Protocol I5B-MC-JGDL(c)

A Phase 1b (Open-Label) / Phase 2 (Randomized, Double-Blinded) Study Evaluating Gemcitabine and Docetaxel With or Without Olaratumab in the Treatment of Advanced Soft Tissue Sarcoma

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Approval Date: 19-Jul-2017

1. Protocol I5B-MC-JGDL(c)

A Phase 1b (Open-Label) / Phase 2 (Randomized, Double-Blinded) Study Evaluating Gemcitabine and Docetaxel With or Without Olaratumab in the Treatment of Advanced Soft Tissue Sarcoma

Olaratumab (LY3012207)

This is a Phase 1b/2 study in the treatment of patients with advanced or metastatic soft tissue sarcoma. The study consists of a Phase 1b part and Phase 2 part. The Phase 1b part is a single-arm, open-label, dose-escalation study to determine the recommended dose of olaratumab for the Phase 2 part. The Phase 2 part is a randomized, double-blinded, placebo-controlled study to evaluate efficacy and safety of olaratumab with gemcitabine plus docetaxel compared with placebo with gemcitabine plus docetaxel.

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Approval Date: 19-Jul-2017 GMT

2. Synopsis

Study Rationale

The platelet-derived growth factor receptor alpha (PDGFRα) antibody olaratumab in combination with doxorubicin demonstrated a significant improvement in overall survival (OS) over doxorubicin alone in patients with advanced soft tissue sarcoma (STS) (Tap et al. 2016). Since some patients may not be appropriate candidates for doxorubicin-based chemotherapy, or have received prior anthracycline treatment, exploring olaratumab combinations with other chemotherapeutic agents that are often used in STS treatment is of considerable interest. Study I5B-MC-JGDL is a multicenter Phase 1b/2 study of olaratumab in combination with gemcitabine and docetaxel in patients with advanced or metastatic STS, not amenable to treatment with surgical resection or radiotherapy with curative intent. The first part (Phase 1b) of the study will consist of an open-label, single-arm, dose-escalation assessment of the safety and tolerability of olaratumab administered at 15 mg/kg (Days 1 and 8) or 20 mg/kg (Days 1 and 8) with gemcitabine (900 mg/m^2 [fixed dose rate: 10 mg/m^2/minute] Days 1 and 8) and docetaxel (75 mg/m^2 Day 8), of a 21-day cycle. After the dose of olaratumab in combination with gemcitabine and docetaxel has been determined from the analysis of the Phase 1b part, the Phase 2, randomized, double-blinded, placebo-controlled part of the study will open to enrollment. Approximately 256 patients will be randomized in Phase 2 in a 1:1 ratio to Arm A (olaratumab plus gemcitabine and docetaxel) or Arm B (placebo plus gemcitabine and docetaxel).

Clinical Protocol Synopsis: Study I5B-MC-JGDL

Name of Investigational Product: Olaratumab (LY3012207)	
Title of Study: A Phase 1b (Open-Label) / Phase 2 (Randomized, Double-Blinded) Study Evaluating Gemcitabine and Docetaxel With or Without Olaratumab in the Treatment of Advanced Soft Tissue Sarcoma	
Number of Planned Patients: Phase 1b: Entered: Approximately 60 patients Enrolled: Approximately 45 55 patients Phase 2: Entered: Approximately 314 Randomized: 256	**Phase of Development:** 1b/2

Length of Study: approximately 47 months
Planned first patient visit: January 2016
Planned last patient visit: November 2020
Phase 1b planned analysis: All patients in Phase 1b have received at least 1 cycle: safety and pharmacokinetics (PK)
Planned interim safety analyses in the Phase 2 part of the study:

1. Approximately 60 patients in Phase 2 have completed at least 2 cycles of treatment: required safety, PK data if needed.
2. Every 6 months thereafter until approximately 1 year after completing enrollment: required safety, PK data if needed.

Planned interim efficacy analyses in the Phase 2 part of the study:

1. After 40 OS events in olaratumab-pretreated patients.

Objectives:

The primary objective of the Phase 1b part is to determine a recommended Phase 2 dose of olaratumab that may be safely administered in combination with gemcitabine and docetaxel to patients with locally advanced or metastatic STS.

The primary objective of the Phase 2 part is to compare the overall survival (OS) in olaratumab-naïve patients with locally advanced or metastatic STS treated with olaratumab plus gemcitabine and docetaxel versus placebo plus gemcitabine and docetaxel.

The secondary objectives of Phase 1b part are to:

- characterize the safety and toxicity profile of olaratumab in combination with gemcitabine and docetaxel
- evaluate the PK and immunogenicity of olaratumab in combination with gemcitabine and docetaxel
- evaluate the PK of gemcitabine and docetaxel in combination with olaratumab
- document any antitumor activity of gemcitabine and docetaxel in combination with olaratumab

A secondary objective of the Phase 2 part is to compare OS in olaratumab-pretreated patients with locally advanced or metastatic STS treated with olaratumab plus gemcitabine and docetaxel versus placebo plus gemcitabine and docetaxel.

The secondary objectives of the Phase 2 part are to compare olaratumab plus gemcitabine and docetaxel versus placebo plus gemcitabine and docetaxel in both olaratumab-naïve and olaratumab-pretreated groups, for the following:

- progression-free survival (PFS)
- objective response rate (ORR) (complete response [CR] + partial response [PR])
- disease control rate (DCR; CR + PR + stable disease)
- patient-reported outcomes (PROs): Pain, Health-related Quality of Life (HRQoL), and health status
- safety and tolerability
- evaluate the PK and immunogenicity of olaratumab

The exploratory objectives for both Phase 1b and Phase 2 are:

- to explore biomarkers associated with clinical outcome and/or pathogenesis of STS
- to explore the exposure response relationship of olaratumab for efficacy and/or safety

The exploratory objectives for Phase 2 are:

- to evaluate change in tumor size from baseline to best overall response
- assessment of the association between clinical variables, such as histological subtypes, and clinical outcomes

Study Design: This trial is a Phase 1b open-label, dose-escalation part followed by a randomized, double-blind, placebo-controlled Phase 2 study of olaratumab plus gemcitabine and docetaxel in patients with locally advanced or metastatic STS, not amenable to treatment with surgical resection or radiotherapy with curative intent. In the Phase 1b part, 2 cohorts (15 mg/kg or 20 mg/kg) will be studied to determine the olaratumab dose that may be safely administered in combination with gemcitabine and docetaxel. After the dose of olaratumab in combination with gemcitabine and docetaxel has been determined from the Phase 1b part, the Phase 2 part of the study will open to enrollment. In Phase 2, approximately 256 patients will be randomized 1:1, in a double-blinded manner, to Arm A (olaratumab plus gemcitabine and docetaxel) or Arm B (placebo plus gemcitabine and docetaxel). Randomization will be stratified by prior treatment with olaratumab (yes versus no), number of prior systemic therapies for locally advanced or metastatic disease (0 versus ≥1), histological tumor type (leiomyosarcoma versus non-leiomyosarcoma), Eastern Cooperative Oncology Group performance status (ECOG PS) (0 versus 1), and prior pelvic radiation (yes versus no). Patients will continue treatment until there is documented disease progression, unacceptable toxicity, death, or other discontinuation criteria are met.

Diagnosis and Main Criteria for Inclusion and Exclusions: Patients at least 16 years of age, ECOG PS 0 to 1, gemcitabine and docetaxel naïve, with histologically confirmed, locally advanced, unresectable or metastatic STS, and not amenable to curative treatment with surgery or radiotherapy. Patients with gastrointestinal stromal tumor or Kaposi's sarcoma will be excluded. Patients previously enrolled in Study I5B-MC-JGDJ or any other blinded study with olaratumab are not eligible to participate in this trial.

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 over approximately 60 minutes

For the Phase 1b part: Olaratumab will be administered at a dose of 15 mg/kg or 20 mg/kg on Days 1 and 8 of each 21-day cycle.

For the Phase 2 part: Olaratumab will be administered at the dose determined by the analysis in the Phase 1b part on Days 1 and 8 of each 21-day cycle.

Reference Therapy, Dose, and Mode of Administration:

For the Phase 1b and 2 parts:

Gemcitabine is a commercially available product and should be stored, reconstituted, and discarded per manufacturer's instructions. Gemcitabine is administered at a dose of 900 mg/m^2 over approximately 90 minutes (fixed dose rate: 10 mg/m^2/minute) on Days 1 and 8 of each 21-day cycle.

Docetaxel is a commercially available product and should be prepared and administered according to the manufacturer's instructions. Docetaxel is administered at a dose of 75 mg/m^2 (IV) over approximately 60 minutes on Day 8 of each 21-day cycle.

For the Phase 2 part:

Placebo: injection for IV use, supplied in single-use vials, administered to patients as an IV infusion over approximately 60 minutes on Days 1 and 8 of each 21-day cycle

Planned Duration of Treatment: Treatment continues until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met. In the event of permanent discontinuation of olaratumab/placebo therapy due to an olaratumab/placebo-related toxicity, patients may continue on gemcitabine and docetaxel treatment per protocol. If either gemcitabine or docetaxel are permanently discontinued due to toxicity, the patient should discontinue active treatment with the gemcitabine/docetaxel combination. However, the patient may continue treatment with olaratumab/placebo alone, at the discretion of the investigator. Any changes in treatments being added to or removed from patient care will be recorded on the eCRF.

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

Long-term follow-up (postdiscontinuation): Patients that discontinue study treatment for reasons other than progression will be followed every 6 weeks (±7 days) until progressive disease (PD), thereafter every 3 months (±7 days) for the first year, 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 in the Phase 2 part.

