

Protocol (d) 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

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Approval Date: 12-Jan-2017

1. Protocol I5B-MC-JGDJ(d)

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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Olaratumab (LY3012207)

I5B-MC-JGDJ is a global, multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 trial that will compare the safety and efficacy in patients with advanced or metastatic STS after treatment with doxorubicin (75 mg/m² on Day 1) plus olaratumab (loading dose of 20 mg/kg on Days 1 and 8 in Cycle 1, followed by 15 mg/kg on Days 1 and 8 in subsequent cycles) versus doxorubicin (75 mg/m² 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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Amendment (d) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 12-Jan-2017 GMT

2. Synopsis

Study Rationale

This Phase 3 study is a global, multicenter, randomized, double-blind, placebo-controlled, parallel-group 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 >8 cycles.

Clinical Protocol Synopsis: Study I5B-MC-JGDJ

Name of Investigational Product: Olaratumab (LY3012207)	
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	
Number of Planned Patients: Entered/Screened: Approximately 600 Enrolled/Randomized: Approximately 460 Completed (number of patients who will complete the overall survival [OS] endpoint): Approximately 322	Phase of Development: 3
Length of Study: Approximately 4 years First patient visit: 14-Sep-2015 Planned last patient visit (excluding the continued access period): 3Q2019 Planned interim analysis: 60% (at least 194 overall survival [OS] events from the intention-to-treat [ITT] population)	
<p>Objectives: The primary objective is to compare doxorubicin plus olaratumab versus doxorubicin plus placebo with respect to OS in 2 populations:</p> <ol style="list-style-type: none"> (1) Patients with advanced or metastatic soft tissue sarcoma (STS) not amenable to treatment with surgery or radiotherapy with curative intent (2) Patients with advanced or metastatic leiomyosarcoma (LMS) not amenable to treatment with surgery or radiotherapy with curative intent <p>The secondary objectives of the study are to compare doxorubicin plus olaratumab versus doxorubicin plus placebo with respect to:</p> <ul style="list-style-type: none"> • Progression-free survival (PFS) • Objective response rate (ORR) (complete response [CR] + partial response [PR]) • Disease control rate (DCR; CR + PR + stable disease [SD]) • Patient-reported outcomes (PROs): Pain, Health-related Quality of Life (HRQoL), and health status • Duration of response (DoR) • Duration of disease control (DDC) • Safety and tolerability • Pharmacokinetics (PK) and immunogenicity <p>Additional prespecified objectives include, but are not limited to:</p> <ul style="list-style-type: none"> • Assessment of the association between biomarkers and clinical outcomes • Assessment of the association between clinical variables, such as histological subtypes, and clinical outcomes 	
<p>Study Design: Study I5B-MC-JGDJ is a global, multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 trial that will compare the efficacy and safety in patients with advanced or metastatic STS treated with doxorubicin (75 mg/m² on Day 1) plus olaratumab (loading dose of 20 mg/kg on Days 1 and 8 in Cycle 1, followed by 15 mg/kg on Days 1 and 8 in subsequent cycles) versus doxorubicin (75 mg/m² 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:</p> <ul style="list-style-type: none"> • Number of prior systemic therapies for advanced/metastatic disease (0 versus ≥1) <p>Note: Any therapy administered in the adjuvant/neoadjuvant setting will not be considered as a prior line of</p>	

therapy here.

- Histological tumor type (leiomyosarcoma versus liposarcoma versus undifferentiated pleomorphic versus other STS types)
- Eastern Cooperative Oncology Group performance status (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.

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 a loading dose of 20 mg/kg on Days 1 and 8 in Cycle 1, followed by 15 mg/kg on Days 1 and 8 in subsequent cycles. 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/m²) is to be administered on Day 1 of each 21-day cycle, for 8 cycles. Dexrazoxane: Commercially available dexrazoxane may be administered starting at Cycle 1 at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion, prior to the 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): Patients who discontinue study treatment for reasons other than progression will be followed 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 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 (SAP; 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 SAP.

- Progression-free survival (PFS)
- Objective Response Rate (ORR)
- Disease Control Rate (DCR)

- Time to first worsening of the mBPI-sf (Brief Pain Inventory Short Form Modified) “worst pain” score
- Duration of response (DoR)
- Duration of disease control (DDC)
- 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 QLQ-C30 scale 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
- Second PFS (PFS2) after end of study treatment while on subsequent anticancer therapy

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 3 months [±2 weeks] for the first year, every 6 months [±2 weeks] the second year, then annually [±2 weeks] thereafter 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/placebo infusion-related reaction (IRR) serum will be collected as soon as possible after the onset, at the resolution, and 30 days (±3 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 doxorubicin plus olaratumab (investigational arm) versus doxorubicin plus placebo (control arm) with respect to OS in 2 populations:

- (1) Patients with advanced or metastatic STS not amenable to treatment with surgery or radiotherapy with curative intent (referred to below as the ITT population)
- (2) Patients with advanced or metastatic LMS not amenable to treatment with surgery or radiotherapy with curative intent

The study will be considered positive if either the ITT or LMS populations (or both) show a statistically significant improvement in OS.

Investigative sites will screen approximately 600 patients to enroll 460 patients in 1:1 randomization (230 patients in the investigational arm and 230 patients in the control arm). Enrollment will be conducted so that approximately 200 patients with LMS and 260 patients with other (non-leiomyosarcoma) histology will be randomized. The final analysis will occur only after both a minimum of 131 OS events have been observed in randomized patients with LMS, and a minimum of 322 OS events have been observed in randomized patients overall.

The statistical analysis will be conducted using a statistical testing plan according to the graphical method of Maurer and Bretz (2013). Under this testing scheme, the primary analysis for OS can be tested in both the LMS population

and in the full ITT population, splitting and sharing alpha so as to control the family-wise type 1 error rate across these 2 populations, across interim and final analyses, and also across a prespecified sequence of endpoints (OS and selected secondary endpoints).

The Lan-DeMets form of the O'Brien-Fleming alpha-spending function will be applied for OS and each selected secondary endpoint.

The final total of 131 OS events in the LMS population provides 80% statistical power for a one-sided log-rank test at a 0.005 alpha level, assuming the true OS hazard ratio (HR) in LMS patients is 0.55.

The final total of 322 OS events in the ITT population provides 80% statistical power for a one-sided log-rank test at a 0.02 significance level, assuming the true OS HR in STS patients is 0.723.

An interim efficacy analysis for OS is planned after 194 OS events (60% of the final OS events) have been observed in the ITT population. Time to event analyses at the interim and final analysis time points will be based on the stratified log-rank test, stratified by the randomization strata: number of prior systemic therapies for advanced/metastatic disease (0 versus ≥ 1), histological tumor type (leiomyosarcoma versus liposarcoma versus undifferentiated pleomorphic versus other STS types), and ECOG PS (0 versus 1). The exact testing boundaries will depend on the exact number of events and 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). All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint.

The interim analysis 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 analysis.

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 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 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 graded using CTCAE version 4.0. Other safety data, such as laboratory tests, ECGs, echocardiogram (ECHO) or MUGA scans, 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.

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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.
AESI	adverse event of special interest
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).
β-HCG	beta human chorionic gonadotropin
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
DDC	duration of disease control
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
H₀	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: <ol style="list-style-type: none"> 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 <p>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.</p>
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
LMS	leiomyosarcoma
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 investigational 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
UK	United Kingdom
ULN	upper limit 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 United Kingdom (UK) and United States (US), respectively, of 3300 (ESMO 2014) and 10,000 (ACS 2014). Soft tissue sarcoma 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 STS. A recent Phase 3 trial performed by the European Organization for the Research and Treatment of Cancer (EORTC) randomized patients with STS 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 (PFS) compared with those randomized to single agent doxorubicin. However, there was no significant difference in overall survival (OS) between the 2 treatment arms. In view of these findings, single-agent doxorubicin is considered the standard treatment option for many patients with metastatic STS (NCCN 2011; ESMO 2014; Schöffski et al. 2014). Doxorubicin and ifosfamide are often reserved for patients with symptomatic disease or for those in whom 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 PFS or OS (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 alpha (PDGFR α). This antibody possesses high affinity binding for PDGFR α 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/PDGFR α 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 PDGFR α on tumor tissues, including osteosarcoma, chondrosarcoma, prostate cancer, breast cancer, ovarian cancer, and others. In malignant disease, the PDGF/PDGFR α axis is effective in promoting tumor growth and proliferation through both autocrine and paracrine mechanisms. PDGFR α is expressed on stromal cells, as well as the cancer cells themselves, within certain tumors. Furthermore, studies have shown that PDGF/PDGFR α 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 (Study I5B-MC-JGDG [JGDG]), titled 'A Phase 1b/2 Randomized Phase 2 Study Evaluating the Efficacy of Doxorubicin With or Without a Human Anti-PDGFR α Monoclonal Antibody (IMC-3G3) in the Treatment of Advanced Soft Tissue Sarcoma.' The investigational 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. As of a data cutoff date of 16 May 2015, the combination of olaratumab and doxorubicin in this trial showed a statistically significant and clinically meaningful improvement in median OS (11.8-month improvement; hazard ratio [HR]=0.463; p=0.0003) over doxorubicin alone. Furthermore, in the primary analysis (using the intention-to-treat [ITT] population based on investigator assessment), the study met the protocol-defined final significance level for PFS (2-sided alpha=0.1999). The combination of olaratumab and doxorubicin improved median PFS by 2.5 months over doxorubicin alone (stratified HR=0.672 [95% confidence interval (CI): 0.442, 1.021]; p=0.0615), corresponding to a 32.8% reduction in the risk of progression or death. Grade ≥ 3 treatment-emergent adverse events (TEAEs) were reported in 79.7% of patients in the investigational Arm A and 69.2% of patients in the control Arm B. Grade ≥ 3 adverse events (AEs) occurring in at least 10% of patients in Arm A included *neutropenia* (consolidated term), *anemia* (consolidated term), and febrile neutropenia. In Arm B, the Grade ≥ 3 AEs occurring in at least 10% of patients included febrile neutropenia and *neutropenia* (consolidated term). The safety profile of the combination of olaratumab and doxorubicin was consistent with the known toxicities of doxorubicin.

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 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 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.

5.3.1. Olaratumab Dose Rationale

The current dose-selection strategy for Phase 3 Study JGDJ is based on the integrated safety, efficacy, and PK data for olaratumab across previous Phase 1 and Phase 2 studies.

In 2 Phase 1 dose-escalation trials (JGDC and JGDF) and in the 2 Phase 2 monotherapy studies (JGDE and JGDH), single-agent olaratumab has consistently been well tolerated, with no dose-limiting toxicities observed up to a dose of 20 mg/kg administered every 2 weeks and up to a dose of 15 mg/kg administered of Day 1 and Day 8 of a 21-day cycle. When used in combination with liposomal doxorubicin in Study JGDA (olaratumab dose of 20 mg/kg every 2 weeks), and with paclitaxel/carboplatin in Study JGDB (olaratumab dose of 15 mg/kg Day 1 and Day 8 every 3 weeks), a higher rate of toxicities such as neutropenia and infections was observed versus the comparator agents. In Study JGDG, an increase in neutropenia and mucositis, but not in neutropenic sepsis or febrile neutropenia, has been observed compared to single-agent doxorubicin. Overall, these toxicities are consistent with the toxicity profile of the combination agents used, and are considered monitorable and acceptable for the patient populations studied.

Interim survival data from Study JGDG show the combination of olaratumab 15 mg/kg with doxorubicin 75 mg/m² provides a significant benefit compared to single-agent doxorubicin in patients with advanced metastatic STS without an increase in serious toxicity. A matched case-control analysis per exposure quartiles based on the trough olaratumab serum concentration at the end of Cycle 1 ($C_{\min,1} < 61 \mu\text{g/mL}$, N=15) tend to experience disease progression within the first 2 cycles of treatment, and unlike the other quartiles, did not show PFS or OS improvement. Interim results from a population PK (PopPK) model performed on PK data from 4 studies (JGDB, JGDE, JGDG, and JGDH) indicate that steady-state olaratumab serum levels are not achieved until Cycle 3. Together, these findings suggest that clinical outcome for the lowest exposure quartile could be improved if patients were able to achieve therapeutic steady-state serum concentration levels ($C_{\min,1} \geq 61 \mu\text{g/mL}$) of olaratumab earlier in treatment, before disease progression.

Simulations performed with the current PK model indicate that loading doses of 20 mg/kg administered on Day 1 and Day 8 of Cycle 1 would allow steady-state olaratumab serum levels to be achieved with the first administration and would minimize the number of patients whose $C_{\min,1}$ falls below 61 $\mu\text{g/mL}$ during the first 2 cycles. Additionally, a dose of 20 mg/kg

olaratumab administered on Day 1 and Day 8 during the first cycle, followed by 15 mg/kg administered on Day 1 and Day 8 of all the subsequent cycles, is predicted to yield maximum serum concentrations within the overall range observed in Study JGDG. Therefore, olaratumab safety risks related to high serum concentrations or exposure using this loading dose approach are expected to be similar to those in Study JGDG.

The dosing strategy adopted for Study JGDJ therefore consists of a loading cycle wherein a dose of 20 mg/kg will be administered on Day 1 and Day 8, followed by 15 mg/kg administered on Day 1 and Day 8 of every subsequent cycle. This dosing strategy is expected to minimize the number of patients exposed to sub-therapeutic olaratumab serum levels without an increased risk of toxicity, thereby optimizing the benefit-risk ratio.

5.4. Rationale for Amendments

5.4.1. Rationale for Amendment (a)

The rationale for amendment (a) was based on feedback received from global regulatory authorities and compliance with local regulatory requirements for submissions. Major changes for amendment (a) included the following:

- Leiomyosarcoma (LMS) was added as a specific population to be tested within the primary objective, and is now co-primary with the STS (ITT) population.
- Pleomorphic was added to the stratifications factors
- Due to regional/institutional differences dexrazoxane dosing was modified
- PFS2 was added to the efficacy endpoints
- Cardiovascular monitoring was increased
- Gatekeeping methods have been included for OS, PFS, ORR, and DoR
- Grade 1 liposarcoma patients are now included under certain conditions
- The olaratumab dosing regimen was modified
- Management of infusion-related reactions was modified
- Single interim analysis will be performed based on 60% of overall OS events (194) in the ITT population and 72 events from the LMS
- Analysis of OS will be based on the stratified log-rank test analyzed by the randomization strata, excluding region.

