rank test, stratified by the same stratification factors used in the analysis of the primary endpoint OS.

PFS will be compared between the two treatment groups based on log-rank test, stratified by CRF stratification factors. PFS survival curves, the median with 95% CI and survival rates at various time points for each treatment group will be estimated using Kaplan-Meier method

(Kaplan and Meier 1958). The HR will be estimated using a stratified Cox regression model, stratified by randomization strata (CRF data).

The following sensitivity analyses will be performed for PFS:

- Time to component events of PFS, such as time to new metastases, etc.
- Unstratified log-rank test and Cox models
- Stratified log-rank test and Cox models, stratified by strata at randomization (IWRS data)
- Analysis including both radiographic and symptomatic progressions as PFS events
- Analysis for the per-protocol population
- Sensitivity analysis for various PFS censoring rules (for example, post-discontinuation systemic anticancer therapy, missing 2 or more tumor assessments prior to PD/death, etc.; more details will be specified in SAP)
- Univariate and multivariate Cox regression model will be used to explore potential prognostic and/or predictive factors.

12.2.7.2. Analysis of Tumor Response

The BOR (Best Overall Response) will be determined using the RECIST v.1.1 guidelines.

The ORR will be calculated as the number of patients who achieve a best overall response of CR or PR, divided by the total number of patients randomized to the corresponding treatment group (ITT population). Additionally, a subgroup analysis will be performed for patients with measurable disease and for patients with nonmeasurable but evaluable disease. Patients who do not have a tumor response assessment for any reason are considered as nonresponders and are included in the denominator when calculating the response rate. The ORR with 95% CI observed in each treatment group will be summarized and compared using the Cochran-Mantel-Haenszel test adjusting for the CRF strata at time of OS final analysis.

Disease Control Rate (DCR), the proportion of patients who have best overall response of CR or PR or SD, is defined as the number of patients with a CR, a PR or an SD, divided by the number of patients in the analysis population. The DCR will be analyzed using the same approach as ORR.

12.2.7.3. Additional Efficacy Analyses

Additional analyses of the measures defined in Section 10.1.4, as well as any other pre-planned efficacy analyses will be defined in the Statistical Analysis Plan.

12.2.8. Pharmacokinetic and Immunogenic Analyses

Pharmacokinetics:

Pharmacokinetics analyses will be conducted on all patients who have received at least 1 dose of study treatment and have had PK samples collected.

Mean population PK parameters for olaratumab in serum (clearance, volume of distribution, and half-life) and inter-individual PK variability will be computed for this study using nonlinear

mixed-effect modelling implemented in [redacted] in order to describe the average dose-concentration relationship in the target population. Covariate effects (such as age, weight and sex) on the PK parameters of olaratumab in serum will also be investigated.

PK data collected for doxorubicin will be analyzed using descriptive methods.

Exploratory PK/PD analyses may also be conducted to characterize the exposure-response (biomarker) relationship in this study. The PK and PK/PD analyses will be reported as separate stand-alone reports for this study. Additional analyses such as exposure-response using TTP and/or other appropriate clinical endpoints may be performed, if warranted by the data.

The version of any software used for the analysis will be documented, and the program will meet Lilly requirements of software validation. It is possible that other validated equivalent PK software programs may be utilized if appropriate, warranted, and approved by global PK management.

Immunogenicity:

Incidence of anti-olaratumab antibodies will be tabulated. The potential impact of immunogenicity on olaratumab exposure will be evaluated in the population PK modeling exercises where immunogenicity will be evaluated as a covariate. In addition, graphical assessments will be conducted, as appropriate, to compare drug exposure between ADA negative and ADA positive patients at correspondent visits, or before and after ADA development for patients who developed ADA.

In the event of an infusion-related reaction, the immunogenicity and olaratumab serum concentrations will be tabulated.

12.2.9. Translational Research Analyses

Biomarker assay results will be summarized and correlated with clinical outcomes.