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

In the Phase 2 part, 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
- 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 sustained worsening of The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0 (EORTC 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 PS
- second PFS (PFS2) after end of study treatment while on subsequent anticancer therapy

Safety:

Phase 1b: will include a Cycle 1 dose-limiting toxicity (DLT) evaluation period

Phase 1b and 2: Safety will be evaluated based on reported adverse events (AEs), physical examinations, vital signs, laboratory tests, and electrocardiograms (ECGs). 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 EORTC QLQ-C30 and health status 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. For those patients who discontinued for reasons other than PD, a full due diligence will be taken to collect PRO measures during long-term follow-up, every 6 weeks [±7 days] until PD.

Immunogenicity: Blood samples will be collected to evaluate immunogenicity at baseline, during the study, and at the 30 day follow-up visit. In the event of an olaratumab/placebo infusion-related reaction (IRR), serum will be collected as close as possible to the onset of the IRR, at the resolution of the IRR, and 30 days (±3 days) after the IRR.

Pharmacokinetics:

Phase 1b: PK parameters, such as maximal concentration (C_{max}), time of C_{max} (t_{max}), area under the concentration-time curve (AUC), volume of distribution at steady state (V_{ss}), clearance (CL), and half-life ($t_{1/2}$) for olaratumab, gemcitabine and its metabolite (dFdU), and docetaxel

Phase 2: Population PK parameters for olaratumab

Biomarkers: Assessment of the association between biomarkers and clinical outcomes

Statistical Methods:

Statistical:

Efficacy: Phase 2: The primary objective is to compare OS in olaratumab-naïve patients with locally advanced or metastatic STS treated with olaratumab plus gemcitabine and docetaxel versus placebo plus gemcitabine and docetaxel. Patients will be randomized 1:1 to the 2 treatment arms. The intention-to-treat (ITT) sample size of 166 for olaratumab-naïve patients (83 in the experimental arm and 83 in the control arm) was selected assuming the final analysis of OS will occur after 108 OS events have been observed (35% censoring).

The final total of 108 OS events in the olaratumab-naïve patients (deaths) provides 80% statistical power for a two-sided log-rank test at a 0.20 significance level (assuming the true OS hazard ratio [HR] is 0.665). An OS HR of 0.665 corresponds approximately to an increased median survival from 15 months (estimated from published clinical data in various types of patients with locally advanced or metastatic STS) in placebo plus gemcitabine and docetaxel to 22.5 months for olaratumab plus gemcitabine and docetaxel.

An additional 90 olaratumab-pretreated patients (45 in the experimental arm and 45 in the control arm) will be randomized to compare the same regimens as a secondary objective.

The primary efficacy outcome for the Phase 2 part of the study is OS in the olaratumab-naïve cohort of the ITT population. Analysis of OS will be based on the stratified log rank test, stratified by the 3 of the 4 randomization strata; that is, number of prior systemic therapies for locally advanced or metastatic disease (0 versus ≥1), histological tumor type (leiomyosarcoma versus non-leiomyosarcoma), and ECOG PS (0 versus 1).

Overall survival curves, the median with 95% confidence interval (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 the aforementioned 3 randomization strata. All ITT population will be included in the analysis of this endpoint. The same OS analyses will also be performed separately for the olaratumab-pretreated cohort of the ITT population.

Safety: The safety analyses will be performed on the safety population defined as all enrolled patients in Phase 1b and all randomized patients in Phase 2, who received at least 1 dose, including a partial dose, of any study treatment.

In the Phase 1b part, DLT will be summarized by cohort in the patients who are evaluable for DLT assessments and be listed by patient. For Phase 1 b and Phase 2, the 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 will be summarized. Additionally, for Phase 1b and Phase 2 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 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, 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, 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. Data will be separately summarized using descriptive statistics. Analyses of time to worsening of pain as well as HRQoL scales will be conducted.

Immunogenicity: Incidence of treatment-emergent anti-olaratumab antibodies and any additional related assays will be tabulated. Correlation to olaratumab drug level, efficacy, and safety will be assessed, as appropriate.

Pharmacokinetics:
Phase 1b part: the PK parameter estimates for olaratumab, gemcitabine and its metabolite (dFdU), and docetaxel will be calculated by standard noncompartmental methods. Descriptive statistics will be calculated for PK parameters, but no formal statistical analysis is planned.
Phase 2 part: PK parameters for olaratumab (CL, exposure, V_{ss}, and $t_{1/2}$) and inter-individual PK variability will be computed using nonlinear mixed effect modeling implemented in NONMEM. Gemcitabine, dFdU, and docetaxel plasma levels will be reported using descriptive methods.

Exploratory biomarkers: Assay results will be summarized and correlated with clinical outcomes.

Interim analysis:
There will be safety interim reviews for both Phase 1b and Phase 2 parts. In addition, an interim efficacy analysis is planned for the Phase 2 part of the study.
The safety review for Phase 1b will be conducted by Lilly clinical research personnel. The study investigators and the Lilly clinical research physician/clinical research scientist (CRP/CRS) will make the determination regarding dose escalation based upon their review of the safety/tolerability data and the PK data from the previous cohorts. In addition, an interim safety review will be conducted prior to proceeding to Phase 2 including safety and PK.

An independent data monitoring committee (iDMC) will be established to conduct Phase 2 safety interim reviews. The first iDMC meeting to review interim data will occur when approximately 60 patients (approximately 30 patients from each arm) have received at least 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 regularly thereafter.

An interim efficacy analysis is planned for the Phase 2 part of the study. After observing 40 OS events among the olaratumab-pretreated cohort of the ITT population, interim analysis will occur. Any positive interim efficacy results may be used for planning of additional separate clinical studies, but will not be used to modify the design and conduct of this current trial.

3. Table of Contents

A Phase 1b (Open-Label) / Phase 2 (Randomized, Double-Blinded) Study Evaluating Gemcitabine and Docetaxel With or Without Olaratumab in the Treatment of Advanced Soft Tissue Sarcoma

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4. Abbreviations and Definitions

Term	Definition
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
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study required by some ethical review boards [ERBs]) or (required by some institutional review boards [IRBs]).
AST	aspartate aminotransferase
AUC	area under the curve
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
blinding/masking	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
CI	confidence interval
CNS	central nervous system
collection database	A computer database where clinical trial data are entered and validated.

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 study treatment 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 (CRS), global safety physician, or other medical officer.
CRS	clinical research scientist
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
dFdU	2',2'-difluorodeoxyuridine
DLT	dose-limiting toxicity
DoR	duration of response
ECG	Electrocardiogram
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/randomize	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. Phase 1b part: Enroll Phase 2 part: Randomize
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.

EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0
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.
FSH	follicle-stimulating hormone
GCP	good clinical practice
G-CSF	granulocyte-colony-stimulating factor
GIST	gastrointestinal stromal tumors
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
IgG1	immunoglobulin G subclass 1
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient substance or placebo being tested, or used as a reference, in a clinical trial. Investigational product (IP) includes a product with a marketing authorization when: 1. used or assembled (formulated or packaged) in a way different from the authorized form, 2. used for an unauthorized indication, or 3. used to gain further information about the authorized form.

investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRR	infusion-related reaction
ITT	intention-to-treat The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive web-response system
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
LMS	Leiomyosarcoma
mBPI-sf	modified Brief Pain Inventory-short form
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
Olaratumab naïve	A study participant who has never received olaratumab prior to enrollment or randomization
Olaratumab pretreated	A study participant who has previously received commercially available olaratumab, as defined by the inclusion criteria
ORR	overall 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
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor

PET	positron emission tomography
PFS	progression-free survival
PFS2	second progression-free survival (after end of study treatment while on subsequent anticancer therapy)
PK	Pharmacokinetics
PR	partial response
PRO/ePRO	patient-reported outcome/electronic patient-reported outcome
PS	performance status
PT	Preferred Term
QTc	corrected QT interval
randomize	the process of assigning patients to an experimental group on a random basis
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
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).
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
STS	soft tissue sarcoma
Study completion	This Phase 1b/2 study will be considered complete after the final analysis/evaluation of overall survival is performed.
Study Treatment	olaratumab/placebo, gemcitabine, and docetaxel
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.
UK	United Kingdom
ULN	upper limits of normal
US	United States
VAS	visual analog scale

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5. Introduction

5.1. Soft Tissue Sarcoma

Soft tissue sarcoma (STS) is a heterogeneous group of malignant tumors that arise from tissue of mesenchymal origin. Soft tissue sarcoma arises primarily from the embryonic mesoderm, with some neuroectodermal contribution and differentiation to non-epithelial extraskeletal tissue, including striated skeletal and smooth muscle, adipose, and fibrous tissue (Sharma et al. 2013; D'Angelo et al. 2014; Linch et al. 2014). There are approximately 50 different types of STS that can be found in almost any anatomic location (American Cancer Society 2014; Linch et al. 2014). STS is rare, comprising approximately 1% of adult cancers. The annual incidence of STS in the United Kingdom (UK) and United States (US) is 3300 and 10,000, respectively (Jemal et al. 2009; National Cancer Institute 2013). A multidisciplinary setting with teams specializing in the treatment of STS is the best treatment approach for these tumors. Management of localized disease is usually with curative intent, using surgical resection with or without radiotherapy and chemotherapy. In spite of initial aggressive management, there is a frequent recurrence of local inoperable or metastatic disease, and at this point systemic therapy plays a prominent role in the multidisciplinary management of STS (Linch et al. 2014).

The mainstay therapy for treating advanced-stage STS has been chemotherapy, which in the first-line setting has provided overall response rates of approximately 25% (Linch et al. 2014). Even with the use of chemotherapy, advanced-stage STS is usually fatal and there remains a need for novel and effective therapies. Doxorubicin either alone or in combination has served as the initial treatment for metastatic sarcoma for many years. Various other drug combinations have also been explored (Linch et al. 2014).