5.4.2. Rationale for Amendment (b)

The rationale for amendment (b) was based on global regulatory authority feedback, regulatory guidance and compliance with local regulatory requirements for submissions. Additional changes were made by the sponsor to address issues of subject safety and to improve the efficiency of study implementation and conduct. Major changes for amendment (b) included the following:

- Exclusion criteria were deleted
- Grade 4 nonhematologic toxicity as related to study therapy is now considered a basis for study drug discontinuation

- Duration of Response was deleted from secondary objectives.
- O'Brien-Fleming alpha spending will now be used for all efficacy boundaries
- bisphosphonate osteoclast inhibitors are now allowed, denosumab is still not permitted.

5.4.3. Rationale for Amendment (c)

The rationale for amendment (c) was based on global regulatory authority feedback, regulatory guidance and compliance with local regulatory requirements for submissions. Additional changes were made by the sponsor to address issues of subject safety and to improve the efficiency of study implementation and conduct. Major changes for amendment (c) included the following:

- Germany was directed to refer to Addendum (7)

5.4.4. Rationale for Amendment (d)

The rationale for amendment (d) was to increase subject safety and to improve the efficiency of study implementation and conduct. Major changes for amendment (d) included the following:

- Patients receiving anticoagulants are now eligible to participate
- Long-term follow-up for survival and patient reported outcome collection were updated so that these events are concurrent with the collection of ECG data
- Efficacy interim stopping rules were removed from the protocol plan, as the intention is to continue the study until the final analysis with the sponsor remaining blinded to aggregate data by study arm until the final analysis.
- Urine protein creatinine ratio of spot urine can now be used in place of 24-hour urine protein excretion

See [Attachment 9](#) for more details.

6. Objectives

6.1. Primary Objective

The primary objective is to compare doxorubicin plus olaratumab versus doxorubicin plus placebo with respect to OS in 2 populations:

- (1) Patients with advanced or metastatic STS not amenable to treatment with surgery or radiotherapy with curative intent
- (2) Patients with advanced or metastatic leiomyosarcoma (LMS) 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:

- PFS
- Objective response rate (ORR) (complete response [CR] + partial response [PR])
- Disease control rate (DCR) (CR + PR + stable disease [SD])
- Patient-reported Outcomes (PROs): Pain, Health-related Quality of Life (HRQoL), and health status
- Duration of response (DoR)
- Duration of disease control (DDC)
- 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 by local pathology review 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. The duration of the screening period is 14 days for the majority of procedures ([Attachment 1](#)); certain noted procedures may be performed within 28 days of randomization. Individuals who do not meet the criteria for participation in this study within the extended 28-day screening period (screen failure) may be re-screened. Note that repeating laboratory tests during the 28-day screening period does not constitute re-screening. Screening laboratory tests may not be repeated more than once to meet eligibility during the 28-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 STS not amenable to curative treatment with surgery or radiotherapy. Patients with a diagnosis of Grade 1 liposarcoma are eligible if there is histological or radiographic evidence of evolution to more aggressive disease. Patients with Kaposi's sarcoma and gastrointestinal stromal tumors (GIST) will be excluded.

Note: Evidence of disease progression is required for patients that are not newly diagnosed.

- [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 and are considered appropriate candidates for anthracycline therapy. All previous anticancer treatments must be completed ≥ 3 weeks (21 days) prior to first dose of study drug.
- [8] The patient has resolution of adverse events and of all clinically significant toxic effects of prior locoregional therapy, surgery, radiotherapy, or systemic anticancer therapy to \leq Grade 1, by National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0.
- [9] Availability of tumor tissue is mandatory for study eligibility. The patient must have consented to provide archived formalin-fixed paraffin embedded (FFPE) tumor tissue or be subject to a pre-treatment re-biopsy of primary or metastatic tumor tissue for future central pathology review and translational research (if archived tissue is unavailable) (refer to Section [10.4.2.3](#) regarding tissue collection parameters).
- [10] The patient has adequate hematologic, organ, and coagulation function within 2 weeks (14 days) prior to randomization:
- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$. Granulocyte colony-stimulating factor (G-CSF) cannot be administered within 2 weeks (14 days) prior to randomization.
 - Platelet count $\geq 100 \times 10^9/L$
 - Hemoglobin ≥ 9.0 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 Cockcroft-Gault formula)
 - Proteinuria ≤ 1000 mg in 24 hours (if routine urinalysis indicates $\geq 2+$ proteinuria)
 - Total bilirubin below upper limit of normal (ULN) (except for patients with Gilbert's Syndrome, who must have a total bilirubin < 3 mg/dL)
 - Alanine aminotransferase/aspartate aminotransferase (AST/ALT) $\leq 3.0 \times$ ULN; if the liver has tumor involvement, AST and ALT $\leq 5.0 \times$ ULN are acceptable.
 - The patient has an adequate coagulation function as defined by International Normalized Ratio (INR) or prothrombin time (PT) $\leq 1.5 \times$ ULN, and partial thromboplastin time (PTT or aPTT) $\leq 1.5 \times$ ULN if not receiving anticoagulation therapy. For patients receiving anticoagulants, exceptions to these coagulation parameters are allowed if they are within the intended or expected range for their therapeutic use. Patients must have no history of active bleeding (defined as within 14 days of first dose of study drug) or pathological condition that carries a

high risk of bleeding (for example, tumor involving major vessels or known esophageal varices).

- [11] The patient has left ventricular ejection fraction (LVEF) $\geq 50\%$ assessed within 28 days prior to randomization.
- [12] Females of child-bearing potential must have a negative serum pregnancy test within 7 days prior to randomization.
- (a) Exceptions: 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 6 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.
- [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 or anthracenediones; the patient has received treatment with olaratumab or has participated in a prior olaratumab trial.
- [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 nonhematologic 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] Exclusion criterion [23] has been deleted.
- [24] The patient has a QTcB interval of >450 msec for males and >470 msec for females on screening electrocardiogram (ECG) utilizing Bazett's correction (refer to formula in [Table JGDJ.7](#)).
- [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 study treatment from another trial involving an investigational agent or use of non-approved drug or device within 28 days of being randomized in this trial, 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] Exclusion criterion [28] has been deleted.
- [29] The patient has a known investigator-assessed active fungal, bacterial, or 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

For sites in Germany: this section is replaced by Section 7.3.1 as laid down in protocol addendum, I5B-MC-JGDJ(7), dated 04 November 2015 in Annex to this protocol.

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/CRS 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 or Sponsor decision
 - the investigator/physician or Lilly, for any reason, but considering the rights, safety, and well-being of the patients(s) and in accordance with International Conference on Harmonisation (ICH) / Good Clinical Practices (GCP) guidelines and local regulations, stops the study or stops the patient's participation in the study
 - if the patient, for any reason, requires treatment with another therapeutic agent or procedure 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
- evidence of progressive disease
- unacceptable toxicity
- pregnancy
- 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 (for example, by phone calls, certified letters, etc.) 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. Prior to discontinuation, the ERB (which approved the trial) will be notified according to local regulation.

8. Investigational Plan

8.1. Summary of Study Design

Study I5B-MC-JGDJ is a global, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 trial in patients with advanced or metastatic STS who are doxorubicin naïve but who may have had any number of prior systemic cytotoxic therapies. Previous therapy must be completed ≥ 3 weeks (21 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:

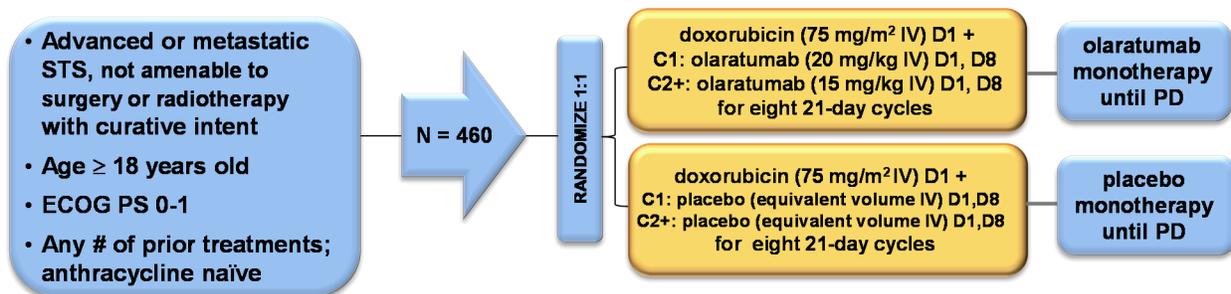
- Number of prior systemic therapies for advanced/metastatic disease (0 versus ≥ 1)
NOTE: Any therapy administered in the adjuvant/neoadjuvant setting will not be considered as a prior line of therapy here.
- Histological tumor type (leiomyosarcoma versus liposarcoma versus undifferentiated pleomorphic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

Patients assigned to the investigational arm will receive 2 loading doses of olaratumab at 20 mg/kg on Days 1 and 8 in Cycle 1 followed by doxorubicin 75 mg/m² IV on Day 1 of a 21-day cycle, then 15 mg/kg IV on Days 1 and 8 followed by doxorubicin 75 mg/m² IV on Day 1 of a 21-day cycle in all subsequent cycles. Patients assigned to the control arm will receive placebo (equivalent volume) IV on Days 1 and 8 followed by doxorubicin 75 mg/m² 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.

Starting with Cycle 1, the 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: C1 = Cycle 1; C2+ = Cycle 2 and beyond; D = day;
 ECOG PS = Eastern Cooperative Oncology Group Performance Status;
 IV = intravenous, N = number of randomized patients; PD = progressive disease;
 STS = soft tissue sarcoma.

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 (study entry) 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 electronic case report form (eCRF) 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 assessed for progression every 6 weeks (± 7 days) until PD.
 - **Follow-up for survival** - Patients will be followed every 3 months (± 2 weeks) for the first year, every 6 months (± 2 weeks) the second year, then annually [± 2 weeks] thereafter 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 olaratumab 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 randomization.

Imaging and tumor assessment will be performed every 6 weeks (± 7 days), irrespective of treatment cycles, as calculated from randomization. Imaging requirements include CT scan or magnetic resonance imaging (MRI) of chest, abdomen, and pelvis. Other areas may be scanned, when clinically indicated. Digital images are to be sent to a third-party organization (TPO) for storage. 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 72 hours (3 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 \pm 3 days). The start of study treatment will be considered Cycle 1 Day 1 (C1D1).

Patients in the investigational **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 infusion-related reaction (IRR) after the D1 and D8 infusions of olaratumab in the first 2 cycles, no observation period is required for subsequent treatment cycles. In the event that a Grade 1 or 2 IRR occurs after Cycle 2, the 1-hour observation period will be reinstated for a minimum of 2 cycles. The reinstated observation period may be suspended after 2 cycles if the patient shows no further signs or symptoms of an IRR.

- Doxorubicin (after the olaratumab administration and 1-hour observation period, if instituted) on Day 1 of every 3-week cycle administered according to institutional guidelines and/or clinical practice, as an IV injection or as an infusion to be administered in less than 60 minutes for 8 cycles. Starting with Cycle 1, dexrazoxane may be administered at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion according to instructions provided in the Pharmacy Manual for this study, beginning 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 placebo during the first 2 cycles, no observation period is required for subsequent treatment cycles. In the event that a Grade 1 or 2 IRR occurs after Cycle 2, the 1-hour observation period will be reinstated for a minimum of 2 cycles. The reinstated observation period may be suspended after 2 cycles if the patient shows no further signs or symptoms of an IRR.
- Doxorubicin (after the placebo administration and 1-hour observation period, if instituted) on Day 1 of every 3-week cycle administered according to institutional guidelines and/or clinical practice, as an IV injection or as an infusion to be administered in less than 60 minutes for 8 cycles. Starting with Cycle 1, dexrazoxane may be administered IV at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion according to instructions provided in the Pharmacy Manual for this study, beginning 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 radiological 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) as calculated from randomization until objective radiographic evidence of PD.

8.1.2. Postdiscontinuation Follow-Up Period Assessments

Postdiscontinuation short-term and long-term follow-up assessments will be conducted as described in the Study Schedule ([Attachment 1](#)). Adverse event (AE) information will be collected until at least 30 days after the last dose of study treatment. After the 30-day short-term follow-up visit, only new and ongoing SAEs deemed related to study treatment will be collected.

Long-term follow-up will continue as long as the patient is alive and has not withdrawn consent to follow-up or the study has completed (as defined in [Section 8.1.3](#)).

For patients who discontinue study treatment for any reason without objectively measured PD, imaging studies and tumor assessments are obtained every 6 weeks (± 7 days), irrespective of treatment cycles as calculated from randomization, until documented progression.

For patients that discontinue study treatment after objectively measured PD, the following information 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:

- details on all subsequent anticancer treatment (start/stop dates and treatments administered)
- first post-study treatment disease progression date
- survival status

8.1.3. Study Completion and End of Trial

[Figure JGDJ.2](#) is a diagram of the study period and continued access period. [Section 12.2.13](#) provides the details on the interim analyses. This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) once it has been determined by Lilly that the evaluation of efficacy and safety are sufficient and complete. Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred.

Upon study completion, investigators and patients may be unblinded to study treatment assignment. Patients receiving olaratumab and experiencing ongoing clinical benefit and no undue risks may continue to receive olaratumab in the continued access period. The continued access period begins after study completion and will continue until the end of trial.

“End of trial” refers to the date of the last visit or last scheduled procedure for the last patient.