12.2.10. Analyses of Patient-Reported Outcomes (PROs)

Patient-reported outcomes are measured through the following:

- mBPI-sf (Brief Pain Inventory [Short Form] Modified)
- EORTC QLQ-C30 (The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30)
- EQ-5D-5L (EuroQol 5-Dimension 5-Level)

For each instrument (mBPI-sf, EORTC QLQ-C30, and EQ-5D-5L), percentage compliance will be calculated as the number of completed assessments divided by the number of expected assessments (that is, patients still on study and alive). Percentage compliance and reasons for non-compliance will be summarized by treatment arm and time point.

Data will be separately summarized by treatment and time point using descriptive statistics. The main efficacy measure for the pain endpoint will be the time to first worsening of the mBPI-sf

"worst pain" score. Time to first worsening in pain will be described using the method of Kaplan and Meier and analyzes will be made between the 2 arms by a log-rank test. "Worsening" will be defined as either a "worst pain" increase of ≥2 points postbaseline (Farrar et al. 2001; Rowbotham 2001) or an analgesic drug class increase of ≥1 level. However, other approaches to defining clinically meaningful worsening in pain might be considered. Further details will be provided in the Statistical Analysis Plan.

Additionally, time to first worsening of QLQ-C30 summary scores (see Section 10.2) will be analyzed using Kaplan-Meier and Cox methods. Further statistical analysis to be performed for PROs will be defined and detailed in the Statistical Analysis Plan.

12.2.11. Safety Analyses

All safety summaries and analyses will be based upon the safety population as defined in Section 12.2.1, unless otherwise indicated, and include:

- Adverse events (AE) will be summarized by MedDRA® System Organ Class/preferred term, classified from verbatim terms. The incidence and percentage of patients with at least one occurrence of a preferred term will be included, according to the most severe NCI-CTCAE Version 4.0 grade. Causality (relationship to study drug), action taken, and outcome will be summarized separately. Duration of AE will be determined and included in the listings.

- Study drug exposure will be summarized for each arm with following variables: number of infusion (except capecitabine), number of cycles, duration of therapy, cumulative dose, dose intensity and relative dose intensity.

- Laboratory results will be classified according to the NCI-CTCAE, Version 4.0. Incidence of laboratory abnormalities will be summarized.

- Hospitalizations due to AEs, transfusions, and vital signs will be summarized.

12.2.12. Subgroup Analyses

Subgroup analyses of PFS and OS will be performed and will be detailed in the Statistical Analysis Plan.

12.2.13. Interim Analyses

A limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to an interim or final database lock, in order to initiate the final population pharmacokinetic/pharmacodynamic model development processes for interim or final analyses. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

An independent data monitoring committee (iDMC) will be established to conduct safety reviews. The membership, roles, and responsibilities of the iDMC are defined in the iDMC Charter (a separate document).

There will be no prespecified rules for stopping or modifying the trial due to safety concerns. The iDMC members will review unblinded interim safety data to determine whether there are sufficient safety concerns to justify modifying the study or the termination of study treatment and/or enrollment.

Only the iDMC is authorized to evaluate unblinded safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

Unblinding details are provided in the blinding section of the protocol (Section 9.5).

IDMC safety reviews will be performed for **all randomized patients** approximately twice per year, with the first such review taking place roughly 6-10 months after the first patient has randomized. Details as to the process and communication plan will be provided in the iDMC Charter.

Two interim efficacy analyses will be performed by an independent Data Monitoring Committee (iDMC) as described in Section 12.1. The iDMC Charter (a separate document) will provide detailed guidance for the conduct of the interim analyses and describe the process for recommending changes to the trial in the event that interim OS results are statistically significant. In the event of a statistically significant interim result for OS according to the specifications of Section 12.2.1 and the iDMC Charter, investigative sites will be informed that the study has met its primary objective and thus confirmed the efficacy of olaratumab in combination with doxorubicin. It is recommended that any patients currently receiving study treatment at the time of a positive interim result should continue his/her study treatment as originally planned. This recommendation is appropriate given that any positive interim result will not support the use of olaratumab in patients who have (currently or previously) received treatment with single-agent doxorubicin.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or, where permitted by local law or regulation, by the patient's legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study treatments.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at the investigative sites. All ICFs must be compliant with the ICH guideline on GCP.