In recent years, some groups have reported that the combination of gemcitabine plus docetaxel is effective against metastatic STS due to its broad spectrum of activity and has a favorable toxicity profile (in comparison with doxorubicin and ifosfamide) (Ravi et al. 2015). Maki et al (2007) studied the combination of gemcitabine plus docetaxel versus gemcitabine alone in 122 patients with metastatic STS. In this study, gemcitabine (fixed dose rate of 900 mg/m^2 on Days 1 and 8) in combination with docetaxel (100 mg/m^2 on Day 8) yielded a longer progression-free survival (PFS) (6.2 months versus 3 months) and overall survival (OS) (17.9 months versus 11.5 months) when compared to gemcitabine alone. The most common Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 to 4 toxicity was thrombocytopenia (38%). Grade 3 to 4 thrombocytopenia was 35% and 40% in the gemcitabine (N=49) and gemcitabine plus docetaxel (N=73) arms, respectively (Maki et al. 2007).

In the randomized Phase 3 trial of doxorubicin versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic STS (Judson et al. 2014), doxorubicin in combination with ifosfamide had a higher overall response (ORR) (26% versus 14%) and a longer PFS (7.4 months versus 4.6 months), although there was no significant difference in OS. The most common Grade 3 to 4 toxicity in the combination arm was febrile neutropenia (46%). Ifosfamide-related Grade 2 encephalopathy occurred in 2% (4 of 224) of patients and ifosfamide-related Grade 3 encephalopathy occurred in 4% (10 of 224) of patients. Only 5 cases of treatment-related renal dysfunction occurred, all in the doxorubicin plus ifosfamide arm (Judson et al. 2014).

Hensley et al (2008a, 2008b) studied the combination of gemcitabine and docetaxel in patients with leiomyosarcomas (LMS). Gemcitabine was administered at a fixed dose rate of 900 mg/m^2 over 90 minutes on Days 1 and 8 while docetaxel was administered at 100 mg/m^2 on Day 8. Objective response rates were 36% and 27% when the combination was used as first-line and second-line agents, respectively. When the combination was used as first-line therapy (N= 42; Hensley et al 2008b), myelosuppression was the major toxicity: neutropenia Grade 3 in 5% of patients, Grade 4 in 12%; anemia Grade 3 in 24%; and thrombocytopenia Grade 3 in 9.5%, Grade 4 in 5%. Fatigue was Grade 3 in 17% of patients. When the combination was used as second-line therapy (N= 51; Hensley et al. 2008a), the predominant toxicity was uncomplicated myelosuppression: thrombocytopenia Grade 3 (29%), Grade 4 (10.4%); neutropenia Grade 3 (12.5%), Grade 4 (8.3%); anemia Grade 3 (20.8%), Grade 4 (4.2%). While pulmonary toxicity was reported, no patient had drug-related pneumonitis/hypoxia-type toxicity.

A French study group (Pautier et al. 2012) compared, prospectively, the gemcitabine and docetaxel combination to gemcitabine monotherapy in advanced LMS after anthracycline failure. In a group of 90 patients, they confirmed the efficacy of both regimens; the 3-month PFS rates in the gemcitabine monotherapy arm and gemcitabine plus docetaxel arm were 57% and 71% in the uterine group and 68% and 53% in the non-uterine group, respectively, with no significant difference between the 2 arms.

A more recent Phase 2 study (N=44) conducted in first-line metastatic / advanced LMS patients in London demonstrated that gemcitabine plus docetaxel is an active regimen with 70.5% and 59.1% patients with no progression at 3 and 6 months, respectively (Seddon et al. 2015a). The most common Grade 3 or 4 toxicities were fatigue (30%), anemia (24%), dyspnea (16%), neutropenia (12%), and infection (any, 12%). Thrombocytopenia Grade 3 or 4 was 7% (Seddon et al. 2015a). In a recently completed randomized Phase 3 trial of gemcitabine plus docetaxel versus doxorubicin in the first-line treatment of patients with unresectable or metastatic STS, there was no statistical difference in the 6-month PFS rate, median PFS, and OS between the 2 treatment arms (Seddon et al. 2015b). Gemcitabine was administered at a fixed dose rate of 675 mg/m2 on Days 1 and 8 while docetaxel was administered at 75 mg/m2 on Day 8. Significant Grade 3 to 4 toxicities included febrile neutropenia of 20.3% and 11.9% in the doxorubicin (N=128) and gemcitabine plus docetaxel (N=126) arms, respectively. Grade 3 to 4 oral mucositis was 12.5% and 1.6% in the doxorubicin and gemcitabine plus docetaxel arms, respectively. However, Grade 3 to 4 fatigue was more common in the combination arm, 13.5%

versus 6.3%. Grade 3 to 4 diarrhea was also more common in the combination arm, 7.9% versus 1.6% (Seddon et al. 2015b). Although the PFS hazard ratio (HR) favored the doxorubicin arm (1.28 [95% confidence interval {CI} 0.98-1.67]; p=0.07), it was concluded that doxorubicin remains a first-line standard and confirmed gemcitabine/docetaxel activity in patients with unresectable or metastatic STS (Seddon et al. 2015b).

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 (PDGFRα). This antibody possesses high affinity binding for PDGFRα and blocks platelet-derived growth factor (PDGF)-AA, -BB, and -CC from binding to the receptor. In addition to blocking ligand-induced cell mitogenesis and receptor autophosphorylation, olaratumab inhibits ligand-induced phosphorylation of the downstream signaling molecules Akt and mitogen-activated protein kinase (Loizos et al. 2005; Study Report IMC-3G3-01).

In normal mesenchymal biology, PDGF/PDGFR signaling has a significant role in mesenchymal stem cell differentiation, growth of mesenchymal cells, angiogenesis, and wound healing (Andrae et al. 2008; Ng et al. 2008; Li et al. 2014). PDGF/PDGFRα signaling has been implicated in the pathogenesis of multiple cancers, including osteosarcoma, chondrosarcoma, prostate cancer, breast cancer, ovarian cancer, and others. In malignant disease, the PDGF/PDGFRα axis promotes tumor growth and proliferation through both autocrine and paracrine mechanisms. PDGFRα is expressed on stromal cells, as well as the cancer cells themselves, within certain tumors. Furthermore, studies have shown that PDGF/PDGFRα signaling affects tumor vasculature through paracrine mediation of vascular endothelial growth factor production (Shah et al. 2010). Additional information is available in the olaratumab investigator's brochure (IB).

5.3. Study Rationale

The randomized Phase 2 part of Study I5B-IE-JGDG ([JGDG; [IMCL CP15-0806]; olaratumab plus doxorubicin versus doxorubicin alone) met its protocol-defined primary endpoint of PFS. The combination of olaratumab and doxorubicin (investigational arm) in this trial showed a statistically significant and clinically meaningful improvement in median OS (11.8-month improvement; HR=0.463; p=0.0003) over doxorubicin alone (control arm). 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% 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 and 69.2% of patients in the control arm. Grade ≥3 adverse events (AEs) occurring in at least 10% of patients in the investigational arm included *neutropenia* (consolidated term; 54.7% [investigational arm] versus 33.8% [control arm]), *anemia* (consolidated term; 12.5% versus 9.2%), and febrile neutropenia (12.5% versus 13.8%). Although the incidence of neutropenia was increased in the

investigational arm, the combination of olaratumab and doxorubicin did not result in an increased overall incidence of febrile neutropenia or infections. In general, the overall safety profile of the combination of olaratumab and doxorubicin was consistent with the known toxicities of doxorubicin.

While doxorubicin alone or in combination has been the mainstay of treatment for decades, (Linch et al. 2014), in more recent years, gemcitabine plus docetaxel has demonstrated to be an effective treatment against metastatic STS (Maki et al. 2007; Hensley et al. 2008a, 2008b, 2013). In a patient-derived xenograft model of human liposarcoma, olaratumab in combination with gemcitabine plus docetaxel inhibited tumor growth to a greater extent than docetaxel plus gemcitabine alone (p=0.05).

The positive efficacy results seen with olaratumab in combination with doxorubicin in Study JGDG (Tap et al. 2016) warrant further study of olaratumab with gemcitabine plus docetaxel, another active treatment regimen, for patients with advanced or metastatic STS.

Study I5B-MC-JGDL will evaluate the efficacy and safety of olaratumab, in combination with docetaxel and gemcitabine (fixed dose rate: 10 mg/m^2/minute) in patients with locally advanced or metastatic STS. The study will allow this evaluation in both olaratumab-naïve and olaratumab-pretreated populations. Olaratumab-naïve patients are those who may be ineligible for treatment with doxorubicin or for whom gemcitabine/docetaxel is more appropriate as initial chemotherapy than doxorubicin.

More information about the known and expected benefits, risks, and reasonably anticipated AEs of olaratumab may be found in the 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.

5.4. Rationale for Selection of Dose

Olaratumab:

The current dose-selection strategy for this study is based on the integrated safety, efficacy, and pharmacokinetics (PK) data for olaratumab across previous Phase 1 and Phase 2 studies. In 2 Phase 1 dose-escalation trials (Studies I5B-IE-JGDC and I5B-IE-JGDF) and in the 2 Phase 2 monotherapy studies (Studies I5B-IE-JGDE and I5B-IE-JGDH), single-agent olaratumab has consistently been well tolerated, with no dose-limiting toxicities (DLTs) observed up to a dose of 20 mg/kg administered every 2 weeks and up to a dose of 15 mg/kg administered on Days 1 and 8 of a 21-day cycle. When used in combination with liposomal doxorubicin in Study I5B-IE-JGDA (olaratumab dose of 20 mg/kg every 2 weeks), and with paclitaxel plus carboplatin in Study I5B-IE-JGDB (olaratumab dose of 15 mg/kg Days 1 and 8 every 3 weeks), a higher rate of toxicities such as neutropenia and infections was observed versus the comparator agents. As of 30 June 2016, 790 patients have received olaratumab through Phase 1, Phase 2, and Phase 3 studies . In Study JGDG, although there was a higher incidence of some known doxorubicin

toxicities such as mucositis, nausea/vomiting, and diarrhea, these were monitorable, predominantly Grade ≤ 2, and did not lead to a higher incidence of treatment discontinuation. 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.