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

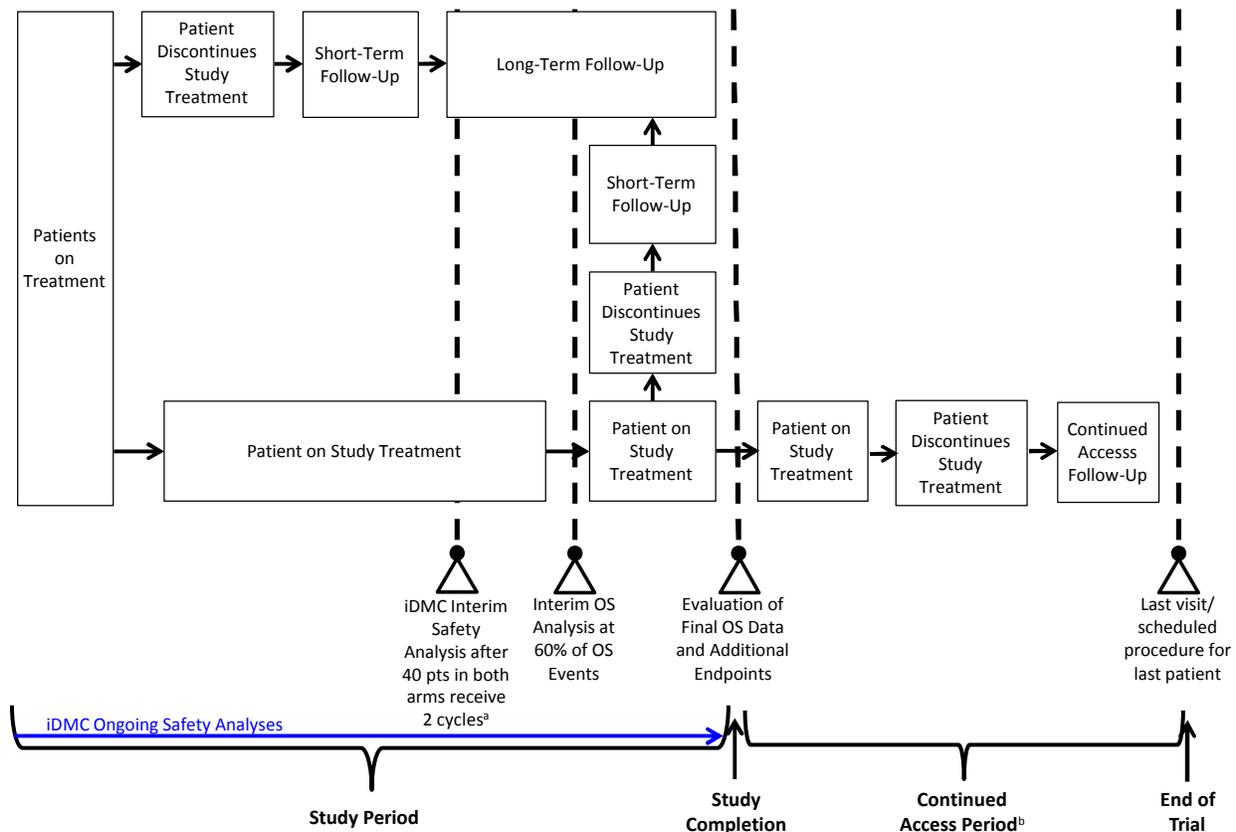


Figure JGDJ.2. Study period and continued access diagram.

8.1.4. Continued Access Period

Lilly will notify investigators when the continued access period begins and ends.

The continued access period will apply to this study only if at least 1 patient is still on olaratumab 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.

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, concomitant medication, 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 may initiate a consultation with an appropriate expert (such as cardiac) if additional expertise is needed regarding evaluation of any safety signals. The iDMC will communicate back to Lilly Senior Management Designee (SMD) about their assessment.

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

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

The first iDMC meeting to review interim data for monitoring the loading dose will occur when approximately 80 patients (approximately 40 patients from each arm) have received 2 cycles of treatment or discontinued all study treatment due to any reasons prior to Day 8 in Cycle 2.

Subsequent iDMC meetings will occur approximately every 6 months thereafter. Enrollment and treatment will continue during the iDMC safety assessments. In the event a safety signal is detected, additional meetings may occur as needed. 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

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) \pm 3 day cycle:

- Investigational Arm A: doxorubicin (75 mg/m² IV infusion) on Day 1 plus olaratumab (loading doses of 20 mg/kg IV infusion) on Days 1 and 8 of Cycle 1, followed by doxorubicin (75 mg/m² IV infusion) on Day 1 plus olaratumab (15 mg/kg IV infusion) on Days 1 and 8 of Cycles 2 to 8.
- Control Arm B: doxorubicin (75 mg/m² IV infusion) on Day 1 plus placebo (equivalent volume IV infusion) on Days 1 and 8 of Cycles 1 to 8.

Patients who complete 8 cycles of combination treatment will continue to receive olaratumab/placebo monotherapy at the same dose and schedule until there is documented disease progression, unacceptable toxicity, death, or other discontinuation criteria are met. No crossover will be permitted.

[Table JGDJ.1](#) shows the treatment regimens.

Table JGDJ.1. Treatment Regimens/Dosing Schedule

	Study Drug	Dose	Route	Timing
ARM A	Olaratumab ^a	20 mg/kg (C1) 15 mg/kg (C2+)	IV	approximately 1 hour infusion Day 1 and Day 8 of each 21-day cycle
	1-hour (+5 minutes) Observation Period ^b followed by			initial 2 cycles
	Doxorubicin ^c	75 mg/m ² (C1-C8)	IV	IV injection on Day 1 of each 21-day cycle
OR				
ARM B	Placebo ^a	equivalent volume (C1+)	IV	approximately 1 hour infusion Day 1 and Day 8 of each 21-day cycle
	1-hour (+5 minutes) Observation Period ^b followed by			initial 2 cycles
	Doxorubicin ^c	75 mg/m ² (C1-C8)	IV	IV injection on Day 1 of each 21-day cycle

Abbreviations: C = Cycle; IRR = infusion-related reaction; IV = intravenous; PO = orally.

- ^a Premedicate all patients with the following (or equivalent) medications: a histamine H1 antagonist (eg, diphenhydramine) and dexamethasone intravenously 30–60 minutes prior to the olaratumab doses on Days 1 and 8 of Cycle 1. For subsequent cycles, premedicate all patients with a histamine H1 antagonist (eg, diphenhydramine) intravenously 30–60 minutes prior to each dose of olaratumab. Additional premedication may be provided at the investigator's discretion. Premedication **must be** provided in the setting of a prior Grade 1-2 olaratumab/placebo IRR, as detailed in Section 9.4.1.1.1. All premedication administered must be adequately documented in the eCRF.
- ^b A 1-hour (+5 minutes) Observation Period is required after the administration of the initial 2 cycles of olaratumab/placebo. During the Observation Period, collect vital signs 3 times: 1) within 15 minutes (+5 minutes) prior to olaratumab/placebo infusion, 2) within 1 hour (+5 minutes) after completion of the olaratumab/placebo infusion, and 3) within 1 hour (+5 minutes) after completion of the doxorubicin infusion. If there is no evidence of an IRR during the initial 2 cycles of olaratumab/placebo, then no observation period is required for subsequent treatment cycles. In the event an IRR occurs thereafter, then the 1-hour observation period should be reinstated, see Section 9.2.1. Thereafter (Cycles 3+), obtain vital signs 2 times: 1) within 15 minutes (+5 minutes) prior to olaratumab/placebo infusion and 2) within 1 hour (+5 minutes) after completion of the doxorubicin infusion.
- ^c Administer doxorubicin according to institutional guidelines and/or clinical practice as an IV injection or as an infusion in less than 60 minutes. Decrease the rate of doxorubicin administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur. Infusion or injection start and end times will need to be recorded. Starting with Cycle 1, dexrazoxane may be administered at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion according to instructions provided in the Pharmacy Manual for this study, beginning within 30 minutes prior to the 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

Infusion-related reactions, including Grade 3-5 IRR events, have been observed with olatumab. To date, Grade 3-5 IRR events have primarily occurred during the first cycle of olatumab treatment. Therefore, premedicate all patients with the following (or equivalent) medications: a histamine H1 antagonist (eg, diphenhydramine) and dexamethasone intravenously 30–60 minutes prior to the olatumab/placebo doses on Days 1 and 8 of Cycle 1.

For subsequent cycles, premedicate all patients with a histamine H1 antagonist (eg, diphenhydramine) intravenously 30-60 minutes prior to each dose of olatumab/placebo.

Premedication with additional agents may be provided at investigator discretion.

Premedication **must be** provided in the setting of a prior Grade 1 or 2 olatumab/placebo IRR, as detailed in Section 9.4.1.1.1.1. All premedication administered must be adequately documented in the eCRF.

Given the emetogenic potential of doxorubicin, premedication with antiemetics per institutional guidelines is recommended. Additional premedication may be provided at investigator discretion.

If doxorubicin premedication is required prior to the doxorubicin infusion, this must be done after the completion of olatumab/placebo infusion, not before the olatumab/placebo infusion. This premedication may be administered immediately following the end of the observation period (if applicable) or after the completion of the olatumab/placebo infusion.

Starting with Cycle 1, dexrazoxane may be administered IV at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion, according to instructions provided in the Pharmacy Manual for this study, beginning no later than 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.

9.2. Materials and Supplies

Olatumab 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.

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

Olaratumab/Placebo Drug Product: The drug product must be stored under refrigeration at 2°C to 8°C (36°F-46°F) with protection from direct light. Do not freeze and/or shake olaratumab/placebo drug product. Stability studies have demonstrated that the drug product can withstand transient excursion to room temperature without adverse effect; however, storage at this temperature is not recommended.

Please refer to the pharmacy manual for olaratumab/placebo dosing solution for infusion.

CAUTION: Infusion-related reactions may occur during or following olaratumab/placebo administration (see Section 9.4.1.1.1 for a definition of Grade 3 and 4 IRRs). During the administration of olaratumab/placebo, 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 cycles of olaratumab/placebo. If there is no evidence of an IRR during the initial 2 cycles of olaratumab/placebo, then no observation period is required for subsequent treatment cycles. In the event that a Grade 1 or 2 IRR occurs after Cycle 2, the 1-hour observation period will be reinstated for a minimum of 2 cycles. The reinstated observation period may be suspended after 2 cycles if the patient shows no further signs or symptoms of an IRR.

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 IRR to doxorubicin, the investigator should follow the manufacturer's recommendations and clinical guidelines in the management of the patient.

Doxorubicin 75 mg/m² is administered IV. The dose of doxorubicin should be reconstituted in 100 mL of normal saline. Administer doxorubicin as an IV injection or as an infusion in less than 60 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 (2°C to 8°C). 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. Dexrazoxane should be started within 30 minutes prior to the doxorubicin infusion.

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 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 48 strata or cells), defined by the following 4 prognostic factors:

- Number of prior systemic therapies for advanced/metastatic disease (0 versus ≥ 1)
NOTE: Any therapy administered in the adjuvant/neoadjuvant setting will not be considered as a prior line of therapy here.
- Histological tumor type (leiomyosarcoma versus liposarcoma versus undifferentiated pleomorphic sarcoma versus other STS types)
- 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. After randomization, patients should receive their first dose of treatment within 72 hours (3 days) whenever possible (up to 3 additional days delay of first dose of treatment will be permitted due to holidays, weekends, bad weather, or other unforeseen circumstances and will not count as a protocol deviation).

9.4. Selection and Timing of Doses

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

Refer to Section 5.3.1 for the olaratumab dose rationale in this study.

The dose of olaratumab/placebo administered will be determined by measuring the patient's weight in kilograms on Days 1 and 8 of each cycle. The dose 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 $\geq 10\%$ (increase or decrease) from the weight used to calculate the prior dose, the olaratumab/placebo dose will not need to be recalculated. A $\pm 5\%$ variance in the calculated total dose will be allowed for ease of dose administration.

Patients will receive combination treatment with olaratumab/placebo + doxorubicin for 8 cycles, followed by olaratumab/placebo as monotherapy 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 Delays, Modifications, and Discontinuations

After treatment has been initiated, in order to **start** the **next** cycle the following criteria must be fulfilled:

- ANC $\geq 1.0 \times 10^3/\mu\text{L}$ (1000/ μL ; $\geq 1.0 \times 10^9/\text{L}$)

Note that in order to administer single-agent olaratumab/placebo on Day 8, ANC must be $\geq 750/\mu\text{L}$; $\geq 0.75 \times 10^9/\text{L}$. If the ANC is $< 750/\mu\text{L}$, the Day 8 administration of olaratumab/placebo may be delayed for a maximum of 7 days. If the ANC level has not increased to $\geq 750/\mu\text{L}$ within 7 days, then the Day 8 olaratumab/placebo dose in that cycle should be skipped and dosing resumed on Day 1 of the following cycle if criteria for dosing are met. If all dosing criteria are met, a delay or omission of the Day 8 olaratumab/placebo dose should not result in a delay of the Day 1 olaratumab/placebo dose of the following cycle.

- Platelets $\geq 100 \times 10^3/\mu\text{L}$ (100,000/ μL ; $\geq 100 \times 10^9/\text{L}$)
- Hemoglobin ≥ 8 g/dL
- Creatinine clearance ≥ 45 mL/min (refer to [Attachment 5](#) for the Cockcroft-Gault formula)
- Total bilirubin below ULN. In patients with Gilbert's syndrome, total bilirubin should be < 3 mg/dL.
- AST and ALT $\leq 3.0 \times \text{ULN}$, or $\leq 5 \times \text{ULN}$ if the transaminase elevation is due to liver metastases
- Nonhematologic toxicity must be less than Grade 2, except for those not deemed clinically significant by the investigator, or electrolyte abnormalities (for example, potassium, magnesium, phosphate).

Delays:

In general, dose delays of 1 study drug (olaratumab/placebo or doxorubicin) due to toxicity guidances outlined in Sections 9.4.1.1.1 and 9.4.1.1.2 will not necessitate delays of the other study drug.

To maintain a concomitant administration schedule of olaratumab/placebo and doxorubicin on Day 1 of the first 8 cycles, a delay in olaratumab/placebo administration will be allowed to match the corresponding delay in doxorubicin due to toxicity. For the same reason, a delay in doxorubicin administration will be allowed to match the corresponding delay in olaratumab/placebo due to toxicity. Treatment may be delayed for up to 21 days (1 equivalent cycle) 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 (2 equivalent cycles) from last dose, then the patient must be discontinued from study therapy.

Dose Modifications:

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 the event of an alteration in olaratumab/placebo dose due to an olaratumab/placebo-related toxicity, doxorubicin need not be altered, and the planned doxorubicin schedule should be maintained.