Documentation of ERB/IRB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative sites.

The study site's IRB/ERBs should be provided with the following:

- The current IB and updates during the course of the study
- The ICF
- Relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

- 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
- International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guideline (E6)
- ICH Guideline, Clinical Investigation of Medicinal Products in the Pediatric Population (E11)
- Applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERBs/IRBs.

Some of the obligations of Lilly will be assigned to a TPO.

An identification code assigned by the investigator to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Physicians with a specialty in medical oncology with a specialty in soft tissue sarcoma will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The Lilly responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol JGDJ Study Schedule

Study Schedule, Protocol I5B-MC-JGDJ

Perform procedures as indicated.

	Screening[a]	Treatment Period				Follow-up	
		Cycles 1-8		Cycle 9+		Short Term Follow-up	Long Term Follow-up
Day	**NA**	**Day 1 (±3)**	**Day 8 (±3)[b,d]**	**Day 1 (±3)[b,d]**	**Day 8 (±3)[b,d]**	**30 days (±7) after last dose**	
Eligibility Assessments							
Informed Consent[e]	X						
Medical History	X						
ECOG performance status	X	X		X		X	
ECG	X[h]	X		X[i]		X	
Echocardiogram (ECHO) or MUGA	X[h]	X[i]		X[i]		X	
Safety Assessments							
Physical Exam[j,k]	X	X		X		X	
Vital Signs[l,m]	X	X	X	X	X	X	
Adverse Event Assessment[n]		X		X		X	
Concomitant Medication Assessment	X[o]	X		X		X	
Laboratory Assessments (See Attachment 2 for details)							
Hematology Profile	X[c]	X	X	X	X	X	
Coagulation Profile	X[c]	X[j]		X[j]		X	
Chemistry Profile	X[c]	X		X		X	
Urinalysis[r]	X[c]	X		X		X	
Pregnancy Test	X[f]	X[g]		X[g]		X[g]	
Pharmacogenetic (DNA) Sample	X	See Attachment 7 (whole blood sample)					
Immunogenicity[p]	See Attachment 7 for specific time points						
Efficacy Assessments							
Imaging Studies (CT/MRI)	X[h]	X[s]		X[s]		X[s]	X[s]
RECIST v1.1 Tumor Assessments	X[h]	X[s]		X[s]		X[s]	X[s]
Survival Data							X[t]

	Screening[a]	Treatment Period				Follow-up	
		Cycles 1-8		Cycle 9+		Short Term Follow-up	Long Term Follow-up
Day	**NA**	**Day 1 (±3)**	**Day 8 (±3)[b,d]**	**Day 1 (±3)[b,d]**	**Day 8 (±3)[b,d]**	**30 days (±7) after last dose**	
Other Assessments							
PK Assessment	See Attachment 7 for specific time points						
Biomarker Assessment	See Attachment 7 (plasma sample)						
Biopsy/Tumor Tissue Submission[u]	X						
Health Outcomes Measures							
mBPI-sf[v]		X		X		X	X
EORTC QLQ C30[v]		X		X		X	X
EQ-5D-5L[v]		X		X		X	X
Clinical Drug Supplies							
Administer olaratumab/ placebo		X	X	X	X		
Administer doxorubicin		X[w]					
Administer dexrazoxane		X[x]					

a All screening evaluations are performed within 14 days prior to randomization, unless otherwise specified. Upon completion of all screening evaluations to confirm a patient's eligibility, the site will register the patient by the IWRS.