In addition, final PFS and OS data from Study JGDG show that the combination of olaratumab 15 mg/kg with doxorubicin 75 mg/m^2 provides a significant benefit compared to single-agent doxorubicin in patients with advanced metastatic STS, without an increase in serious toxicity.

Based on the available clinical evidence, the Phase 1b part of this study will start the olaratumab dose escalation at 15 mg/kg. Based on the safety and PK results from the dose escalation at the end of the Phase 1b part of this study, an appropriate dose will be selected for the Phase 2.

Gemcitabine and Docetaxel:

The combination of gemcitabine and docetaxel is an effective option for patients with metastatic sarcoma and has been studied using a diverse range of doses and across subtypes (Maki et al. 2007).

Infusion of gemcitabine at a fixed-dose rate refers to infusing gemcitabine at a continuous rate enabling the maintenance of the gemcitabine concentration at a level that will optimize the incorporation of gemcitabine triphosphate, which is the active gemcitabine metabolite, into deoxyribonucleic acid (DNA) (Hensley et al. 2008a). Studies have shown that gemcitabine may have greater activity when given as a fixed-dose rate infusion (10 mg/m^2/min) compared with the recommended schedule (a 30-minute infusion) (Tempero et al. 2003).

Fixed-dose rate gemcitabine (900 mg/m^2 over 90 minutes [fixed dose rate of 10 mg/m^2/min], Days 1 and 8, plus docetaxel 100 mg/m^2 on Day 8) yielded high objective response rates among patients with advanced leiomyosarcoma in both the second-line, and first-line setting (Hensley et al. 2008a, 2008b). However, to increase the tolerability of this chemotherapy regimen a docetaxel dose of 75 mg/m^2, which is lower than 100 mg/m^2, has been selected for this study. Some of the toxicity seen in previous clinical experience (fatigue, asthenia, and fluid retention) was more typical of the docetaxel counterpart, suggesting that this docetaxel dose modification could improve the tolerability of this regimen. This is consistent with the 75-mg/m^2 docetaxel dose chosen in recent Phase 3 GeDDiS trial (Seddon et al. 2015b). Therefore, this Phase 1b/2 trial investigates the efficacy and safety of olaratumab in combination with gemcitabine (900 mg/m^2 over 90 minutes [fixed-dose rate of 10 mg/m^2/min]) and docetaxel (75 mg/m^2) for the treatment of locally advanced or metastatic STS that is not amenable to treatment with surgical resection or radiotherapy with curative intent.

5.5. Rationale for Amendments

5.5.1. 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: new descriptive language on premedication prior to

olaratumab/placebo doses on Days 1 and 8 of Cycle 1 and in subsequent cycles. Clarification was also added related to the olaratumab observation period. Additionally, the introduction was updated to include commonly observed AEs for gemcitabine and docetaxel from published studies, and to include data from the final primary analysis for efficacy and safety for Study I5B-IE-JGDG.

5.5.2. Rationale for Amendment (b)

The protocol was amended to allow for expansion of the olaratumab 20 mg/kg dose level (Cohort 2) by enrolling approximately 15 additional patients. The rationale for adding an additional 15 patients to Cohort 2 is to confirm the safety of the 20 mg/kg dose level prior to opening the Phase 2 randomized double-blinded portion of the trial. Refer to Section 8.1.1 for further details.

5.5.3. Rationale for Amendment (c)

As doxorubicin in combination with olaratumab becomes more common in clinical practice for advanced or metastatic STS, additional evaluation in olaratumab-pretreated patients is warranted in order to understand the effect of olaratumab as continuation therapy with regimens such as gemcitabine/docetaxel that are customarily administered after maximal doxorubicin dosing. Additionally, the concept of continuing a biologic treatment with a change in chemotherapy backbone is supported by evidence of on-going treatment effect of trastuzumab and bevacizumab in multiple lines of therapy in HER2 positive breast cancer and metastatic colon cancer, respectively. Furthermore, resistance to antibody therapy in cancer is via separate mechanisms than chemotherapy resistance, supporting the theory that continued benefit from olaratumab is possible after progressive disease on other chemotherapy regimens. Finally, due to potential effect on PDGFRα expressing stromal cells, continued olaratumab exposure may lead to favorable changes in the tumor microenvironment irrespective of change in chemotherapy regimen. The evaluation of olaratumab in combination with gemcitabine and docetaxel in olaratumab pre-treated patients will be a secondary objective. Ninety patients will be added as this is deemed to be an adequate number to observe a signal for strategic planning of future studies. The protocol amendment also adds an interim efficacy analysis of all study outcomes to allow for timely Phase 3 development strategies.

6. Objectives

6.1. Primary Objective

Phase 1b

The primary objective of the Phase 1b part is to determine a recommended Phase 2 dose of olaratumab that may be safely administered in combination with gemcitabine and docetaxel to patients with locally advanced or metastatic STS.

Phase 2

The primary objective of the Phase 2 part is to compare the OS in olaratumab-naive patients with locally advanced or metastatic STS treated with olaratumab plus gemcitabine and docetaxel versus placebo plus gemcitabine and docetaxel.

6.2. Secondary Objectives

Phase 1b

The secondary objectives of Phase 1b part are the following:

- characterize the safety and toxicity profile of olaratumab in combination with gemcitabine and docetaxel
- evaluate the pharmacokinetics (PK) and immunogenicity of olaratumab in combination with gemcitabine and docetaxel
- evaluate the PK of gemcitabine and docetaxel in combination with olaratumab
- document any antitumor activity of gemcitabine and docetaxel in combination with olaratumab

Phase 2

A secondary objective of the Phase 2 part is to compare OS in olaratumab-pretreated patients with locally advanced or metastatic STS treated with olaratumab plus gemcitabine and docetaxel versus placebo plus gemcitabine and docetaxel.

The secondary objectives of the Phase 2 part are to compare olaratumab plus gemcitabine and docetaxel versus placebo plus gemcitabine and docetaxel in both olaratumab-naïve and olaratumab pre-treated groups, for the following:

- 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
- safety and tolerability
- evaluate the PK and immunogenicity of olaratumab

6.3. Exploratory Objectives

For both Phase 1b and Phase 2

- to explore biomarkers associated with clinical outcome and/or pathogenesis of STS
- to explore the exposure-response relationship of olaratumab for efficacy and/or safety

For Phase 2 Only

- to evaluate change in tumor size from baseline to best overall response
- assessment of the association between clinical variables, such as histological subtypes, and clinical outcomes

7. Study Population

Eligible patients will have a histological diagnosis of locally advanced or metastatic STS, by local pathology review, 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 in order 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.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. 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 or patient's parent/guardian signed an informed consent/assent form and authorization for release of health information for research prior to any study-specific procedures being performed.

[2] The patient is aged ≥16 years at time of consent.

[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 (Atypical Lipomatous Neoplasms) are eligible if there is histological or radiographic evidence of evolution to more aggressive disease.

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 5). 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 may have no more than 2 prior lines of systemic therapies (neoadjuvant and adjuvant therapies will not be considered as a prior line of therapy) for locally advanced or metastatic disease and is suitable to receive gemcitabine and docetaxel therapy. All previous anticancer treatments must have completed ≥ 3 weeks (21 days) prior to first dose of study drug.

- In the Phase 2 part, prior olaratumab/doxorubicin combination therapy in 1 prior treatment line is allowed.
    - Prior olaratumab therapy must have been received with doxorubicin as indicated on the olaratumab label.
    - Prior olaratumab therapy must have included at least 2 full cycles of olaratumab/doxorubicin (i.e. a minimum of 4 doses of olaratumab).
    - Patients, who completed at least 2 cycles of combination olaratumab/doxorubicin therapy then discontinued doxorubicin due to toxicity or maximum dosing and proceeded to olaratumab monotherapy, are eligible.
    - The most recent dose of olaratumab must have been received within 180 days of randomization in this study.

[7] The patient has resolution of adverse events, with the exception of alopecia, and of all clinically significant toxic effects of prior locoregional therapy, surgery, radiotherapy, or systemic anticancer therapy to ≤ Grade 1, by National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0.

[8] Availability of tumor tissue is mandatory for study eligibility. The patient must have consented to provide archived formalin-fixed paraffin-embedded 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 10.4.2.2 regarding tissue collection parameters).

[9] The patient has adequate hematologic, organ, and coagulation function within 2 weeks (14 days) prior to enrollment (Phase 1b) or randomization (Phase 2):

- Absolute neutrophil count (ANC) ≥1.5 x 10^9/L. Granulocyte-colony-stimulating factor (G-CSF) cannot be administered within 2 weeks (14 days) prior to enrollment (Phase 1b) or randomization (Phase 2).
- Platelet count ≥100 x 10^9/L
- Hemoglobin ≥9.0 g/dL. No transfusions are allowed within 2 weeks (14 days) prior to enrollment (Phase 1b) or randomization (Phase 2).
- Serum creatinine ≤1.5 times upper limit of normal (ULN). If creatinine is above the upper limit of normal (ULN), the patient's creatinine clearance is ≥ 45 mL/min (refer to Attachment 8 for the Cockcroft-Gault formula for creatinine clearance).
- Total bilirubin below ULN (except for patients with Gilbert's Syndrome, who must have a total bilirubin <3 mg/dL)
- Alanine aminotransferase/aspartate aminotransferase (ALT/AST) ≤ 3.0 × ULN; if the liver has tumor involvement, AST and ALT ≤5.0 × ULN are acceptable
- The patient has an adequate coagulation function as defined by International Normalized Ratio (INR) ≤1.5 × ULN or prothrombin time (PT) ≤1.5 × ULN, and partial thromboplastin time (PTT or aPTT) ≤1.5 × ULN if not on anticoagulant 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).
- If routine urinalysis indicates ≥2+ proteinuria, patient must have ≤1000 mg protein on a 24-hour urine, or urine protein/creatinine ratio ≤ 1 on spot urine.