Similarly, olaratumab/placebo therapy need not be altered or discontinued for doxorubicin-related toxicity. An alteration in doxorubicin dose will always necessitate a corresponding change in dexrazoxane dose, if administered, in order to maintain a dosage ratio of 10:1 (dexrazoxane:doxorubicin).

Discontinuations:

In general, discontinuation of 1 study drug (olaratumab/placebo or doxorubicin) will not necessitate discontinuation of the other study drug. Any changes in treatments being added to or removed from patient care will be recorded on the eCRF.

In the event of 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 discontinued for doxorubicin-related toxicity. 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.

The following information (in this section and the following subsections) pertains to dose modifications and delays for and management of AEs of concern, which may or may not be associated with olaratumab/placebo therapy, including the following:

- IRR (see Section 9.4.1.1.1.1)
- Hematologic toxicity (see Section 9.4.1.1.1.2)
- Nonhematologic toxicity (see Section 9.4.1.1.1.3)

The following information (in this section and the following subsections) pertains to dose modifications and delays for and management of AEs of concern, which may or may not be associated with doxorubicin therapy, including the following:

- Hematologic toxicity (see Section 9.4.1.1.2.1)
- Cardiovascular toxicity (see Section 9.4.1.1.2.2)
- Hepatic impairment (see Section 9.4.1.1.2.3)
- Nonhematologic toxicity (see Section 9.4.1.1.2.4)

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 the NCI-CTCAE version 4.0 definition of IRRs.

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 or signs occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE terms that best describe the event, and mark “yes” or “no” for hypersensitivity/IRR event flag.

For patients who experience a Grade 1 or 2 IRR, the infusion should be stopped and the patient treated with the following (or equivalent) medications: a histamine H1 antagonist (eg, diphenhydramine) and glucocorticoid (eg, dexamethasone) intravenously, acetaminophen, and oxygen (as indicated), according to standard medical practices. After recovery, the infusion rate should be decreased 50% for the duration of the infusion. After a Grade 1 or 2 IRR, patients should be premedicated with the following (or equivalent) medications: a histamine H1 antagonist (eg, diphenhydramine) and glucocorticoid (eg, dexamethasone) intravenously, and acetaminophen, as appropriate, approximately 30-60 minutes prior to all subsequent olaratumab/placebo infusions.

A Grade 3 or 4 IRR 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/placebo with appropriate supportive care.

If a patient experiences an IRR to olaratumab/placebo, all attempts should be made to obtain an anti-olaratumab/placebo antibody blood sample as close to the onset of the event as possible, at the resolution of the event, and 30 days (± 3 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 IRR. The procedure for sample collection and handling is described in a separate procedural manual.

9.4.1.1.1.2. Hematologic Toxicity

Table JGDJ.2 summarizes the olaratumab dose modifications required in case of hematological toxicities.

Table JGDJ.2. General Guidelines for Olaratumab/Placebo Dose Modification Due to Hematologic Toxicity Deemed Related to Olaratumab/Placebo

Toxicity	Required Dose Modification
<i>Neutropenia</i>	
ANC Grade 1-3	No dose modification required
ANC <500 cells/ μ L (Grade 4)	No treatment administered; treatment cycle delayed
At retreatment:	
If \geq Grade 3 neutropenic fever/infection has occurred	Withhold dose until ANC is 1000 cells/uL or higher; reduce dose to 12 mg/kg (15 mg/kg if toxicity occurs during Cycle 1).
If Grade 4 neutropenia lasting longer than 1 week has occurred	Withhold dose until ANC is 1000 cells/uL or higher; reduce dose to 12mg/kg (15 mg/kg if toxicity occurs during Cycle 1).
Grade 4 ANC without fever/infection	Retreatment with olaratumab/placebo at full dose at investigator's discretion with recommended use of prophylactic G-CSFs
Second incidence of either: 1) \geq Grade 3 neutropenic fever/infection 2) Grade 4 neutropenia lasting longer than 1 week	Second dose reduction to 10 mg/kg
<i>Thrombocytopenia</i>	
Platelets <100,000 cells/ μ L	No treatment administered; treatment delayed until resolved to \geq 100,000 cells/ μ L
<i>Anemia</i>	
Hemoglobin <8 gm/dL	No treatment administered; treatment delayed until resolved to \geq 8 gm/dL

Abbreviations: ANC = absolute neutrophil count; G-CSFs = granulocyte colony-stimulating factors.

9.4.1.1.1.3. Nonhematologic Toxicity

Specific guidelines for dose adjustments in patients who experience olaratumab/placebo IRRs may be found in Section 9.4.1.1.1.1.

General guidelines for dose modification for other nonhematologic toxicities related to olaratumab/placebo are shown in [Table JGDJ.3](#). If more than 2 toxicity-related olaratumab/placebo dose reductions are required, treatment with this agent will be permanently discontinued.

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

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/placebo per protocol, provided that the event does not pose a serious health risk or is easily treated.
Grade 3	For a Grade 3 toxicity not adequately controlled with appropriate supportive care, the dose must be withheld until toxicity is \leq Grade 1 or has returned to pretreatment baseline; then treatment may resume at a reduced dose of 12 mg/kg (15 mg/kg if the toxicity occurs during Cycle 1). If toxicity recurs after therapy resumes, a second dose reduction (to 10 mg/kg) is permitted.
Grade 4	The dose must be withheld until dose toxicity is \leq Grade 1 or has returned to baseline. Permanent discontinuation should be considered for any patient experiencing Grade 4 nonhematological toxicity assessed as related to olaratumab/placebo. However, if resumption of dosing is deemed appropriate by the investigator, treatment may resume only after consultation with the Lilly study physician, with the dose reduced to 10 mg/kg (15 mg/kg if the toxicity occurs during Cycle 1). If Grade 4 toxicity recurs after therapy resumes, olaratumab/placebo treatment will be discontinued.

9.4.1.1.2. Doxorubicin

9.4.1.1.2.1. Hematologic Toxicity

Doxorubicin will not be administered after the initial dose 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 $\geq 100,000$ cells/ μL and nonhematologic toxicities have resolved. For patients who experience \geq 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/m²). 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/m² will be necessary. Therapeutic and prophylactic use of Neulasta[®] (pegfilgrastim) or other G-CSFs will be allowed per current American Society of Clinical Oncology (ASCO; Smith et al. 2006) and National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2014). For 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/m²) 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/ μ L	No doxorubicin administered; treatment cycle delayed.
At retreatment:	
If \geq 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:	Second dose reduction to 45 mg/m ² .
1) \geq Grade 3 neutropenic fever/infection	
2) Grade 4 neutropenia lasting longer than 1 week	

9.4.1.1.2.2. Cardiovascular Toxicity

Cardiotoxicity is a recognized risk of doxorubicin that increases with higher cumulative drug exposure. Cardiac monitoring is conducted by a combination of monitoring of clinical parameters, ECG, and echocardiogram (ECHO) / multigated acquisition (MUGA) scan.

ECG changes, arrhythmias, tachycardia, and/or chest pain should be managed according to clinical practice 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. A decrease in LVEF of $\geq 10\%$ and 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/placebo, provided that the patient meets all other entry criteria (see Section 9.4.1.1).

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 there is clinical or instrumental evidence that further investigations are needed.

9.4.1.1.2.3. Hepatic Impairment

Doxorubicin is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C or total serum bilirubin >5.0 mg/dL). Refer to Section 9.4.1.1 for additional information.

9.4.1.1.2.4. Nonhematologic Toxicity

Permanent discontinuation of doxorubicin should be considered for any patient experiencing Grade 4 nonhematologic toxicity assessed as related to doxorubicin. If the investigator feels re-dosing of doxorubicin is appropriate (except for Grade 4 cardiotoxicities and Grade 4 bilirubin increase which require mandatory discontinuation [see Section 9.4.1.1.2.2 and Section 9.4.1.1.2.3]), treatment may only resume after consultation with the Lilly study physician, with

the dose reduced to 60 mg/m² (or less if agreed by the investigator and Lilly physician). If Grade 4 toxicity recurs after therapy resumes, doxorubicin treatment will be permanently discontinued.

For appropriate management of cardiac toxicities and hepatic impairment, refer to Section 9.4.1.1.2.2 and Section 9.4.1.1.2.3.

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 and/or immunogenicity data that could unblind the study will not be reported to investigative sites or other blinded study 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, investigational medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, surgery for cancer, or investigational medications will be permitted while patients are on study treatment.

Biophosphonate osteoclast inhibitors (eg, zoledronic acid or pamidronate) for treatment of bone metastases will be permitted while patients are on study treatment. However, the osteoclast inhibitor denosumab is a monoclonal antibody and could confound safety analysis in the study if the patient experiences a hypersensitivity reaction to denosumab. Therefore, concomitant use of denosumab will not be permitted.

Appropriate documentation for all forms of premedications, supportive care, and concomitant medications (for example, 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/placebo infusion, not before the olaratumab/placebo 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 must be captured on the eCRFs.

9.6.1.1. Dexrazoxane

Starting with Cycle 1, dexrazoxane may be administered IV at the investigator's discretion according to instructions provided in the Pharmacy Manual for this study, beginning 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. Investigators should consult the dexrazoxane information provided in the Pharmacy Manual for

this study for administration information (including warnings, precautions, contraindications, adverse reactions, and dose modifications).

Note that as the dose of dexrazoxane administered is 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 (for example, erythropoietin) are permitted, including prophylactic use, during investigational therapy at the discretion of the investigator, according to ASCO guidelines (Smith et al. 2006) and NCCN Guidelines (NCCN 2014).

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 or approved anticancer agents may not be administered to patients on this study. Palliative radiation or surgery 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. Treatment compliance will be monitored by drug accountability records, and treatment administration data are recorded in the patient's medical record and eCRF. An investigator is required to prepare, maintain, and record

all observations and other data pertinent to the investigation on each individual treated in this clinical trial. All data reported on the eCRF must be derived from source documents and be consistent with the source documents.

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 randomization, 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 randomization. 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 all further anticancer treatment, subsequent disease progression date, and 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) as calculated from randomization 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 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 all further anticancer treatments, initial subsequent disease progression date, and 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 SAP (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 SAP.

- Progression-free survival (PFS)
- Objective Response Rate (ORR)
- Disease Control Rate (DCR)
- Time to first worsening of the mBPI-sf (Brief Pain Inventory Short Form Modified) "worst pain" score
- Duration of Response (DoR)
- Duration of Disease Control (DDC)
- 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 QLQ-C30 scale 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
- Second PFS (PFS2) after end of study treatment while on subsequent anticancer therapies

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 3 months [± 2 weeks] for the first year, every 6 months [± 2 weeks] the second year, then annually [± 2 weeks] thereafter 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. Whenever possible, if administration is not possible prior to all other procedures, every effort should be made to administer at the same time point in each visit and questionnaire must be completed prior to 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). The mBPI-sf is administered per the Study Schedule ([Attachment 1](#)). The recall period is the past 24 hours or previous week and completion time is typically 5 to 7 minutes.

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 JGDJ.5](#). 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 an mBPI-sf “worst-pain baseline score of 8 or more will not be included in the analysis.

Table JGDJ.5. 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.

The EQ-5D 5L population will include all patients who completed at least 1 baseline assessment followed by at least 1 EQ-5D 5L assessment after 1 dose of study drug.

EQ-5D 5L responses may be incorporated into cost utility analyses, but will not be included in the clinical study report.

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 postdiscontinuation 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.6](#) presents a summary of AE and SAE reporting guidelines. [Table JGDJ.6](#) also shows which database or system is used to store AE and SAE data.

Table JGDJ.6. 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, before the patient receives the first dose of study treatment, site personnel will record the occurrence and nature of any AEs and any change in the preexisting condition(s). All AEs and SAEs related to protocol procedures are reported to Lilly or its designee via eCRF.

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.

10.3.1.3. Adverse Events of Special Interest (AESI)

Adverse events of special interest are events that have been identified as safety signals during preclinical or early clinical trials or based on class effects of similar drugs. These events will be monitored prospectively in the clinical developmental program. Each event is defined by a careful assessment and grouping of individual related MedDRA preferred terms.

AESI for olaratumab/placebo

Infusion-related reactions

AESIs for combination of olaratumab/placebo and doxorubicin

Infusion-related reactions

Cardiac arrhythmias and cardiac dysfunction

Refer to Section 9.4.1.1 for special treatment considerations for dose delay, modifications, and discontinuations from olaratumab/placebo and doxorubicin, including adverse events of concern or special interest.

10.3.2. Other Safety Measures

10.3.2.1. Electrocardiograms

A 12-lead electrocardiogram (ECG) is required within 28 days prior to randomization for all patients. Thereafter, 12-lead ECGs will be performed on Day 1 of Cycle 1 through Cycle 9. After Cycle 9, perform ECGs every 3 months (\pm 2 weeks) the first year, every 6 months (\pm 2 weeks) the second year, then annually (\pm 2 weeks) thereafter as long as the patient is alive and has not withdrawn consent to follow-up (refer to [Attachment 1](#)).

Patients who stop doxorubicin prior to Cycle 8 will undergo the same cardiac monitoring frequency described above (refer to [Attachment 1](#)).

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.

[Table JGDJ.7](#) provides the Bazett's QT heart rate correction formula.

Table JGDJ.7. Bazett's QT Heart Rate Correction Formula

Formula	Bazett $QT_c = QT (HR/60)^{1/2} = QT (RR)^{-1/2}$
Type of formula	Nonlinear
Use	Most commonly used in clinical practice
Unique limitations	Over-corrects QT at fast HRs Under-corrects QT at low HRs (the risk of TdP which frequently occurs at low HRs, may not be evident)

Abbreviations: QT_c = corrected QT interval; HR = heart rate; RR = duration of ventricular cardiac cycle;
TdP = torsade de pointes (a polymorphic ventricular tachycardia).

After enrollment, if a clinically significant increase in the QT/corrected QT (QT_c) 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.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation.