b Evaluations, except vital signs must be done on the day of study drug administration.

c Screening evaluations done within 7 days prior to Cycle 1 Day 1 (C1D1) do not have to be repeated unless otherwise specified. Laboratory assessments may be done within 7 days prior to D1 of each cycle.

d In case of dose interruption, these evaluations will also be done at minimum frequency every 21 days (±3 days).

e Written informed consent must be obtained prior to any study-specific screening evaluations. Baseline radiographic assessment of disease will be performed within 21 days prior to randomization; scans performed prior to the date of consent may be used provided they are within 21 days of C1D1.

f Serum β-HCG pregnancy test (women of childbearing potential only) within 7 days prior to randomization. If the serum pregnancy test performed for inclusion purposes is positive, confirm by repeating the serum and performing a urine pregnancy test.

g Urine pregnancy test on D1 of every cycle or per local practice (whichever is of shorter duration) and at short-term follow-up visit. If the urine pregnancy test performed on D1 of the cycle is positive, confirm with a serum pregnancy test.

h Within 28 days prior to randomization.

i Echocardiograms or MUGA scans must be performed prior to treatment within 7 days prior to Day 1 of Cycle 5 and 7, at the end of Cycle 8, and when clinically indicated. After Cycle 9, perform ECGs, echocardiograms or MUGA scans every 3 cycles until PD or treatment discontinuation, whichever comes first.

j Perform every other cycle.
k Physical exam includes height (Screening only), weight, and BSA measurement.
l Vital sign measurements include temperature, pulse rate, and blood pressure.
m Obtain vital signs prior to and after the completion of the olaratumab/placebo infusion and within one hour after completion of the doxorubicin infusion. For patients taking dexrazoxane, obtain vital signs prior to dexrazoxane.
n All AEs considered at least possibly-related to study treatment will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.
o Concomitant medications will be recorded including any taken within 30 days prior to study medication.
p When possible, an immunogenicity sample will be collected at the same time as the PK sample. If a patient experiences an infusion-related reaction (IRR) to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
q Performed every 6 weeks (±7 days) (or as clinically indicated for coagulation profile and UA).
r Includes a routine urinalysis (UA), and if clinically indicated, a microscopic analysis. If routine analysis indicates > 2+ proteinuria, then a 24-hour urine must be collected and must demonstrate ≤ 1000 mg of protein in 24 hours.
s Imaging studies and tumor assessments are be obtained every 6 weeks (±7 days), irrespective of treatment cycles as calculated from randomization, until documented progression for patients with CR, PR, or SD, and/or for patients who have discontinued study treatment due to toxicity or reasons other than PD.
t Following PD, patients will be contacted every 2 months (±7 days) to obtain survival information and subsequent anticancer treatment (if applicable) for the first 2 years, then every 6 months (±14 days) until the patient's death or overall study completion.
u Mandatory archived tumor tissue or tumor tissue from biopsy (if adequate archived samples are unavailable) for biomarkers and tumor type (refer to Section 10.4.2.3 for details).
v The Patient Reported Outcomes (PRO) Measures will be collected on Day 1 of every cycle and at the 30-day short term follow-up visit. A full due diligence will be taken to collect PRO measures during long-term follow-up (every 6 weeks [±7 days] until PD, thereafter every 2 months [±7 days] for the first 2 years, then every 6 months [±14 days] until the patient's death or overall study completion).
w Administered to all patients for the first 8 cycles (unless previous unacceptable toxicity).
x Dexrazoxane is recommended for all patients receiving 5 or more cycles of doxorubicin.

Study Schedule, Protocol I5B-MC-JGDJ

Perform procedures as indicated.