[10] Females of child-bearing potential must have a negative serum pregnancy test within 7 days prior to enrollment (Phase 1b) or randomization (Phase 2).

(a) Exceptions: Females <u>not</u> 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

[11] Females of child-bearing potential and males must agree to use highly effective contraceptive precautions during the trial and up to 3 months following the last dose of study treatment. 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.

[12] 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:

[13] The patient is diagnosed with gastrointestinal stromal tumor (GIST) or Kaposi sarcoma.

[14] The patient has active central nervous system (CNS) or leptomeningeal metastasis (brain metastasis) at the time of enrollment (Phase 1b) or randomization (Phase 2). 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 enrollment (Phase 1b) /randomization (Phase 2) to rule out brain metastasis.

[15] The patient has received prior treatment with gemcitabine or docetaxel

Note: Patients previously enrolled in the I5B-MC-JGDJ or any other blinded study with olaratumab are not eligible to participate in this trial.

[16] The patient has history of another primary malignancy, with the exception of

- Curatively treated non-melanomatous skin cancer or
- Curatively treated cervical carcinoma in situ or
- Non-metastatic prostate cancer, treated only with observation or
- Other primary nonhematologic malignancies or solid tumors treated with curative intent, no known active disease, and no treatment administered during the last 3 years prior to enrollment (Phase 1 b) or randomization (Phase 2).

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

[18] The patient has a serious cardiac condition, such as congestive heart failure; New York Heart Association Class III/IV heart disease; unstable angina pectoris, cardiac stenting within 6 months of enrollment (Phase 1b) or randomization (Phase 2); myocardial infarction within the last 3 months; valvulopathy that is severe, moderate, or deemed clinically significant; or arrhythmias that are symptomatic or require treatment.

[19] Females who are pregnant or breastfeeding.

[20] 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 enrolled (Phase 1 b) or randomized (Phase 2) 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.

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

[22] The patient has Grade 3 or 4 peripheral neuropathy by NCI-CTCAE Version 4.0.

[23] The patient has a history of Grade 3 or 4 infusion-related reaction (IRR) to olaratumab or discontinued olaratumab due to other significant toxicity.

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 enrolled (Phase 1b) and randomized (Phase 2) patients who discontinue, regardless of whether or not they received study treatment, will have procedures performed as shown in the Study Schedule (Attachment 1).

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

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

7.3.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the Sponsor must be notified. If the Sponsor identifies a patient who did not meet enrollment criteria and who was

inadvertently enrolled, the investigator site will be notified. A discussion must occur between the Sponsor clinical research physician (CRP)/clinical research scientist (CRS) and the investigator to determine whether the patient may continue in the study, with or without investigational product (IP). Inadvertently enrolled patients may be maintained in the study and on study treatment when the Lilly CRP/CRS agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without study treatment if the Lilly CRP/CRS does not agree with the investigator's determination it is medically appropriate for the patient to continue.

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/CRS and the investigator determine 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 or Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice
    - the investigator decides that the patient should be discontinued from study treatment or from the study
    - the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drugs occurs prior to introduction of the new agent
- patient decision
    - the patient or the patient's designee (for example, parents or legal guardian) requests that the patient be withdrawn from the study drug or study
- evidence of progressive disease (Attachment 5)
- 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 (Phase 1b) or randomized (Phase 2) patients who are lost to follow-up, including enrolled or randomized 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 good clinical practices (GCP).

7.3.5. Discontinuation of the Study

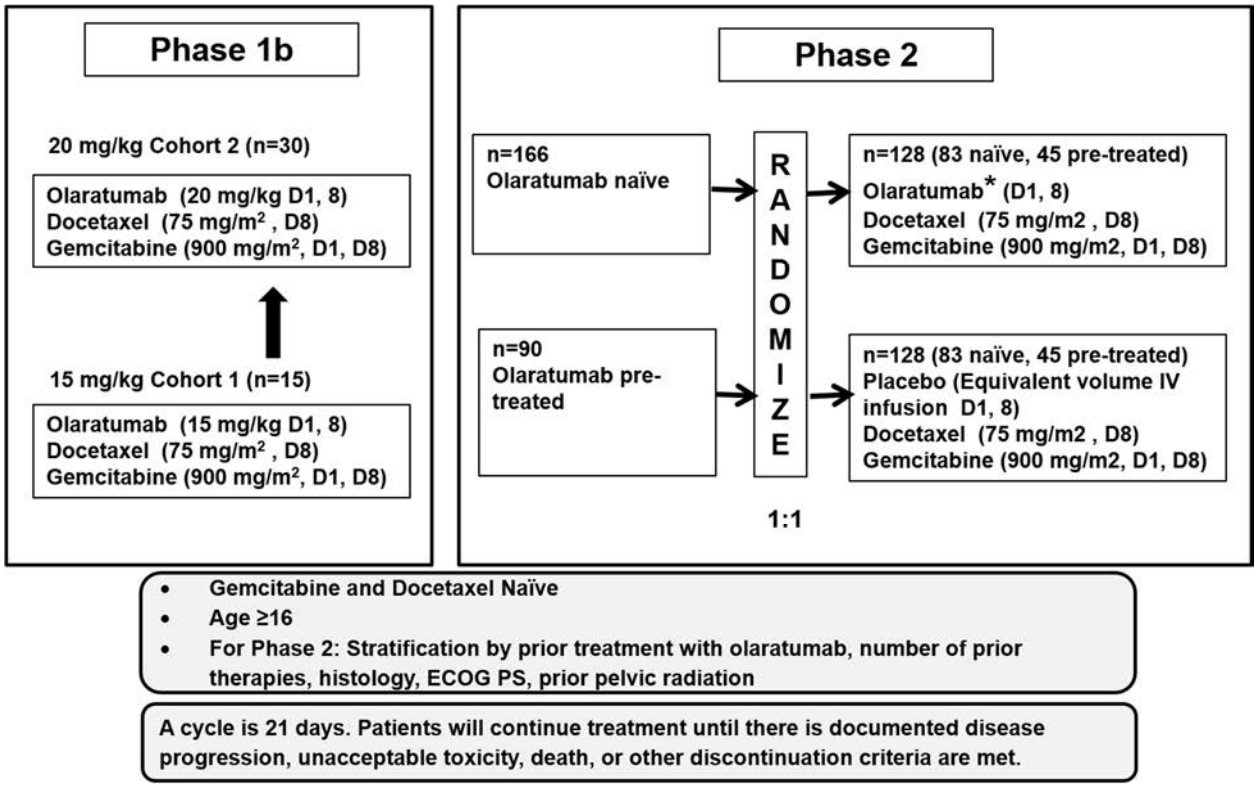
The study will be discontinued if Lilly judges discontinuation of the study necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP. Prior to discontinuation, the ERB or IRB (which approved the trial) will be notified according to local regulation.

8. Investigational Plan

8.1. Summary of Study Design

Study I5B-MC-JGDL is a multicenter Phase 1b/2 study of olaratumab in combination with gemcitabine and docetaxel in patients with locally advanced or metastatic STS, not amenable to treatment with surgical resection or radiotherapy with curative intent. The first part (Phase 1b) of the study will consist of an open-label, single-arm, dose-escalation assessment of the safety and tolerability of olaratumab administered at 15 mg/kg (Days 1 and 8) or 20 mg/kg (Days 1 and 8) with gemcitabine (900 mg/m^2 [fixed dose rate: 10 mg/m^2/minute], Days 1 and 8) and docetaxel (75 mg/ m^2, Day 8), on a 21-day cycle (Figure JGDL.1). After the dose of olaratumab in combination with gemcitabine and docetaxel has been determined from the analysis of the Phase 1b part, the Phase 2, randomized, double-blinded, placebo-controlled part of the study will open to enrollment. Patients will be randomized in a 1:1 ratio in a double-blinded manner to Arm A (olaratumab plus gemcitabine and docetaxel) or Arm B (placebo plus gemcitabine and docetaxel). Figure JGDL.1 illustrates the study design.

Patients will continue treatment until there is documented disease progression, unacceptable toxicity, death, or other discontinuation criteria are met.



Abbreviations: D = Day 1; IV = intravenous; n= number of patients.
* Based on the outcome of the Phase 1b part, the dose selected for the Phase 2 part of JGDL will be either 15 mg/kg or 20 mg/kg. Depending on the safety and pharmacokinetic profile of these dose levels, it is possible that an intermediate dosing regimen of 2 loading doses of 20 mg/kg during Cycle 1 followed by 15 mg/kg in every subsequent cycle could be utilized in Phase 2, as is being studied in the Phase 3 Study JGDJ.

Figure JGDL.1. Illustration of study design.

8.1.1. Phase 1b Dose Escalation

The Phase 1b part is a single-arm dose escalation to determine the recommended dose of olaratumab for the Phase 2 part that may be safely administered in combination with gemcitabine (900 mg/m^2) and docetaxel (75 mg/m^2) in patients with locally advanced or metastatic STS. This dose escalation has a starting olaratumab dose of 15 mg/kg and the highest olaratumab dose of 20 mg/kg. No intrapatient dose escalation is permitted. Patients in any cohort who do not complete Cycle 1 treatment for reasons other than a DLT will be replaced.

The DLT assessment will be performed as outlined in Section 9.4.1.1. The safety data for the cohort will be reviewed prior to dose escalation or dose determination for Phase 2. The total number of patients with DLTs, the type of DLTs, and relevant PK information will be considered prior to making a decision. At the time of analysis of safety data for Phase 1b, if review of the

data determines that G-CSF use is required with this combination, then this requirement will be implemented in the Phase 2 part.

15 mg/kg Olaratumab Dose Level (Cohort 1)

Approximately 15 patients will be treated with olaratumab at 15 mg/kg, in combination with gemcitabine and docetaxel, in the first cohort.