10.3.2.2. Echocardiograms/MUGA Scans

An ECHO or MUGA scan is required within 28 days prior to randomization for all patients. Thereafter, perform ECHO or MUGA scans within 7 days prior to start of treatment in Cycles 5, 7, and 9. After Cycle 9 (for patients with resting LVEF $\geq 50\%$), perform ECHO or MUGA scans every 3 months (± 2 weeks) the first year, every 6 months (± 2 weeks) the second year, then annually (± 2 weeks) thereafter as long as the patient is alive and has not withdrawn consent to follow-up (refer to [Attachment 1](#)).

Patients who stop doxorubicin prior to Cycle 8 (with resting LVEF $\geq 50\%$) will undergo the same cardiac monitoring frequency described above; perform ECHO or MUGA scans every 3 months (± 2 weeks) the first year, every 6 months (± 2 weeks) the second year, then annually (± 2 weeks) thereafter as long as the patient is alive and has not withdrawn consent to follow-up (refer to [Attachment 1](#)).

For patients with LVEF $< 50\%$ or other cardiac dysfunction, perform more frequently, if clinically indicated.

10.3.3. Safety Monitoring

The Sponsor will monitor blinded 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 cardiac events such as:
 - myocardial failure, dysfunction
 - myocardial ischemia or infarction
 - arrhythmias
 - cardiovascular insufficiency
- adverse events of special interest (as defined in Section [10.3.1.3](#))

If a patient experiences elevated alanine aminotransferase (ALT) $> 5 \times$ ULN and elevated total bilirubin $> 2 \times$ ULN, clinical and laboratory monitoring should be initiated by the investigator. For patients entering the study with ALT $> 3 \times$ ULN, monitoring should be triggered at ALT $> 2 \times$ 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 AESI. Each event is defined by a careful assessment and grouping of individual related MedDRA preferred terms.

1. Cardiac dysfunction
2. Arrhythmias

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. Eligibility for inclusion in this clinical trial will be based on local clinical laboratory results (not transcribed onto eCRFs) and duplicate samples will be submitted to the central laboratory. 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 Central Pathology Review and 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, PDGFR α , and PDGFR α 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 STS, 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 the diagnosis of STS and histologic subtype, and for exploratory biomarker research. In the event that archived tissue is not available at study entry, a pre-treatment tumor biopsy of primary or metastatic tissue will be required (treatment can be initiated after tissue collection, without the need to wait for availability of tissue analysis results). The specific tissue amount required and processing and shipping instructions are detailed in the Pathology Letter provided to each site. 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 diagnostic pathology reports accompanying archival tissue will also be required.

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 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 30 days (\pm 3 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.

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

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 eCRFs, 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 eCRF 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 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 trial is to compare doxorubicin plus olaratumab versus doxorubicin plus placebo with respect to OS in 2 populations:

- (1) Patients with advanced or metastatic STS not amenable to treatment with surgery or radiotherapy with curative intent (referred to below as the ITT population)
- (2) Patients with advanced or metastatic LMS not amenable to treatment with surgery or radiotherapy with curative intent

Population (1) will be analyzed for efficacy among all randomized study patients (the ITT population). Population (2) will be analyzed as the subset of randomized patients with LMS. The study will be considered a positive study if either the ITT or LMS populations (or both) show a statistically significant improvement in OS with the regimen of doxorubicin plus olaratumab.

The study will enroll 460 patients in 1:1 randomization (230 patients in the investigational arm and 230 patients in the control arm). Enrollment will be conducted so that approximately 200 patients with LMS and 260 patients with other (non-LMS) histology will be randomized. The final analysis will occur only when both a minimum of 131 OS events have been observed in randomized patients with LMS, and a minimum of 322 OS events have been observed in randomized patients overall.

The statistical analysis will be conducted using a statistical testing plan according to the graphical method of Maurer and Bretz (2013) so as to control the overall type I error rate at 0.025 (one-sided) or equivalently, 0.05 (two-sided). The graphical approach can be characterized by first defining a set of pre-specified null hypotheses that are organized graphically by providing initial alphas for each hypothesis and weights for each edge of the graph which will determine the propagation of α through the entire hypothesis testing scheme. The graph is shown in [Figure JGDJ.3](#).

The hypotheses are;

Primary objectives: H_{11} : OS in the LMS population

H_{12} : OS in the ITT population

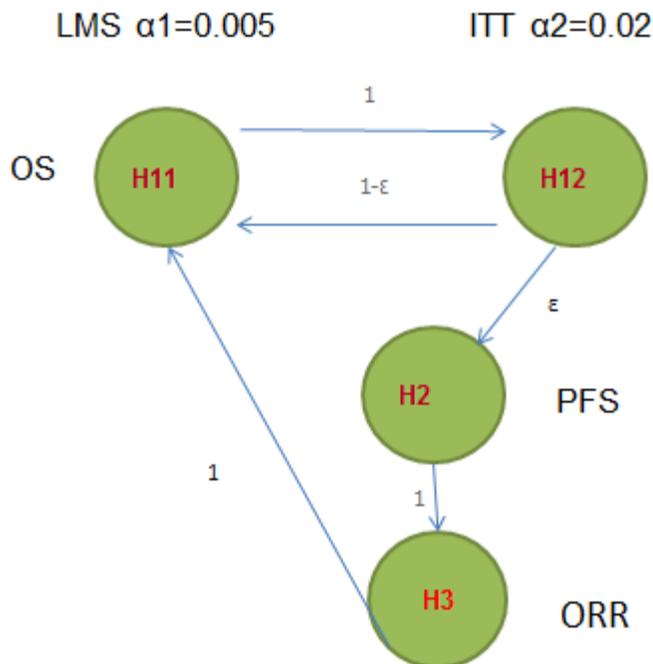
Secondary objectives: H_2 : PFS in the ITT population

H_3 : ORR in the ITT population

Initially the overall one-sided alpha of 0.025 is split between the primary objectives of OS in the LMS population (H_{11}) and OS in the ITT population (H_{12}), with H_{11} tested at a one-sided $\alpha_1=0.005$ and H_{12} tested at a one-sided $\alpha_2=0.02$. Zero alpha is initially assigned to the other hypotheses.

The initial weights for each edge of the graph are shown in Figure JGDJ.3. The weight of the line from H_{11} to H_{12} is 1 indicating that H_{12} receives all of the alpha allotted to H_{11} if H_{11} is rejected, and similarly, the weight of the line from H_{12} to H_{11} is $1 - \epsilon$, where ϵ is set equal to 0.001, indicating that H_{11} receives virtually all of the alpha allotted to H_{12} if H_{12} is rejected.

Assigning $\epsilon=0.001$ initially focuses virtually all the alpha on the primary endpoints. The iterative process of subsequent updating of the graph and redistribution of α is described in more detail in the SAP and is repeated until no further hypotheses can be rejected.



Abbreviations: ITT = intention-to-treat; LMS = leiomyosarcoma; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.
 ϵ is set equal to 0.001.

Figure JGDJ.3. Graphical representation of testing sequence.

The power and associated sample sizes for the hypotheses that form the primary objective are based on the initial allocation of alpha. The total of 131 OS events at the final analysis in the LMS subpopulation provides 80% statistical power for a one-sided log-rank test at a 0.005 alpha level, assuming the true OS HR in LMS patients is 0.55. The total of 322 OS events at the final analysis in the ITT population provides 80% statistical power for a one-sided log-rank test at a 0.02 significance level, assuming the true OS HR in STS patients is 0.723.

There is one interim analysis for efficacy planned for this study. This analysis will be performed in order to provide the IDMC and regulatory authorities an opportunity to review interim safety and efficacy data together. There will be no formal statistical hypotheses tested at the interim for primary and secondary efficacy outcomes. There will be no alpha-spending associated with the

interim analysis; study follow-up and data collection will continue as planned until the final analysis regardless of the nature of the interim efficacy results. Only the IDMC and regulatory authorities will be allowed access to unblinded interim data. This single interim efficacy analysis is planned to occur after 194 OS events (60% of the final OS events) have been observed in the ITT population.

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 SAP. 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 baseline, efficacy, and health outcome analyses. A key subset of the ITT population is the LMS population (randomized patients with LMS). Unless otherwise indicated, all efficacy analyses will be performed for both the full ITT population and the LMS population.

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 the interim and final analysis time points will be based on the stratified log-rank test, stratified by the randomization strata, excluding region; that is, number of prior systemic therapies for advanced/metastatic disease (0 versus ≥ 1), histological tumor type (leiomyosarcoma versus liposarcoma versus undifferentiated pleomorphic versus other STS types) and ECOG PS (0 versus 1). Region (North America versus Europe versus ROW) is included in the randomization so as to ensure balance between treatments within regions for subgroup analysis, but is not included as a stratification factor in the primary analysis as including it could result in small or empty strata due to the resulting increase in the number of strata from 16 to 48.

Overall 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.

A single interim analysis is planned for efficacy as described in Section [12.1](#).

12.2.7. Other Analyses of Efficacy

12.2.7.1. Progression-Free Survival

A precise definition of events and censoring for PFS 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.

Progression-free survival will be compared between the 2 treatment groups based on log-rank test, stratified by stratification factors. Progression-free 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.

12.2.7.2. 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 SAP.

12.2.8. Pharmacokinetic and Immunogenicity 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.

If warranted by the data, PK/PD analyses using OS, PFS, and/or other appropriate clinical endpoints will also be conducted to characterize the exposure-response relationship in this study. The PK and PK/PD analyses will be reported as separate standalone reports for this study.

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. However, for patients who test positive for anti-drug antibodies (ADA), their ADA titers will be listed over time and associated PK information (for example, plasma concentration) will be listed in subsequent cycles for each patient.

In the event of an IRR, 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 analyses 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 SAP.

Additionally, time to first worsening of QLQ-C30 scale 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 SAP.

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, 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 SAP.

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 final database lock, in order to initiate the final population pharmacokinetic/pharmacodynamic model development processes for 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 (that is, a separate iDMC charter 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).

The iDMC safety reviews will be performed for **all randomized patients**. The first iDMC meeting to review interim data will occur when approximately 80 patients (approximately 40 patients from each arm) have received 2 cycles of treatment or discontinued all study treatment due to any reasons prior to Day 8 in Cycle 2. Subsequent iDMC meetings will occur approximately every 6 months thereafter. Enrollment and treatment will continue during the iDMC safety assessments. In the event a safety signal is detected, additional meetings may occur as needed. Details as to the process and communication plan will be provided in the iDMC Charter.

Interim PK analyses of the approximately 80 patients (approximately 40 patients from each arm) that will accompany the iDMC safety review will be performed by a Lilly PK scientist independent from the study team. These data will be provided to the iDMC upon request.

Interim efficacy analysis will be performed by the iDMC as described in Section 12.1. The iDMC Charter (a separate document) will provide detailed guidance for the conduct of the interim analyses.

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
- ICH 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. Country-Specific Protocol Addenda

Revisions to the protocol are made to comply with local law and regulatory requirements and to address feedback received from competent authority reviews. Where applicable, these changes are outlined in a country-specific protocol addendum associated with this protocol. Participating investigators or their designee will promptly submit the country-specific protocol addendum to applicable ERBs/IRBs in accordance with their local procedures. After reading the addendum, each investigator will sign the protocol addendum signature page, send a copy of the signed page to a Lilly representative, and subsequently comply with any local requirements contained in the relevant addendum.

13.3.2. Investigator Information

Physicians with a specialty in medical oncology with a specialty in STS will participate as investigators in this clinical trial.

13.3.3. 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.

13.3.4. 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.

14. References

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Attachment 1. Protocol JGDJ Study Schedule

Study Schedule, Protocol I5B-MC-JGDJ

Perform procedures as indicated. All screening/baseline evaluations are performed within 14 days prior to randomization, unless otherwise specified. Upon completion of all screening/baseline evaluations to confirm a patient’s eligibility, the site will register the patient by the IWRS.

Baseline Schedule

Study Period	Baseline	
Cycle	BL	
Visit	0	
Duration	Up to 14 days (except where noted)	
Relative Day from Randomization	≤14	≤7

Procedure Category	Protocol Sections	Procedure			Comments
Study Entry/ Enrollment	7 13.1	Informed Consent	X (within 28 days of randomization)		Written informed consent must be obtained prior to any study-specific screening evaluations. For screening purposes, required assessments performed prior to the date of consent may be used provided they are noted exceptions.
	7.1, 7.2, 9.3	Inclusion/Exclusion Evaluation and IWRS		X	The patient will be randomized via IWRS after meeting inclusion/exclusion criteria. After randomization, patients should receive their first dose of treatment within 72 hours (3 days) whenever possible.
Medical History	10.3.1	Medical History	X		Any preexisting and pretreatment toxicity (treatment or disease related) should be documented and recorded as part of the pretreatment medical history. Disease characteristics at initial diagnosis and at study entry will be collected. All adverse events must be recorded after signing the informed consent.
	7	Demography	X		Date of birth, sex, and race/ethnicity will be collected at baseline.
	7	Prior Treatment Therapies of Underlying Disease	X		Prior treatment includes any treatment for underlying disease, including maintenance therapy. Start and stop dates should be documented as well. Previous therapy must be completed ≥ 4 weeks (28 days) prior to randomization.
Physical Examination	7	Physical Examination		X	Physical examination at baseline includes height, weight, and BSA measurement.
	7.1 Att. 4	ECOG Performance Status		X	Refer to Attachment 4 for details.
	7	Vital signs		X	Vital signs include blood pressure, pulse, and temperature.
Concomitant Medications	9.6	Concomitant Medications	X (within 30 days of C1D1)		Concomitant medications will be recorded, including any taken within 30 days prior to start of study treatment.
	7.1 Att. 2	Hematology	X		Screening evaluations done within 7 days prior to randomization do not have to be repeated.
	7.1 Att. 2	Serum Chemistry	X		Screening evaluations done within 7 days prior to randomization do not have to be repeated.
	7.1 Att. 2	Coagulation Profile	X		Screening evaluations done within 7 days prior to randomization do not have to be repeated.