Continued Access Period Schedule

		Study Period	Continued Access Treatment Period	Continued Access Follow-Up Period	
		Cycle	X-Y	Follow-Up	
		Visit	501-5XX	901	
		Duration	1	30 ± 7 days	
Procedure Category	**Protocol Section**	**Procedure**			**Comments**
Adverse Events Collection/CTC AE Grading		Toxicity assessment	X	X	All AEs/SAEs will be followed for up to 30 days after the patient and investigator agree that the patient will no longer continue study treatment.
Concomitant meds/premed-ications			X		
Lab/Diagnostic Tests		Immunogenicity/Pharmacokinetics	X	X	If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
Study Treatment		Administer olaratumab	X		

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; IRR = infusion-related reaction; PK = pharmacokinetics.

Continued access follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment in the continued access period, and lasts until the continued-access follow-up visit is completed, approximately 30 days (±7 days) later.

Attachment 2. Protocol JGDJ Clinical Laboratory Tests

All laboratory screening evaluations are to be performed within 14 days prior to randomization, unless otherwise specified. On-study clinical laboratory tests assayed for patient safety (such as hematology, serum chemistry, coagulation, and pregnancy tests) are to be collected prior to study treatment.

Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a,b]
Hemoglobin	**Serum Concentrations of the following:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT)
Neutrophils	Aspartate aminotransferase (AST)
Lymphocytes	Gammaglutamyl transferase
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Glucose, random
Coagulation Test[a]	Albumin
Prothrombin time (PT)	Total protein
International normalized ratio (INR)	Chloride
	Thyroid-stimulating hormone
Urinalysis[a]	Direct bilirubin
Specific gravity	
pH	**Pregnancy test**[a,e]
Protein	
Glucose	**Follicle-stimulating hormone (FSH)**[a,f]
Ketones	
Blood	**Exploratory Biomarker Tests**[d]
Urine leukocyte esterase	Refer to Section 10.4.2
Other[d]	
Immunogenicity samples	
PK samples	

Abbreviations: WOCBP = women of childbearing potential

a Assayed by local or investigator-designated laboratory

b Duplicate samples will also be assayed by Lilly-designated laboratory.

c If urinary protein is ≥2+ at evaluations, a 24-hour urine collection (to assess protein) must be collected and must be ≤1000 mg of protein in 24 hours.

d Assayed by a sponsored-designated (central) laboratory. Refer to Attachment 7.

e Serum pregnancy test will be performed at screening in females of childbearing potential only (if the baseline serum test is positive, a repeat serum and urine pregnancy test will be done; if those results are positive, the investigator is to consult with the Lilly CRP regarding if dosing should occur and which follow-up laboratory tests are performed). While on-study, urine pregnancy test will be performed in females of childbearing potential only on D1 of every cycle or per local practice (whichever is of shorter duration) and at short-term follow-up visit. If the serum pregnancy test performed for inclusion purposes is positive confirm by repeating the serum and performing a urine pregnancy test. If the urine pregnancy test performed on D1 of each cycle is positive, confirm with a serum pregnancy test.

f Performed only at screening in menopausal women that have experienced spontaneous amenorrhea for 6 to 12 months. To be done for women only when needed to confirm postmenopausal status.

Attachment 3. Protocol JGDJ Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; IgG =immunoglobin G; IgM = immunoglobin M; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

[a] Assayed by Lilly-designated laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 4. Protocol JGDJ ECOG Performance Status

ECOG Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead.

Source: Oken et al. 1982.

Attachment 5. Protocol JGDJ Creatinine Clearance Formula

Note: This formula is to be used for calculating creatinine clearance (CrCl) from **local laboratory results only.**

For serum creatinine concentration in mg/dL:

$$\textbf{CrCl} = \frac{(\textbf{140} - \textbf{age}^{a}) \times (\textbf{wt}) \times \textbf{0.85} \text{ (if female), or } \times \textbf{1.0} \text{ (if male)}}{\textbf{72} \times \textbf{serum creatinine } (mg/dL)} \quad (\text{mL/min})$$

For serum creatinine concentration in μmol/L:

$$\textbf{CrCl} = \frac{(\textbf{140} - \textbf{age}^{a}) \times (\textbf{wt}) \times \textbf{0.85} \text{ (if female), or } \times \textbf{1.0} \text{ (if male)}}{\textbf{0.81} \times \textbf{serum creatinine } (\mu mol/L)} \quad (\text{mL/min})$$

[a] age in years, weight (wt) in kilograms.