Of the DLT-evaluable patients in the 15-mg/kg cohort, if one-third or more patients with DLTs are observed, no further dose escalation of olaratumab will occur. If review of safety data indicates that DLTs of prolonged neutropenia and/or febrile neutropenia occurred that might be prevented by more extensive prophylactic use of G-CSF, then additional patients may be added to this cohort to determine if such G-CSF use would provide an overall DLT rate acceptable for Phase 2 study, after discussion with study investigators. Otherwise, if the DLT criteria are met or exceeded despite these measures, then the Phase 2 part of the study will not open.

20 mg/kg Olaratumab Dose Level (Cohort 2)

Of the DLT-evaluable patients in the 15-mg/kg cohort, if fewer than one-third of patients with DLTs are observed, a new cohort with approximately 15 patients will be treated with olaratumab at 20 mg/kg in combination with gemcitabine and docetaxel, using the same DLT criteria described above for the 15-mg/kg olaratumab dose level.

If the DLT criteria are met or exceeded for the olaratumab 20-mg/kg dose level, and review of safety data indicates that DLTs of prolonged neutropenia and/or fever neutropenia occurred that might be prevented by more extensive prophylactic use of G-CSF, then additional patients may be added to this cohort to determine if such G-CSF use would provide an overall DLT rate acceptable for Phase 2, after discussion with study investigators. A PK analysis of the 15-mg/kg and 20-mg/kg olaratumab dose levels will also be performed to determine if the serum levels observed in this study are consistent with those previously associated with a positive benefit/risk in the STS patient population.

Of the DLT-evaluable patients in the 20-mg/kg cohort, if fewer than one-third of patients with DLTs are observed, then the 20-mg/kg dose level may be chosen for Phase 2 study.

Patients in each cohort will continue treatment until there is documented disease progression, unacceptable toxicity, death, or other discontinuation criteria are met.

Expansion of the 20 mg/kg Olaratumab Dose Level (Cohort 2)

The 15-mg/kg olaratumab dose level (Cohort 1) safety review has been completed with 19 DLT-evaluable patients (Cycle 1). There were no DLTs observed in Cohort 1. Based on the safety review of Cohort 1, escalation to the 20-mg/kg olaratumab dose level (Cohort 2) was implemented.

In the 18 DLT-evaluable patients enrolled in Cohort 2, DLTs were observed in 3 patients (Grade 3 febrile neutropenia in 2 patients, one of whom had bacteremia, and a Grade 3 elevation of

hepatic transaminases in 1 patient). Two patient deaths were observed in Cohort 2, one on Cycle 2 Day 9 (patient died in his sleep) and one on Cycle 3 Day 5 (chest pain and cardiac arrest). The first patient had a history of hypertension and prior MI, and the second patient had a history of coronary artery bypass graft surgery, cardiac stent placement, and peripheral vascular disease; both deaths were deemed unrelated to study treatment by their investigators. PK analysis of Cohort 2 patients indicated that the olaratumab C_{max} and AUC of the DLT patients were similar to other patients in the cohort. The 2 patients who had died in Cohort 2 had olaratumab C_{max} and AUC very close to the median of Cohort 2, and their values overlapped with some patients from Cohort 1. Altogether, these clinical and PK findings indicated it was unlikely that the 2 deaths in Cohort 2 were due to an olaratumab-related factor. Although the DLT rule was not exceeded in Cohort 2 (3 out of 18 patients), after discussion with study investigators, it was decided that it was reasonable to further confirm patient safety at the 20-mg/kg dose level prior to initiation of the Phase 2 portion of the study by enrolling approximately 15 additional patients to Cohort 2.

8.1.2. Phase 2

After the dose of olaratumab in combination with gemcitabine and docetaxel has been determined from the Phase 1b part, the Phase 2 randomized, double-blinded part of the study will open to enrollment. In the Phase 2 part, approximately 256 patients will be randomized 1:1 to receive either olaratumab plus gemcitabine and docetaxel (Arm A) or placebo plus gemcitabine and docetaxel (Arm B). Out of the 256 patients, 166 will be olaratumab naïve and 90 will be olaratumab pretreated patients. Randomization will be stratified by prior treatment with olaratumab (yes versus no), number of prior systemic therapies for locally advanced or metastatic disease (0 versus ≥1), histological tumor type (leiomyosarcoma versus non-leiomyosarcoma), ECOG performance status (PS) (0 versus 1), and prior pelvic radiation (yes versus no).

Patients will continue treatment until there is documented disease progression, unacceptable toxicity, death, or other discontinuation criteria are met.

8.1.3. Definitions of Study Periods

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

- **Baseline:** begins when the ICF is signed and ends at the first study treatment (or at discontinuation, if no treatment is given).
- **Study Period:** begins at the first study treatment and ends at study completion. The study period does not include the continued access period.
    - The unblinded Phase1b part will be completed prior to opening the Phase 2 part of the study to randomization. Continuation of the study into Phase 2 will be dependent on data from the Phase 1 b part.
    - **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 CRF as the Date of Discontinuation from study treatment.

- **Postdiscontinuation 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 and continues until the patient's death, or until the patient is lost to follow-up or overall study completion.
    - ***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 progressive disease (PD).
    - ***Follow-up for survival*** - Patients will be followed every 3 months (±7 days) for the first year, then every 6 months (±14 days) until the patient's death or overall study completion.

- **Continued Access Period:** Phase 1b and Phase 2 continued access period begins after completion of the Phase 1b and Phase 2 parts, respectively, and ends at the end of trial. During the continued access period, patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met. The continued access period includes continued access follow-up.
  - **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.

8.1.4. Baseline and Study Treatment Period Assessments

Baseline radiographic assessment of disease will be performed within 28 days prior to enrollment in Phase 1b and randomization in Phase 2; 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 enrollment (Phase 1 b) or randomization (Phase 2). Imaging requirements include computed tomography (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 for storage. It is recommended that CT imaging of the abdomen/pelvis be performed with intravenous (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 enrollment (Phase 1b) or randomization (Phase 2), 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).

Patients in both arms will receive any necessary premedication if needed (see Section 9.1.1) prior to the infusion of study therapy at each treatment cycle.

A treatment cycle will be defined as 3 weeks (21 days ± 3 days). The start of study treatment will be considered Cycle 1 Day 1.

Phase 1b:

- Olaratumab (15 or 20 mg/kg IV infusion) on Days 1 and 8 of every 3-week cycle over 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 Day 1 and Day 8 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 reinstituted for a minimum of 2 cycles. The reinstituted observation period may be suspended after 2 cycles if the patient shows no further signs or symptoms of an IRR.
- Gemcitabine (900 mg/m^2, IV infusion) on Days 1 and 8 over 90 minutes (fixed-dose rate of 10 mg/m^2/minute), after olaratumab infusion
- Docetaxel (75 mg/m^2 IV infusion) on Day 8 over 60 minutes, after gemcitabine

Phase 2:

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

- Olaratumab on Days 1 and 8 of every 21-day cycle over 60 minutes, followed by a 1-hour observation period for the first 2 cycles. If there is no evidence of an IRR after the Day 1 and Day 8 infusions 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 reinstituted for a minimum of 2 cycles. The reinstituted observation period may be suspended after 2 cycles if the patient shows no further signs or symptoms of an IRR. The dose of olaratumab will be determined from the Phase 1b part of the study. Depending on the safety and PK profile of the Phase 1b dose levels, it is possible that an intermediate dosing regimen of 2 loading doses of 20 mg/kg during Cycle 1 followed by 15 mg/kg in every subsequent cycle could be utilized in Phase 2, as is being studied in the Phase 3 Study JGDJ.
- Gemcitabine (900 mg/m^2, IV infusion) on Days 1 and 8 over 90 minutes (fixed-dose rate of 10 mg/m^2/minute), after olaratumab infusion
- Docetaxel (75 mg/m^2 IV infusion) on Day 8 over 60 minutes, after gemcitabine

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

- Placebo (IV infusion) on Days 1 and 8 of every 21-day cycle over 60 minutes, followed by a 1-hour observation period for the first 2 cycles. If there is no evidence of an IRR after the Day 1 and Day 8 infusions 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 reinstituted for a minimum of 2 cycles. The reinstituted observation period may be suspended after 2 cycles if the patient shows no further signs or symptoms of an IRR.
- Gemcitabine (900 mg/m^2, IV infusion) on Days 1 and 8 over 90 minutes (fixed-dose rate of 10 mg/m^2/minute), after olaratumab infusion
- Docetaxel (75 mg/m^2 IV infusion) on Day 8 over 60 minutes, after gemcitabine

Phase 1b and 2

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 9.4.1.2. Dose reductions for olaratumab/placebo will be made in the event of specific treatment-related AEs, as described in Section 9.4.1.2.2. Supportive care guidelines are detailed in Section 9.6.1.

Patients 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.

8.1.5. 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 to follow-up, or the study has not completed as defined in Section 8.1.6.

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 3 months (±7 days) for the first year, then every 6 months (±14 days) until the patient's death, or overall study completion:

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

8.1.6. Study Completion and End of Trial

Phase 1b

The Phase 1b part of the study will be considered complete following determination of the recommended Phase 2 dose of olaratumab that may be safely administered in combination with gemcitabine plus docetaxel to patients with locally advanced or metastatic STS (Figure JGDL.2).

Phase 2

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following final analysis of the OS endpoint (at least 108 OS events in the olaratumab-naïve cohort) has been performed and evaluated, as determined by Lilly (Figure JGDL.3). Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred.

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

Upon study completion, investigators and patients may be unblinded to study treatment assignment for the Phase 2 part. Patients receiving study treatment and experiencing ongoing clinical benefit and no undue risks may continue to receive the study treatment in the continued access period. The continued access period begins after study completion and will continue until the end of trial.