Baseline Schedule

		Study Period	Baseline		
		Cycle	BL		
		Visit	0		
		Duration	Up to 14 days (except where noted)		
		Relative Day from Randomization	≤14	≤7	
Procedure Category	Protocol Sections	Procedure			Comments
Lab/ Diagnostic Tests	Att. 2	Urinalysis	X		Screening evaluations done within 7 days prior to randomization do not have to be repeated. 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 or a urine protein/creatinine ratio must be ≤1 in a spot urine test, prior to proceeding to treatment.
	7.1 Att. 2	Pregnancy Test		X	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 and performing a urine pregnancy test. The results of this test will not be collected on the eCRF.
	7.1 Att. 2	Follicle-stimulating Hormone (FSH)	X		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.
	10.4.2.3 Att. 7	Mandatory Tumor Tissue	X (within 28 days of randomization)		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).
	10.3.2.1	ECG (local)	X (within 28 days of randomization)		A single 12-lead ECG is to be obtained within 28 days prior to randomization (refer to Section 10.3.2.1 for details).
	10.3.2.2	Echocardiogram or MUGA scan	X (within 28 days of randomization)		Within 28 days prior to randomization (refer to Section 10.3.2.2 for details).
Efficacy Assessment	8.1.1 10.1.1 Att. 6	Imaging Studies (CT/MRI) Tumor Assessments (according to RECIST v1.1)	X (within 28 days of randomization)		Within 28 days prior to randomization (refer to Section 10.1.1 and Section 8.1.1 for details).
Patient Disposition			X		At the time that the patient is discontinued from Study Participation, information regarding the patient status will be collected.

Abbreviations: β-HCG = beta human chorionic gonadotropin; BL = baseline; BSA = body surface area; C1D1 = Cycle 1 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FFPE = formalin-fixed paraffin embedded; FSH = follicle-stimulating hormone; IWRS = interactive web-response system; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria In Solid Tumors; v = version.

Study Schedule, Protocol I5B-MC-JGDJ

Perform procedures as indicated.

Treatment Period Schedule

	Study Period	Treatment Period				Comments	
		Cycle (21-day cycle ± 3 days)		9+			
		1 ^a	8 ^a	1 ^a	8 ^a		
Procedure Category	Protocol Section	Procedure					
Physical Examination	10.3.1	Physical Examination	X	X	X	X	Physical examination during treatment period includes weight and BSA measurement. Patients should be weighed on D1 and D8 of each cycle and BSA calculated.
	Att. 4	ECOG Performance Status	X		X		Complete prior to treatment infusion.
	10.3.1	Vital signs	X	X	X	X	Vital signs include blood pressure, pulse, and temperature. During the Observation Period (initial 2 cycles), collect vital signs: 1) within 15 minutes (+5 minutes) prior to olaratumab/placebo infusion, 2) within 1 hour (+5 minutes) after completion of the olaratumab/placebo infusion, and 3) within 1 hour (+5 minutes) after completion of the doxorubicin infusion if applicable. Thereafter (Cycles 3+), obtain vital signs: 1) within 15 minutes (+5 minutes) prior to olaratumab/placebo infusion and 2) within 1 hour (+5 minutes) after completion of the doxorubicin infusion if applicable.
Lab/ Diagnostic Tests	Att. 2	Hematology	X	X	X	X	Laboratory assessments may be done within 3 days prior to D1 and D8 of each cycle. See Attachment 2 for details.
	Att. 2	Serum Chemistry	X		X		Laboratory assessments may be done within 3 days prior to D1 of each cycle. See Attachment 2 for details.
	Att. 2	Coagulation Profile	X		X		Laboratory assessments may be done within 3 days prior to D1 every other cycle or as clinically indicated. See Attachment 2 for details.
	Att. 2	Pregnancy Test	X		X		Serum or urine pregnancy test on D1 of every cycle or per local practice (whichever is of shorter duration). If the pregnancy test performed on D1 of the cycle is positive, confirm with a serum pregnancy test (pregnancy test results are not recorded on the eCRF).
	10.4.4	PK Samples	See Attachment 7 for specific time points				Whole blood samples collected.
10.4.3	Immunogenicity Samples	See Attachment 7 for specific time points				Whole blood samples collected. 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 (± 3 days) days after onset of the IRR event.	

Treatment Period Schedule

	Study Period	Treatment Period				Comments	
		Cycle (21-day cycle ± 3 days)		9+			
		1 ^a	8 ^a	1 ^a	8 ^a		
Relative Day within Cycle (± 3 days)							
Procedure Category	Protocol Section	Procedure					Comments
	10.4.2.2	Pharmacogenetic (DNA) Whole Blood Sample	See Attachment 7 for specific time points.				Whole blood sample collected. It is highly recommended to draw the whole blood sample prior to the first dose (C1D1 at predose); however, it can be collected later during the study if necessary.
	10.4.2.1	Plasma sample for biomarkers	See Attachment 7 for time points.				Plasma sample collected.
	10.3.2.1	ECG	X		X After C9 q3m year 1, q6m year 2, annually there- after	Twelve-lead ECGs are to be performed on Day 1 of Cycle 1 to Cycle 9. After Cycle 9, perform ECGs every 3 months (±2 weeks) the first year, every 6 months (± 2weeks) the second year, and annually (±2 weeks) thereafter. Perform more frequently, if clinically indicated. Patients who stop doxorubicin prior to Cycle 8 will undergo the same cardiac monitoring frequency described above.	
	10.3.2.2	Echocardiogram or MUGA	X C5, C7, and C9		X After C9 q3m year 1, q6m year 2, annually there- after	Echocardiograms or MUGA scans are to be performed within 7 days prior to start of treatment in Cycles 5, 7, and 9. After Cycle 9 (for patients with resting LVEF ≥50%), perform echocardiograms or MUGA scans every 3 months (±2 weeks) the first year, every 6 months (±2 weeks) the second year, and annually (±2 weeks) thereafter. For patients with LVEF <50% or other cardiac dysfunction, perform more frequently, if clinically indicated. Patients who stop doxorubicin prior to Cycle 8 will undergo the same cardiac monitoring frequency described above.	
Health Outcomes	10.2	PRO Assessments (mBPI-sf, EORTC QLQ C30, EQ-5D-5L)	X		X	The Patient Reported Outcome (PRO) measures will be collected on Day 1 of every cycle.	
Efficacy Assessment	8.1.1 10.1.1 Att. 6	Imaging Studies (CT/MRI) Tumor Assessments (according to RECIST v1.1)	X		X	Imaging studies and tumor assessments are to 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. Refer to Section 10.1.1 and Section 8.1.1 for details.	
Adverse Events Collection/CTCAE Grading	10.3.1	Toxicity Assessment	X	X	X	X	All AEs considered at least possibly-related to study treatment will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.
Concomitant Therapy	9.6	Concomitant Medications	X	X	X	X	Concomitant medications will be recorded throughout the treatment period, including those taken during the 30 days after the last dose of all study treatment.

Treatment Period Schedule

		Study Period	Treatment Period				
		Cycle (21-day cycle ± 3 days)	1-8		9+		
		Relative Day within Cycle (± 3 days)	1 ^a	8 ^a	1 ^a	8 ^a	
Procedure Category	Protocol Section	Procedure					Comments
Premedication	9.1.1	Administer dexrazoxane prior to doxorubicin	X				Dexrazoxane is recommended for all patients receiving 5 or more cycles of doxorubicin.
	9.1.1	Administer premedication prior to olaratumab or placebo treatment	X	X	X	X	Premedicate all patients with the following medications (or equivalent): a histamine H1 antagonist (eg, diphenhydramine) and dexamethasone intravenously 30–60 minutes prior to the olaratumab/placebo doses on Days 1 and 8 of Cycle 1. For subsequent cycles, premedicate all patients with a histamine H1 antagonist (eg, diphenhydramine) intravenously 30-60 minutes prior to each dose of olaratumab or placebo.
Study Treatment	9.2.1	Administer olaratumab or placebo	X	X	X	X	Administer until PD, unacceptable toxicity, death, or other withdrawal criteria are met. No crossover will be permitted.
	9.2.2	Administer doxorubicin	X				Administered to all patients for the first 8 cycles (unless previous unacceptable toxicity).
Patient Disposition							At the time that the patient is discontinued from any component of the study treatment or Study Participation, information regarding the patient status will be collected.

a Study procedures will be performed prior to study drug administration, except where noted (such as vital signs). In case of dose interruption, these evaluations will also be done at minimum frequency every 21 days (±3 days).

Abbreviations: BSA = body surface area; C1D1 = Cycle 1 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; D/C = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; IRR = infusion-related reaction; MRI = magnetic resonance imaging; PD = progressive disease; q3c = every 3 cycles; RECIST = Response Evaluation Criteria in Solid Tumors.

Study Schedule, Protocol I5B-MC-JGDJ

Perform procedures as indicated.

Post-Treatment Discontinuation Schedule

Procedure Category	Protocol Section	Procedure	Study Period	Post-discontinuation Follow-Up		Comments
			Visit	Short-Term Follow-Up	Long-Term Follow-Up	
			Duration	30 ± 7 days	802-8XX	
				See footnote for duration		
Physical Examination	10.3.1	Physical examination	X		Physical examination will include weight.	
	Att. 4	ECOG performance status	X			
	10.3.1	Vital signs	X		Includes blood pressure, pulse and temperature.	
Lab/ Diagnostic Tests	Att. 2	Hematology	X		See Attachment 2 for details.	
	Att. 2	Serum chemistry	X		See Attachment 2 for details.	
	Att. 2	Coagulation profile	X		See Attachment 2 for details.	
	Att. 2	Urinalysis	X		Includes a routine urinalysis (UA), and if clinically indicated a microscopic analysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine collection or urine protein/creatinine ration in spot urine test (to assess protein) must be obtained.	
	Att. 2	Pregnancy test	X		Serum or urine pregnancy test. If the pregnancy test is positive, confirm with a serum pregnancy test (pregnancy test results are not recorded on the eCRF). Additional pregnancy tests may be done after short-term follow-up if required by local regulation.	
	10.3.2.1	ECG	X	X	Twelve-lead ECGs are to be performed for all patients at the short-term follow-up. After the patient has stopped receiving doxorubicin and throughout the long-term follow-up, ECGs are to be performed every 3 months (±2 weeks) the first year, every 6 months (±2 weeks) the second year, then annually (±2 weeks) thereafter as long as the patient is alive and has not withdrawn consent to follow-up. Perform more frequently if clinically indicated.	
	10.3.2.2	Echocardiogram or MUGA	X	X	Echocardiogram or MUGA scans are to be performed for all patients at the short-term follow-up. After the patient has stopped receiving doxorubicin and throughout the long-term follow-up, (for patients with resting LVEF ≥50%) perform echocardiogram or MUGA scans every 3 months (±2 weeks) the first year, every 6 months(±2 weeks) the second year, then annually (±2 weeks) thereafter as long as the patient is alive and has not withdrawn consent to follow-up. For patients with LVEF <50% or other cardiac dysfunction, perform more frequently, if clinically indicated.	
10.4.4	PK sample	X		See Attachment 7 .		

Procedure Category	Protocol Section	Procedure	Study Period	Post-discontinuation Follow-Up		Comments
			Visit	Short-Term Follow-Up	Long-Term Follow-Up	
			Duration	801	802-8XX	
			30 ± 7 days	See footnote for duration		
	10.4.3	Immunogenicity sample	X			See Attachment 7. In addition, if a patient experiences an IRR to olaratumab/placebo, blood samples for immunogenicity and PK analysis will be taken at the short-term follow-up after the IRR.
	10.4.2.1	Plasma sample for biomarkers	X			See Attachment 7.
Health Outcomes	10.2	PRO Assessments (mBPI-sf, EORTC QLQ C30, EQ-5D-5L)	X		X	The Patient Reported Outcome (PRO) measures will be collected 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 3 months [±2 weeks] for the first year, every 6 months (±2 weeks) the second year, then annually [±2 weeks] thereafter until the patient’s death or overall study completion).
Efficacy Assessments	10.1.1 Att. 6	Imaging/Tumor Assessments (according to RECIST v1.1)	X (if applicable)		X	For patients who discontinue study treatment for any reason without objectively measured PD, imaging studies and tumor assessments are obtained every 6 weeks (±7 days), irrespective of treatment cycles as calculated from randomization, until documented progression.
	8.1.2	Survival Information, All Subsequent Anti-Cancer Treatments, and Associated Disease Progression Date			X	For patients that discontinue study treatment after objectively measured PD the following information 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: details on all subsequent anticancer treatment (start/stop dates and treatments administered; first post-study treatment disease progression date; and survival status.
Adverse Events Collection/CTCAE Grading	10.3.1	Toxicity assessment	X		X	All AEs considered at least possibly-related to study treatment will be followed until resolution, stabilization, return to baseline, or until deemed irreversible. After the 30-day short-term follow-up visit, only new and ongoing SAEs deemed related to study treatment will be collected.
Concomitant Medication Notation	9.6	Concomitant medications	X			
Patient Disposition			X		X	At the time that the patient is discontinued from Study Participation, information regarding the patient status will be collected.

Abbreviations: AE = adverse event; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; eCRF = electronic case report form; ECOG = Eastern Cooperative Oncology Group; PD = progressive disease; PRO = patient-reported outcome; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

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). The date of this agreement is to be reported on the eCRF as the Date of Discontinuation from study treatment.

Long-term follow-up: begins the day after the patient completes short-term follow-up

- Follow-up for progression: Patients that discontinue study treatment for reasons other than progression will be followed 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.

Study Schedule, Protocol I5B-MC-JGDJ

Perform procedures as indicated.

Continued Access Period Schedule

Procedure Category	Protocol Section	Procedure	Study Period	Continued Access Treatment Period	Continued Access Follow-Up Period	Comments
			Cycle	X-Y	Follow-Up	
			Visit	501-5XX	901	
			Duration	1	30 ± 7 days	
Adverse Events Collection/CTC AE Grading	10.3.1	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 Therapy	9.6	Concomitant Medications	X		Concomitant medications will be recorded throughout the treatment period, including those taken during the 30 days after the last dose of all study treatment.	
Lab/Diagnostic Tests	Att. 7	Immunogenicity/Pharmacokinetics	X	X	If a patient experiences an IRR to olaratumab during the Continued Access Period, 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 (±3 days) after the IRR.	
Premedications	9.1.1	Administer premedication prior to olaratumab treatment	X		Premedicate all patients with a histamine H1 antagonist (eg, diphenhydramine) intravenously 30-60 minutes prior to each dose of olaratumab.	
Study Treatment	9.2.1	Administer olaratumab	X		Administer until evidence of progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria are met.	