Reference: Cockcroft and Gault 1976.

Attachment 6. Protocol JGDJ RECIST Criteria 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable
Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable
All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the case record form (CRF) in millimeters (or decimal fractions of centimeters [cm]).

Nontarget Lesions

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR). Specific guidelines for both prostate-specific antigen (PSA) response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can

remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

Pet Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

Partial Response (PR): At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Nontarget Lesions

Complete Response: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10mm short axis).

Non-CR/ non-PD: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The Best Overall Response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table 1. Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; PR = partial response; SD = stable disease.; PD = progressive disease; NE = inevaluable.

Table 2 is to be used when patients have *nonmeasurable* disease only.

Table 2. Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease ; NE = inevaluable.

[a] non-CR/non-PD is preferred over SD for nontarget disease.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6-8 weeks is reasonable. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed.

In *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 5 weeks measured from randomization..

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Independent Review of Response and Progression

When objective response (CR + PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Attachment 7. Protocol JGDJ Pharmacokinetic, Immunogenicity, and Translational Research Sampling Schedule

It is essential that the exact infusion start and stop times (actual clock readings), as well as infusion parameters (such as, type of infusion pump, flow rate settings) are recorded. The exact time of collection of each venous blood sample will be based on the clock used to record infusion times. It is essential that the pharmacokinetic blood samples not be withdrawn from the same site as the drug infusion.

For samples collected within the first 24 hours, sample collection times may vary ±10% or as specified in the PK sampling schedule.

Pharmacokinetic and Immunogenicity Sampling Schedule

Sample Number	Cycle	Day	Sampling Time	Olaratumab PK[a]	Doxorubicin PK[b]	IG[c]	IG/PK (IRR)[d]
1	1	1	Predose	X		X	X
2			Within 5 min post olaratumab infusion	X			
3		8	Within 15 min prior to olaratumab/placebo infusion	X		X	
4			Within 5 min post olaratumab/placebo infusion	X			
5	2	1	Within 15 min prior to olaratumab/placebo infusion	X			
6			Within 5 min post doxorubicin infusion	X	X		
7		8	Within 15 min prior to olaratumab/placebo infusion	X		X	
8			Within 5 min post olaratumab/placebo infusion	X			
9	3	1	Within 15 min prior to olaratumab/placebo infusion	X		X	
10	4	1	Within 15 min prior to olaratumab/placebo infusion	X		X	
11			Within 5 min post doxorubicin infusion	X	X		
12		8	Within 15 min prior to olaratumab/placebo infusion	X			
13			Within 5 min post olaratumab/placebo infusion	X			
14	5	1	Within 15 min prior to olaratumab/placebo infusion	X		X	
15	6	1	Within 5 min post doxorubicin infusion		X		
16	7	1	Within 15 min prior to olaratumab/placebo infusion	X		X	
17	8	1	Within 5 min post doxorubicin infusion		X		
18	9 and then every other cycle	1	Within 15 min prior to olaratumab/placebo infusion	X		X	
801	30-day follow-up visit	--	Anytime	X		X	

Abbreviation: PK = pharmacokinetic; IG = Immunogenicity

a Samples of approximately 3 mL of whole blood will be drawn into plastic tubes without anticoagulant for measurement of olaratumab in serum in plasma.

b Samples of approximately 3 mL of whole blood will be drawn into plastic tubes without anticoagulant for measurement of doxorubicin in plasma.

c For the immunogenicity assay, approximately 6 mL of whole blood will be drawn into plastic tubes without anticoagulant to generate serum samples.

d For any unscheduled blood draws due to infusion-related reactions (IRR), approximately 4 mL of whole blood will be drawn into plastic tubes without anticoagulant to generate serum samples. If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.