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

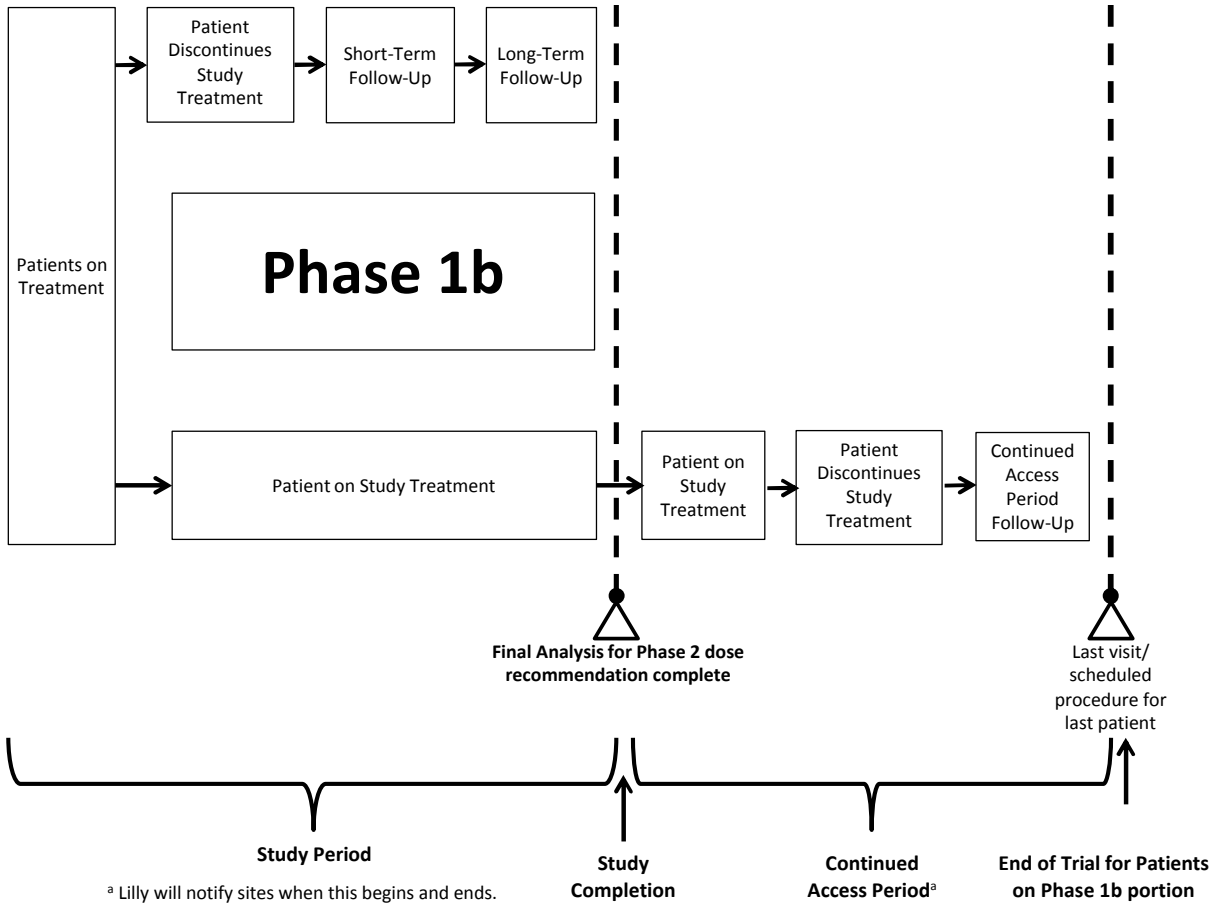
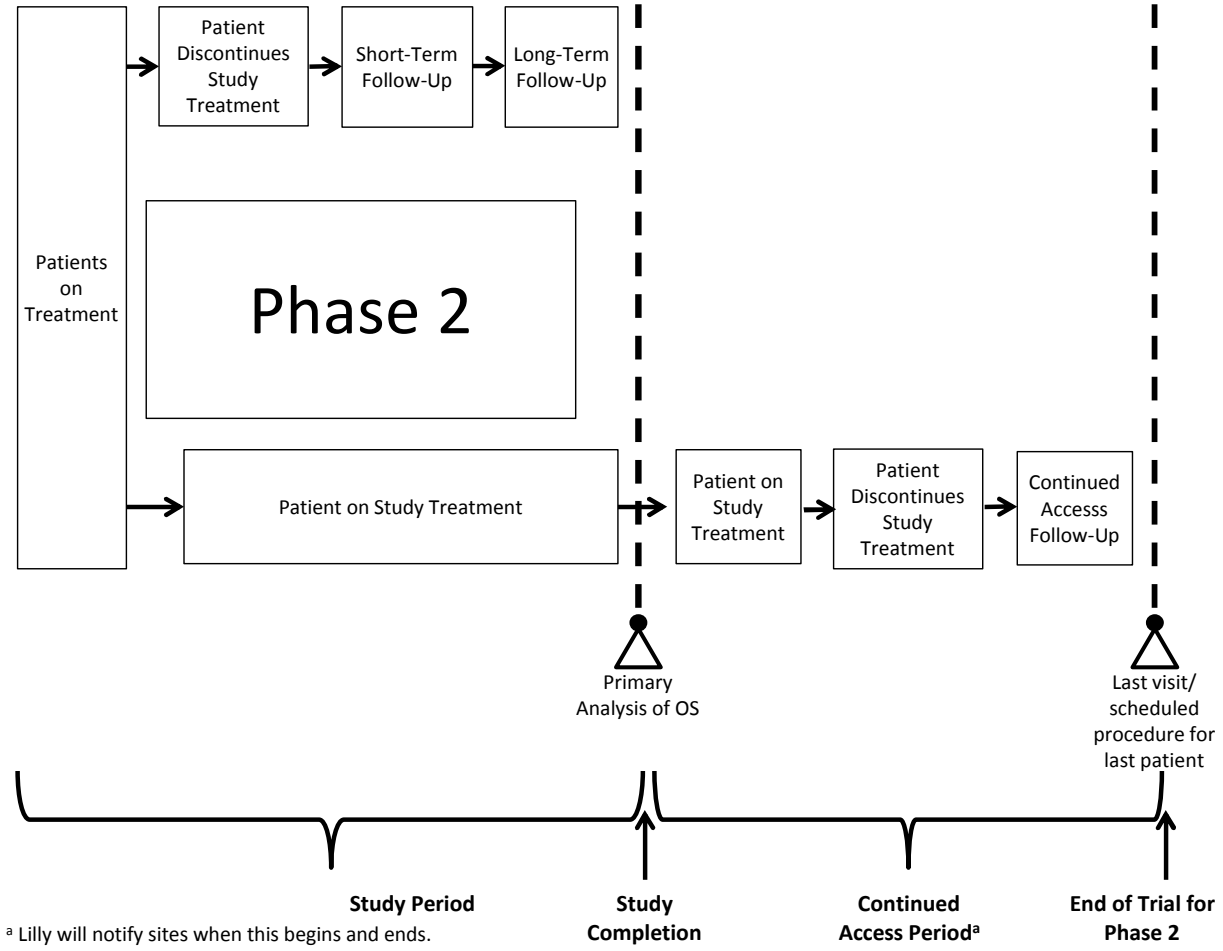


Figure JGDL.2. Phase 1b: Study period and continued access diagram.



Abbreviations: iDMC = independent Data Monitoring Committee; OS = overall survival; PK = pharmacokinetic.
The iDMC safety reviews will occur when approximately 60 patients (approximately 30 patients from each arm) have received at least 2 cycles of treatment or discontinued all study treatment due to any reasons prior to Day 8 in Cycle 2. An interim PK analysis will accompany the iDMC safety review. Subsequent iDMC meetings will occur approximately every 6 months thereafter until approximately 1 year after completing enrollment.

Figure JGDL.3. Phase 2: Study period and continued access diagram.

8.1.7. 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 study treatment when study completion occurs.

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

access period until one of the criteria for discontinuation is met (Section 7.3). During the continued access period, placebo will no longer be administered, and crossover will not be permitted.

During the continued access period, concomitant medication, AEs, SAEs, and study treatment dosing 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 in the event of an infusion-related reaction (IRR).

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.

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.

8.1.8. 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)

Phase 2:

For the Phase 2 part, the independent Data Monitoring Committee (iDMC) will be established to conduct interim safety analyses as specified in Section 12.2.14 and will follow an approved iDMC charter. The iDMC may initiate a consultation with an appropriate expert (if additional expertise is needed regarding evaluation of any safety signals). The iDMC will communicate back to Lilly Senior Management Designee about their assessment.

The iDMC will also review adverse events of special interest (AESIs) for olaratumab, including IRRs.

The first iDMC meeting to review Phase 2 interim safety data will occur when approximately 60 patients (approximately 30 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 12.2.14 for additional details.

Additionally, the iDMC will perform the interim efficacy analysis according to specifications in iDMC charter and study statistical analysis plan.

Independent Review Committee (IRC)

Phase 2:

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

8.1.9. Study Duration

From first patient visit in the Phase 1b part to last patient visit in the Phase 2 part, the estimated study duration is 47 months.

8.2. Discussion of Design and Control

For the Phase 1b dose-escalation study, a nonrandomized, uncontrolled design is being used to identify the recommended dose of olaratumab to be used in the Phase 2 part.

For the Phase 2 part, a randomized, controlled design is being used. 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 (Section 9.3). Assessment of bias is further minimized by the use of a double blind and placebo control.

Investigational treatment administration in the Phase 2 part of this study is double-blind; that is, patients, investigational sites, and the Sponsor study team do not have immediate access to treatment assignments for any patients. This design feature minimizes potential bias due to knowledge of patient's treatment during evaluation of study endpoints, at the patient level or aggregated across patients.