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

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 evaluations are to be performed within 14 days prior to randomization or study drug administration, unless otherwise specified (refer to [Attachment 1](#)). Eligibility for inclusion in this clinical trial will be based on local clinical laboratory results (not transcribed onto eCRFs); duplicate samples will be submitted to the central laboratory. For patient and study site convenience and safety, 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. 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}

Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Mean cell volume
Mean cell hemoglobin concentration
Leukocytes (WBC)
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets

Coagulation Test^a

Prothrombin time (PT or INR)
Partial thromboplastin time (PTT or aPTT)

Urinalysis^{a,c}

Specific gravity
pH
Protein
Glucose
Ketones
Blood
Urine leukocyte esterase

Other^d

Immunogenicity samples
PK samples

Clinical Chemistry^{a,b}

Serum Concentrations of the following:

Sodium
Potassium
Total bilirubin
Alkaline phosphatase
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Gamma-glutamyl transferase
Blood urea nitrogen (BUN)
Creatinine
Uric acid
Calcium
Glucose, random
Albumin
Total protein
Chloride
Bicarbonate
Direct bilirubin

Pregnancy test^{a,e}

Follicle-stimulating hormone (FSH)^{a,f}

Exploratory Biomarker Tests^d

Refer to Section 10.4.2

Abbreviations: aPTT = activated partial thromboplastin time; CRP = clinical research physician; INR = international normalized ratio; PK = pharmacokinetic; WOCBP = women of childbearing potential

a Assayed by local or investigator-designated laboratory

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

c If urinary protein is $\geq 2+$ at evaluations, a 24-hour urine collection (to assess protein) must be collected or urine protein/creatinine ratio in spot urine test must be conducted. Urine protein creatinine ratio of spot urine is an estimation of the 24-hour urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1000 mg. UPC ratio is calculated using one of the following formulae:

A) $[\text{urine protein}]/[\text{urine creatinine}]$ – if both protein and creatinine are reported in mg/dL

B) $[(\text{urine protein}) \times 0.088]/[\text{urine creatinine}]$ – if urine creatinine is reported in mmol/L.

d Assayed by a Sponsor-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 inconclusive, 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, serum or urine pregnancy tests will be performed in females of childbearing potential only on Day 1 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 pregnancy test performed on Day 1 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

Hemoglobin

Hematocrit

RBC

WBC

Neutrophils

Lymphocytes

Monocytes

Eosinophils

Basophils

Platelets

Hepatic Chemistry^a

Total bilirubin

Direct bilirubin

Alkaline phosphatase

ALT

AST

GGT

CPK

Haptoglobin^a

Hepatic Coagulation^a

Prothrombin Time

Prothrombin Time, INR

Hepatic Serologies^{a,b}

Hepatitis A antibody, total

Hepatitis A antibody, IgM

Hepatitis B surface antigen

Hepatitis B surface antibody

Hepatitis B Core antibody

Hepatitis C antibody

Hepatitis E antibody, IgG

Hepatitis E antibody, IgM

Anti-nuclear antibody^a

Anti-smooth muscle antibody^a

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase;

GGT = gamma-glutamyl transferase; IgG = immunoglobulin G; IgM = immunoglobulin 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:*

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

For serum creatinine concentration in $\mu\text{mol/L}$:

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

^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 (\pm 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, total dose infused and if intended dose was given) 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 of study drug administration, sample collection times may vary $\pm 10\%$ or as specified in the PK sampling schedule.

Pharmacokinetic and Immunogenicity Sampling Schedule

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

Abbreviation: PK = pharmacokinetic; IG = Immunogenicity; IRR = infusion-related reaction.

- a Samples of approximately 3 mL of whole blood will be drawn into plastic tubes without anticoagulant for measurement of olaratumab in serum.
- b Samples of approximately 3 mL of whole blood will be drawn into plastic tubes with 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 IRRs, 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/placebo, 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 (± 3 days) after the IRR.
- e Pretreatment PK samples may be collected up to 60 minutes prior to the olaratumab infusion and must be prior to administering any premedication.

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	Prior to olaratumab/placebo infusion ^d	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 (Cycle 1 Day 1 at predose); 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.
- d Pretreatment samples may be collected up to 60 minutes prior to the olaratumab infusion.

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 ^a
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	Fosamprenavir	Dronedarone
Rifabutin	Grapefruit juice, starfruit, Seville orange	Efavirenz
Rifampin	Indinavir	Erythromycin
Rifapentine	Indinavir and ritonavir	FK1706
St. John's wort	Itraconazole	Fluconazole
	Ketoconazole	Fluvoxamine
	Lopinavir and ritonavir	Haloperidol
	Mibefradil	Imatinib
	Miconazole	Metronidazole
	Nefazodone	Norfloracin
	Nelfinavir	Protease inhibitors
	Nicardipine	Quinidine
	Posaconazole	Schisandra sphenanthera extract
	Quinidine	Sertraline
	Ritonavir	Tetracycline
	Saquinavir	Tofisopam
	Telithromycin	Verapamil
	Theophylline	
	Troleandomycin	
	Voriconazole	

^a Aprepitant is allowed when given according to local practice and institutional guidelines and if no alternative anti-emetic is recommended.

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

Attachment 9. Protocol JGDJ Amendment (d) Summary 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

Overview

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, has been amended. The new protocol is indicated by Amendment (d) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- 1) Inclusion criterion [10] was updated to allow patients receiving anticoagulants to participate in the study.
- 2) Inclusion criterion [13] was updated to be consistent with the doxorubicin prescribing information.
- 3) Long-term follow-up for survival and patient reported outcomes were updated so that the collection of this information is concurrent with the collection of ECG data during long-term follow-up.
- 4) Dosing information was clarified for those instances where infusion times at the maximal rate is longer than 60 minutes.
- 5) Clarification of dose delays, modifications, and discontinuations based on hemoglobin levels and nonhematologic toxicity have been made.
- 6) The method of reporting infusion-related reactions was clarified.
- 7) The language for the efficacy interim analysis has been updated to state that only the IDMC and regulatory authorities will have access to the unblinded results. Therefore, there will be no alpha-spending associated with this interim analysis.
- 8) Urine analysis (UA) has been removed from the beginning of each cycle, since it is no longer needed in this setting. Previously, primary purpose for the UA was to determine the presence of significant proteinuria. Proteinuria as a side effect is no longer considered to be related to olaratumab. Urine Analysis will continue to be obtained at baseline and at V801 including urine protein studies if needed.
- 9) Language added to allow use of urine protein creatinine ratio or a 24-hour urine protein excretion. Urine protein creatinine ratio of spot urine is an estimation of the 24-hour urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1000 mg. UPC ratio is calculated using one of the following formulae:
 - a) $\frac{\text{urine protein}}{\text{urine creatinine}}$ – if both protein and creatinine are reported in mg/dL

- b) $[(\text{urine protein}) \times 0.088] / [\text{urine creatinine}]$ – if urine creatinine is reported in mmol/L.
The spot urine test has been preferred by some investigators rather than the 24-hour urine collection.

10) Other edits for clarity and consistency were made.

Revised Protocol Sections

Note: Deletions have been identified by ~~strikethroughs~~.
Additions have been identified by the use of underline.

2. Synopsis

Clinical Protocol Synopsis: Study I5B-MC-JGDJ

Criteria for Evaluation:

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 ~~32~~ months [± 2 weeks ~~7 days~~] for the first ~~2~~ years, ~~then~~ every 6 months [± 2 weeks ~~14 days~~] the second year, then annually [± 2 weeks] thereafter until the patient's death or overall study completion).

Statistical Methods:

The primary objective of this study is to compare doxorubicin plus olaratumab (investigational arm) versus doxorubicin plus placebo (control arm) with respect to OS in 2 populations:

- (1) Patients with advanced or metastatic STS not amenable to treatment with surgery or radiotherapy with curative intent (referred to below as the ITT population)
- (2) Patients with advanced or metastatic LMS not amenable to treatment with surgery or radiotherapy with curative intent

The study will be considered positive if either the ITT or LMS populations (or both) show a statistically significant improvement in OS.

Investigative sites will screen approximately 600 patients to enroll 460 patients in 1:1 randomization (230 patients in the investigational arm and 230 patients in the control arm). Enrollment will be conducted so that approximately 200 patients with LMS and 260 patients with other (non-leiomyosarcoma) histology will be randomized. The final analysis will occur only after both a minimum of 131 OS events have been observed in randomized patients with LMS, and a minimum of 322 OS events have been observed in randomized patients overall.

The statistical analysis will be conducted using a statistical testing plan according to the graphical method of Maurer and Bretz (2013). Under this testing scheme, the primary analysis for OS can be tested in both the LMS population and in the full ITT population, splitting and sharing alpha so as to control the family-wise type 1 error rate across these 2 populations, across interim and final analyses, and also across a prespecified sequence of endpoints (OS and selected secondary endpoints).

The Lan-DeMets form of the O'Brien-Fleming alpha-spending function will be applied for OS and each selected secondary endpoint.

The final total of 131 OS events in the LMS population provides 80% statistical power for a one-sided log-rank test at a 0.005 alpha level, assuming the true OS hazard ratio (HR) in LMS patients is 0.55.

The final total of 322 OS events in the ITT population provides 80% statistical power for a one-sided log-rank test at a 0.02 significance level, assuming the true OS HR in STS patients is 0.723.

An interim efficacy analysis for OS is planned after 194 OS events (60% of the final OS events) have been observed in the ITT population. Time to event analyses at the interim and final analysis time points will be based on the stratified log-rank test, stratified by the randomization strata: number of prior systemic therapies for advanced/metastatic disease (0 versus ≥ 1), histological tumor type (leiomyosarcoma versus liposarcoma versus undifferentiated pleomorphic versus other STS types), and ECOG PS (0 versus 1). The exact testing boundaries will depend on the exact number of events and 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). All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint.

The interim analysis 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 analysis 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.

5.4. Rationale for Amendments

5.4.1. Rationale for Amendment (a)

The rationale for amendment (a) was based on feedback received from global regulatory authorities and compliance with local regulatory requirements for submissions. Major changes for amendment (a) included the following:

- Leiomyosarcoma (LMS) was added as a specific population to be tested within the primary objective, and is now co-primary with the STS (ITT) population.
- Pleomorphic was added to the stratifications factors
- Due to regional/institutional differences dexrazoxane dosing was modified
- PFS2 was added to the efficacy endpoints
- Cardiovascular monitoring was increased
- Gatekeeping methods have been included for OS, PFS, ORR, and DoR
- Grade 1 liposarcoma patients are now included under certain conditions
- The olaratumab dosing regimen was modified
- Management of infusion-related reactions was modified
- Single interim analysis will be performed based on 60% of overall OS events (194) in the ITT population and 72 events from the LMS
- Analysis of OS will be based on the stratified log-rank test analyzed by the randomization strata, excluding region.

5.4.2. Rationale for Amendment (b)

The rationale for amendment (b) was based on global regulatory authority feedback, regulatory guidance and compliance with local regulatory requirements for submissions. Additional changes were made by the sponsor to address issues of subject safety and to improve the efficiency of study implementation and conduct. Major changes for amendment (b) included the following:

- Exclusion criteria were deleted
- Grade 4 nonhematologic toxicity as related to study therapy is now considered a basis for study drug discontinuation
- Duration of Response was deleted from secondary objectives.
- O'Brien-Fleming alpha spending will now be used for all efficacy boundaries
- bisphosphonate osteoclast inhibitors are now allowed, denosumab is still not permitted.

5.4.3. Rationale for Amendment (c)

The rationale for amendment (c) was based on global regulatory authority feedback, regulatory guidance and compliance with local regulatory requirements for submissions. Additional changes were made by the sponsor to address issues of subject safety and to improve the efficiency of study implementation and conduct. Major changes for amendment (c) included the following:

- Germany was directed to refer to Addendum (7)

5.4.4. Rationale for Amendment (d)

The rationale for amendment (d) was to increase subject safety and to improve the efficiency of study implementation and conduct. Major changes for amendment (d) included the following:

- Patients receiving anticoagulants are now eligible to participate
- Long-term follow-up for survival and patient reported outcome collection were updated so that these events are concurrent with the collection of ECG data
- Efficacy interim stopping rules were removed from the protocol plan, as the intention is to continue the study until the final analysis with the sponsor remaining blinded to aggregate data by study arm until the final analysis.
- Urine protein creatinine ratio of spot urine can now be used in place of 24-hour urine protein excretion

See Attachment 9 for more details.

7.1 Inclusion Criteria

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

- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$. Granulocyte colony-stimulating factor (G-CSF) cannot be administered within 2 weeks (14 days) prior to randomization.
- Platelet count $\geq 100 \times 10^9/L$
- Hemoglobin ≥ 9.0 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 Cockcroft-Gault formula)
- Proteinuria ≤ 1000 mg in 24 hours (if routine urinalysis indicates $\geq 2+$ proteinuria)
- Total bilirubin below upper limit of normal (ULN) (except for patients with Gilbert's Syndrome, who must have a total bilirubin < 3 mg/dL)
- Alanine aminotransferase/aspartate aminotransferase (AST/ALT) $\leq 3.0 \times$ ULN; if the liver has tumor involvement, AST and ALT $\leq 5.0 \times$ ULN are acceptable.

- The patient has an adequate coagulation function as defined by International Normalized Ratio (INR) or prothrombin time (PT) $\leq 1.5 \times$ ULN, and partial thromboplastin time (PTT or aPTT) $\leq 1.5 \times$ ULN if not receiving anticoagulation therapy. For patients receiving anticoagulants, exceptions to these coagulation parameters are allowed if they are within the intended or expected range for their therapeutic use. Patients must have no history of active bleeding (defined as within 14 days of first dose of study drug) or pathological condition that carries a high risk of bleeding (for example, tumor involving major vessels or known esophageal varices).

[13] Females of child-bearing potential and males and must agree to use highly effective contraceptive precautions during the trial and up to 63 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.

7.2 Exclusion Criteria

[29] The patient has a known investigator-assessed active fungal, bacterial, or viral infection including human immunodeficiency virus (HIV) or viral (A, B, or C) hepatitis (screening is not required).