Translational Research Sampling Schedule

Sample Number	Cycle	Day	Sampling Time	Plasma for Biomarkers[a]	Whole blood[b]	Tumor Tissue[c]
1	1	1	Predose	X	X	X
10	3	1	Within 15 min prior to olaratumab infusion	X		
801	30-day follow-up visit		Anytime	X		

a Refer to Section 10.4.2.1 for details on whole blood for plasma collection.

b Refer to Section 10.4.2.2 for details on whole blood for DNA collection. It is highly recommended to draw the whole blood sample prior to the first dose. However, it can be collected later during the study if necessary.

c Refer to Section 10.4.2.3 for details on tumor tissue collection.

Attachment 8. Protocol JGDJ CYP3A4, CYP2D6, and P-gp Inhibitors and Inducers of Doxorubicin

CYP3A4 Inducers	Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors
Aminoglutethimide	Clarithromycin	Amiodarone
Bosentan	Chloramphenicol	Amprenavir
Carbamazepine	Cobicistat	Aprepitant
Efavirenz (in liver only)	Conivaptan	Atazanavir
Fosphenytoin	Cremophor EL	Cimetidine
Nafcillin	Cyclosporine	Ciprofloxacin
Nevirapine	Delavirdine	Clotrimazole
Oxcarbazepine	Diclofenac	Darunavir
Pentobarbital	Diltiazem	Darunavir and ritonavir
Phenobarbital	Elvitegravir and ritonavir	Desipramine
Phenytoin	Enoxacin	Doxycycline
Primidone	Erythromycin	Dronedarone
Rifabutin	Fosamprenavir	Efavirenz
Rifampin	Grapefruit juice	Erythromycin
Rifapentine	Indinavir	FK1706
St. John's wort	Indinavir and ritonavir	Fluconazole
	Itraconazole	Fluvoxamine
	Ketoconazole	Haloperidol
	Lopinavir and ritonavir	Imatinib
	Mibefradil	Metronidazole
	Miconazole	Norfloxacin
	Nefazodone	Protease inhibitors
	Nelfinavir	Quinidine
	Nicardipine	Schisandra sphenanthera extract
	Posaconazole	Sertraline
	Quinidine	Tetracycline
	Ritonavir	Tofisopam
	Saquinavir	Verapamil
	Telithromycin	
	Theophylline	
	Troleandomycin	
	Voriconazole	

CYP2D6 Inducers	CYP2D6 Inhibitors	P-glycoprotein 1 (P-gp) Inhibitors
Dexamethasone	Amiodarone	Amiodarone
Rifampin	Celecoxib	Azithromycin
	Chloroquine	Captopril
	Chlorpromazine	Clarithromycin
	Cimetidine	Cyclosporine
	Citalopram	Piperine
	Clomipramine	Quercetin
	Codeine	Quinidine
	Deiavirdine	Quinine
	Desipramine	Reserpine
	Dextroprpoxyphene	Ritonavir
	Diltiazem	Tariquidar
	Doxorubicin	Verapamil
	Entacapone (high dose)	
	Fluoxetine	
	Fluphenazine	
	Fluvaxamine	
	Haloperidol	
	Labetalol	
	Lobeline	
	Lomustine	
	Methadone	
	Mibefradil	
	Moclobemide	
	Nortuloxeline	
	Paroxetine	
	Perphenazine	
	Propafenone	
	Quinacrine	
	Quinidine	
	Ranitadine (ranitidine, Zantac)	
	Risperidone (weak)	
	Ritonavir	
	Serindole	
	Sertraline (weak)	
	Thioridazine	
	Valproic acid	
	Venlafaxine (weak)	
	Vinblastine	
	Vincristine	
	Vinorelbine	
	Yohimbine	