8.1 Summary of Study Design

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

- **Baseline:** begins when the ICF is signed (study entry) 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 electronic case report form (eCRF) 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 assessed for progression every 6 weeks (± 7 days) until PD.

- **Follow-up for survival** - Patients will be followed every 23 months (~~±2 weeks~~~~7 days~~) for the first 2 years, ~~then every 6 months (±2 weeks~~~~14 days)~~ the second year, then annually [~~±2 weeks~~] thereafter 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 olaratumab 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.

9.2.1. Olaratumab/Placebo

~~Please refer to the pharmacy manual for olaratumab/placebo dosing solution for infusion. Prepared Olaratumab/Placebo Dosing Solution for Infusion: Chemical and physical in-use stability for the prepared olaratumab/placebo dosing solution has been demonstrated for up to 24 hours below 25°C (77°F) in the concentration range of 1.2 mg/mL to 6.4 mg/mL. It is recommended that the prepared dosing solution be used immediately in order to minimize the risk of microbial contamination. If not used immediately, the prepared olaratumab/placebo dosing solution must be stored under refrigeration at 2°C to 8°C (36°F-46°F) for duration not to exceed 24 hours. If the prepared solution is held at room temperature (below 25°C [77°F]), it must be used within 8 hours. Do not freeze and/or shake prepared olaratumab/placebo dosing solution for infusion.~~

~~Aseptic technique is to be used when preparing and handling olaratumab/placebo. Patients are to receive loading dose of 20 mg/kg on Days 1 and 8 in Cycle 1, followed by 15 mg/kg of olaratumab/placebo on Days 1 and 8 of each 21-day in subsequent 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 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; subsequent doses may also be recalculated if there is a <10% change in body weight from prior dose and it is 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.~~

~~Olaratumab concentration of below 1.2 mg/ml in prepared dose should be avoided due to dilution of excipients, which are important in maintaining stability.~~

The dose of olaratumab/placebo will be aseptically withdrawn from the vial and transferred to a sterile infusion bag or an evacuated glass container. To prepare the dose, 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.

In some cases, the volume of infusion solution required may exceed the 250 mL scenario described here to keep the infusion solution concentration within the desired range stated above. This situation may be more likely with the required loading dose of 20 mg/kg given in Cycle 1, but may also apply to any subsequent cycle depending on the patient's body weight. In case of dose volumes >250 mL, an empty 500 mL container of acceptable material of construction can be used without addition of any normal saline. A pre-filled container (filled with 0.9% normal saline) of >250 mL size can be used as long as the material of construction is acceptable and the concentration of olaratumab in prepared dose remains within 1.2 mg/mL to 6.4 mg/mL.

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 patients with higher body weight for whom the upper limit of infusion rate is limited or in the setting of prior olaratumab/placebo Grade 1-2 IRR); the infusion duration must always be accurately recorded.

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

9.4.1.1. Dose Delays, Modifications, and Discontinuations

After treatment has been initiated, in order to **start** the **next** cycle the following criteria must be fulfilled:

- $ANC \geq 1.0 \times 10^3/\mu L$ (1000/ μL ; $\geq 1.0 \times 10^9/L$)
Note that in order to administer single-agent olaratumab/placebo on Day 8, ANC must be $\geq 750/\mu L$; $\geq 0.75 \times 10^9/L$. If the ANC is $< 750/\mu L$, the Day 8 administration of olaratumab/placebo may be delayed for a maximum of 7 days. If the ANC level has not increased to $\geq 750/\mu L$ within 7 days, then the Day 8 olaratumab/placebo dose in that cycle should be skipped and dosing resumed on Day 1 of the following cycle if criteria for dosing are met. If all dosing criteria are met, a delay or omission of the Day 8 olaratumab/placebo dose should not result in a delay of the Day 1 olaratumab/placebo dose of the following cycle.
- Platelets $\geq 100 \times 10^3/\mu L$ (100,000/ μL ; $\geq 100 \times 10^9/L$)
- Hemoglobin ≥ 8.9 g/dL
- Creatinine clearance ≥ 45 mL/min (refer to Attachment 5 for the Cockcroft-Gault formula)
- ~~Proteinuria ≤ 1000 mg in 24 hours (if routine urinalysis indicates $\geq 2+$ proteinuria)~~

- Total bilirubin below ULN. In patients with Gilbert’s syndrome, total bilirubin should be <3 mg/dL.
- AST and ALT $\leq 3.0 \times$ ULN, or $\leq 5 \times$ ULN if the transaminase elevation is due to liver metastases
- Nonhematologic toxicity/Olaratumab/Placebo related AE’s that are NCI-CTCAE, v4.0 Grade ≤ 2 or equivalent severity to baseline must be less than Grade 2, except for those not deemed clinically significant by the investigator, or electrolyte abnormalities (for example, potassium, magnesium, phosphate).

9.4.1.1.1.1. Infusion Related Reactions

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 or signs occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE terms that best describe the event, ~~“infusion related reaction”~~ and mark “yes” or “no” for hypersensitivity/IRR event flag ~~any additional terms (including those not listed here) that best describe the event.~~

9.4.1.1.1.2. Hematologic Toxicity

Table JGDJ.2. General Guidelines for Olaratumab/Placebo Dose Modification Due To Hematologic Toxicity Deemed Related To Olaratumab/Placebo

Toxicity	Required Dose Modification
<i>Neutropenia</i>	
ANC Grade 1-3	No dose modification required
ANC <500 cells/ μ L (Grade 4)	No treatment administered; treatment cycle delayed
At retreatment:	
If \geq Grade 3 neutropenic fever/infection has occurred	Withhold dose until ANC is 1000 cells/uL or higher; reduce dose to 12 mg/kg (15 mg/kg if toxicity occurs during Cycle 1).
If Grade 4 neutropenia lasting longer than 1 week has occurred	Withhold dose until ANC is 1000 cells/uL or higher; reduce dose to 12mg/kg (15 mg/kg if toxicity occurs during Cycle 1).
Grade 4 ANC without fever/infection	Retreatment with olaratumab/placebo at full dose at investigator’s discretion with recommended use of prophylactic G-CSFs
Second incidence of either: 1) \geq Grade 3 neutropenic fever/infection 2) Grade 4 neutropenia lasting longer than 1 week	Second dose reduction to 10 mg/kg
<i>Thrombocytopenia</i>	
Platelets <100,000 cells/ μ L	No treatment administered; treatment delayed until resolved to $\geq 100,000$ cells/ μ L
<i>Anemia</i>	

Hemoglobin < 8.9 gm/dLNo treatment administered; treatment delayed until resolved to ≥ 8 gm/dL ~~Grade 1~~

 Abbreviations: ANC = absolute neutrophil count; G-CSFs = granulocyte colony-stimulating factors.

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 $[\pm 7$ days] until PD, thereafter every 23 months $[\pm 2$ weeks ~~7 days~~] for the first 2 years, ~~then~~ every 6 months $[\pm 2$ weeks ~~14 days~~] the second year, then annually $[\pm 2$ weeks] thereafter until the patient's death or overall study completion).

12.1. Determination of Sample Size

~~As~~ There is one interim analysis ~~is for efficacy~~ planned for this study. This analysis will be performed in order to provide the IDMC and regulatory authorities an opportunity to review interim safety and efficacy data together. There will be no formal statistical hypotheses tested at the interim for primary and secondary efficacy outcomes. There will be no alpha-spending associated with the interim analysis; study follow-up and data collection will continue as planned until the final analysis regardless of the nature of the interim efficacy results. Only the IDMC and regulatory authorities will be allowed access to unblinded interim data. The hypothesis has its own alpha-spending function. The Lan-DeMets form of the O'Brien-Fleming alpha-spending function will be used in testing each of the hypotheses. This A single interim efficacy analysis is planned to occur after 194 OS events (60% of the final OS events) have been observed in the ITT population. ~~Planned timing and approximate nominal significance levels based on the initial graph and corresponding approximate OS HR boundaries for the interim analysis and the final analysis are as follows (using EAST[®] 6.3):~~

- ~~Interim analysis:~~
 - ~~ITT population: 194 events, one-sided alpha = 0.00267, corresponding approximately to an HR < 0.669~~
 - ~~LMS population: 72 events, one-sided alpha = 0.00015, corresponding approximately to an HR < 0.427~~
- ~~Final Analysis:~~
 - ~~ITT population: 322 events, one-sided alpha = 0.01915, corresponding approximately to an HR < 0.794~~
 - ~~LMS population: 131 events, one-sided alpha = 0.00495, corresponding approximately to an HR < 0.637~~

~~The number of events shown above for the LMS population at the interim analysis is an estimated value, not a required number for performing the analysis. However, the final analysis will occur only after 131 LMS OS events *and* 322 ITT OS events have been observed.~~

12.2.6. Primary Outcome and Methodology

A single interim analysis is planned for efficacy as described in Section 12.1. ~~The interim analysis boundaries and nominal alpha levels will be calculated at the time of conducting interim and final analyses, with efficacy boundaries and alpha values following O'Brien-Fleming alpha-spending functions. The boundaries presented in Section 12.1 are approximate; actual boundaries will depend on the exact timing of the analyses.~~

12.2.13. Interim Analysis

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 (that is, a separate iDMC charter 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).

The iDMC safety reviews will be performed for **all randomized patients**. The first iDMC meeting to review interim data will occur when approximately 80 patients (approximately 40 patients from each arm) have received 2 cycles of treatment or discontinued all study treatment due to any reasons prior to Day 8 in Cycle 2. Subsequent iDMC meetings will occur approximately every 6 months thereafter. Enrollment and treatment will continue during the iDMC safety assessments. In the event a safety signal is detected, additional meetings may occur as needed. Details as to the process and communication plan will be provided in the iDMC Charter.

Interim PK analyses of the approximately 80 patients (approximately 40 patients from each arm) that will accompany the iDMC safety review will be performed by a Lilly PK scientist independent from the study team. These data will be provided to the iDMC upon request.

Interim efficacy analysis will be performed by ~~an the~~ 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.~~

Attachment 1. Protocol JGDJ Study Schedule

Study Schedule, Protocol I5B-MC-JGDJ

Perform procedures as indicated.

Baseline Schedule

		Study Period	Baseline		
		Cycle	BL		
		Visit	0		
		Duration	Up to 14 days (except where noted)		
		Relative Day from Randomization	≤14	≤7	
Procedure Category	Protocol Sections	Procedure			Comments
Lab/ Diagnostic Tests	Att.2	Urinalysis	X		Screening evaluations done within 7 days prior to randomization do not have to be repeated. 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 <u>or a urine protein/creatinine ratio must be <1 in a spot urine test, prior to proceeding to treatment.</u>
Efficacy Assessment	8.1.1 10.1.1 Att. 6	Imaging Studies (CT/MRI) Tumor Assessments (according to RECIST v1.1)	X (within 28 days of randomization)		Within 28 days prior to randomization (refer to Section 10.1.1 and Section 8.1.1 for details).

Treatment Period Schedule

		Study Period	Treatment Period				
		Cycle (21-day cycle ± 3 days)	1-8		9+		
		Relative Day within Cycle (± 3 days)	1 ^a	8 ^a	1 ^a	8 ^a	
Procedure Category	Protocol Section	Procedure					Comments
Physical Examination	10.3.1	Vital signs	X	X	X	X	Vital signs include blood pressure, pulse, and temperature. During the Observation Period (initial 2 cycles), collect vital signs 3 times : 1) within 15 minutes (+5 minutes) prior to olaratumab/placebo infusion, 2) within 1 hour (+5 minutes) after completion of the olaratumab/placebo infusion, and 3) within 1 hour (+5 minutes) after completion of the doxorubicin infusion <u>if applicable</u> . Thereafter (Cycles 3+), obtain vital signs 2 times : 1) within 15 minutes (+5 minutes) prior to olaratumab/placebo infusion and 2) within 1 hour (+5 minutes) after completion of the doxorubicin infusion <u>if applicable</u> .
Lab/ Diagnostic Tests	<u>Att.2</u>	Coagulation Profile	X		X		Laboratory assessments may be done within 3 days prior to Perform on D1 every other cycle or as clinically indicated. See Attachment 2 for details.
	<u>Att.2</u>	Urinalysis	✘		✘		Laboratory assessments may be done within 3 days prior to D1 of every other cycle or as clinically indicated. 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 (up to 3 business days is allowed if the weekend).
Efficacy Assessment	<u>8.1.1</u> 10.1.1 Att. 6	Imaging Studies (CT/MRI) Tumor Assessments (according to RECIST v1.1)	X		X		Imaging studies and tumor assessments are to 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. Refer to Section 10.1.1 <u>and Section 8.1.1</u> for details.

Study Schedule, Protocol I5B-MC-JGDJ

Perform procedures as indicated.

Post-Treatment Discontinuation Schedule

Procedure Category	Protocol Section	Procedure	Post-discontinuation Follow-Up		Comments	
			Study Period	Post-discontinuation Follow-Up		
			Visit	Short-Term Follow-Up		Long-Term Follow-Up
			Duration	30 ± 7 days		See footnote for duration
Lab/ Diagnostic Tests	Att.2	Urinalysis	X		Includes a routine urinalysis (UA), and if clinically indicated a microscopic analysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine collection or urine protein/creatinine ratio in spot urine test (to assess protein) must be obtained.	
Health Outcomes	10.2	PRO Assessments (mBPI-sf, EORTC QLQ C30, EQ-5D-5L)	X	X	The Patient Reported Outcome (PRO) measures will be collected 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 3 2 months [±2 weeks 7 days] for the first 2 years, then every 6 months [±2 weeks 14 days] the second year, then annually [±2 weeks] thereafter until the patient's death or overall study completion).	

Attachment 2. Protocol JGDJ Clinical Laboratory Tests

Clinical Laboratory Tests

- c If urinary protein is ≥2+ at evaluations, a 24-hour urine collection (to assess protein) must be collected or urine protein/creatinine ratio in spot urine test must be conducted, and must be ≤1000 mg of protein in 24 hours (up to 3 business days is allowed if the weekend). Urine protein creatinine ratio of spot urine is an estimation of the 24-hour urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1000 mg. UPC ratio is calculated using one of the following formulae:
 - A) [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
 - B) [(urine protein) x 0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L.