9. Treatment

9.1. Treatments Administered

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

Phase 1b:

- Olaratumab (15 or 20 mg/kg intravenous [IV] infusion over 60 minutes on Days 1 and 8) plus gemcitabine (900 mg/m^2, IV infusion over 90 minutes [fixed-dose rate of 10 mg/m^2/minute] on Days 1 and 8) plus docetaxel (75 mg/m^2 IV infusion over 60 minutes on Day 8)

Phase 2:

- Investigational Arm A: Olaratumab (15 or 20 mg/kg IV infusion over 60 minutes on Days 1 and 8) plus gemcitabine (900 mg/m^2, IV infusion over 90 minutes [fixed-dose rate: 10 mg/m^2/minute] on Days 1 and 8) plus docetaxel (75 mg/m^2 IV infusion, over 60 minutes on Day 8)
- Control Arm B: Placebo (equivalent volume IV infusion over 60 minutes on Days 1 and 8) plus gemcitabine (900 mg/m^2, IV infusion over 90 minutes on Days 1 and 8) plus docetaxel (75 mg/m^2 IV infusion over 60 minutes on Day 8)

Patients will continue to receive study treatment until there is documented disease progression, unacceptable toxicity, death, or other discontinuation criteria are met.

Table JGDL.1 shows the treatment regimens.

Table JGDL.1. Treatment Regimens/Dosing Schedule

		Study Drug	Dose	Route	Day	Infusion Duration (± 5 minutes)
Phase 1b	15 mg/kg Cohort	Olaratumab[a]	15 mg/kg	IV	Days 1 and 8	over 60 minutes
		1-hour (+5 minutes) observation period[b]			initial 2 cycles	
		Gemcitabine[c]	900 mg/m^2		Days 1 and 8	over 90 minutes
		Docetaxel[d]	75 mg/m^2		Day 8	over 60 minutes
	20 mg/kg Cohort	Olaratumab[a]	20 mg/kg	IV	Days 1 and 8	over 60 minutes
		1-hour (+5 minutes) observation period[b]			initial 2 cycles	
		Gemcitabine[c]	900 mg/m^2		Days 1 and 8	over 90 minutes
		Docetaxel[d]	75 mg/m^2		Day 8	over 60 minutes
Phase 2	Arm A	Olaratumab[a]	Dose determined by the analysis in Phase 1b	IV	Days 1 and 8	over 60 minutes
		1-hour (+5 minutes) observation period[b]			initial 2 cycles	
		Gemcitabine[c]	900 mg/m^2		Days 1 and 8	over 90 minutes
		Docetaxel[d]	75 mg/m^2		Day 8	over 60 minutes
	Arm B	Placebo[a]	equivalent volume	IV	Days 1 and 8	over 60 minutes
		1-hour (+5 minutes) observation period[b]			initial 2 cycles	
		Gemcitabine[c]	900 mg/m2		Days 1 and 8	over 90 minutes
		Docetaxel[d]	75 mg/m^2		Day 8	over 60 minutes

Abbreviations: C1 = Cycle 1; eCRF = electronic case report form; IRR = infusion-related reaction; IV = intravenous; PO = orally.

a Administer olaratumab as an infusion over 60 minutes **(± 5 minutes)**, not to exceed 25 mg/min. Note exceptions when the infusion times of olaratumab are longer than 60 minutes (Section 9.4.1.2.2.1). Premedicate all patients with the following medications (or equivalent) intravenously: a histamine H1 antagonist (for example, diphenhydramine) and dexamethasone 30 to 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 (for example, diphenhydramine) intravenously 30 to 60 minutes prior to each dose of olaratumab. See also Section 9.2.1 for more details. 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 9.4.1.2.2.1. All premedication administered must be adequately documented in the eCRF.

Treatment Regimens/Dosing Schedule (concluded)

b A 1-hour (+5 minutes) Observation Period is required after the administration of olaratumab/placebo during the initial 2 cycles. Whenthe Observation Period is applicable, collect vital signs 4 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, 3) within 1 hour (+5 minutes) after completion of the gemcitabine infusion, and 4) within 1 hour (+5 minutes) after completion of the docetaxel infusion. If there is no evidence of an infusion-related reaction during the initial 2 cycles of olaratumab/placebo, then no observation period is required for subsequent treatment cycles. In the event that a Grade 1 or 2 IRR occurs after Cycle 2, the 1-hour observation period will be reinstituted for a minimum of 2 cycles. The reinstituted observation period may be suspended after 2 cycles if the patient shows no further signs or symptoms of an IRR. See Section 9.2.1. For Cycles 3+, obtain 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 gemcitabine infusion, and 3) within 1 hour (+5 minutes) after completion of the docetaxel infusion.

c Administer gemcitabine as an infusion over 90 minutes (± 5 minutes) (fixed-dose rate: 10 mg/m^2/minute). Premedication for gemcitabine may be administered according to institutional guidelines and/or clinical practice. All premedication administered must be adequately documented in the eCRF. Gemcitabine premedication, if needed, must not be administered before the end of olaratumab/placebo infusion or before completion of the observation period (if applicable).

d Administer docetaxel as an infusion over 60 minutes (± 5 minutes) after gemcitabine. Premedication for docetaxel may be administered according to institutional guidelines and/or clinical practice. All premedication administered must be adequately documented in the eCRF. Docetaxel premedication must not be administered before the end of olaratumab/placebo infusion or before completion of the observation period (if applicable). Exception is given to dexamethasone premedication that is started 1 day prior to docetaxel per package insert.

Please see Section 9.4 for further details regarding dosing calculations of study drugs.

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

All premedication administered must be adequately documented in the electronic case report form (eCRF).

9.1.1.1. Olaratumab or Placebo

Infusion-related reactions, including Grade 3-5 IRR events, have been observed with olaratumab. To date, Grade 3-5 IRRs have occurred during the first cycle of olaratumab treatment. Therefore, premedicate all patients with the following medications (or equivalent)

intravenously: a histamine H1 antagonist (for example, diphenhydramine) and dexamethasone 30 to 60 minutes prior to the olaratumab/placebo doses on Days 1 and 8 of Cycle 1.

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

Premedication with additional agents may be provided at investigator discretion.

All premedication administered must be adequately documented in the eCRF.

9.1.1.2. Gemcitabine

Prophylactic antiemetics will be routinely administered. Additionally, premedication for gemcitabine may be administered according to institutional guidelines and/or clinical practice. All premedication administered must be adequately documented in the eCRF.

Sites should consult the manufacturer's instructions for gemcitabine for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of gemcitabine.

9.1.1.3. Docetaxel

Premedication for docetaxel may be administered according to institutional guidelines and/or clinical practice. Recommended premedication for the docetaxel is corticosteroids such as dexamethasone 8 mg orally twice a day starting the day prior to docetaxel and continuing for 3 days or at the discretion of the investigator. Patients who develop peripheral edema as a side effect of docetaxel may be treated with diuretics at the discretion of the investigator. Additional antiemetic premedication may be employed at the discretion of the investigator. All premedication administered must be adequately documented in the eCRF.

Sites should consult the manufacturer's instructions for docetaxel for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of docetaxel.

9.1.1.4. Granulocyte-Colony Stimulating Factors

G-CSF use is recommended in all cycles for patients with a prior history of pelvic radiation. For all other patients, G-CSF use is recommended per the guidelines outlined in Table JGDL.2.

Patients with a prior history of pelvic radiation who require chemotherapy dose reduction despite prophylactic G-CSF are not required to have prophylactic G-CSF in subsequent cycles if per investigator assessment such chemotherapy dose reductions adequately address the risk of further myelosuppression.

As outlined in Section 9.6.1.1, prophylactic use of G-CSF should consist of at least 5 days of G-CSF (5 micrograms/kg/day subcutaneously) beginning on Day 9, or a single dose of peg-G-CSF (6 mg, subcutaneously) on Day 9 or 10.

9.2. Materials and Supplies

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

Olaratumab/placebo 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.

Gemcitabine and docetaxel will be provided by Lilly. In the event that there are regional restrictions or supply limitations, commercially available gemcitabine and docetaxel may be purchased by the sites.

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 (15°C-25°C) 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 9.4.1.2.2.1 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 (for example, 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 reinstituted for a minimum of 2 cycles. The reinstituted observation period may be suspended after 2 cycles if the patient shows no further signs or symptoms of an IRR. See Section 9.4.1.2.2.1 for management of infusion rate with Grades 1 and 2 IRRs.

9.2.2. Gemcitabine

Gemcitabine is a commercially available product and should be stored, reconstituted and discarded per manufacturer's instructions.

Gemcitabine will be administered at a dose of 900 mg/m^2 (IV) over 90 minutes (fixed-dose rate of 10 mg/m^2/minute) on Days 1 and 8 of each 21-day treatment cycle.

9.2.3. Docetaxel

Docetaxel is a commercially available product. Investigators should consult the manufacturer's instructions for complete packaging, labeling, storage, and stability information.

Docetaxel will be administered at a dose of 75 mg/m^2 (IV) over 60 minutes on Day 8 of each 21-day treatment cycle.

9.3. Method of Assignment to Treatment

Phase 1b:

Upon signing the informed consent form (ICF), the site will register the patient in 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. Patients who meet all criteria for enrollment will be assigned to receive study treatment through the IWRS system. No dose escalations (that is, to the next cohort) can occur without prior discussion and agreement with the responsible Lilly CRP or CRS.

There is no randomization procedure for Phase 1b patients. Phase 1b patients will not participate in Phase 2.

Phase 2:

Upon signing the ICF, the site will register the patient by the 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. Patients who meet all criteria will be randomized into 1 of the 2 treatment arms on a 1:1 basis, using the IWRS.

The IWRS will assign patients to treatment arms according to a stratified method of randomization (that is, independent randomization within each stratum), defined by the following 5 factors:

- Prior treatment with olaratumab (yes versus no)
- Number of prior systemic therapies for locally 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 non- leiomyosarcoma)
- ECOG PS (0 versus 1)
- Prior pelvic radiation (yes versus no)

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).

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. Also, see Section 9.2.1 for further details on

olaratumab/placebo. The dose of gemcitabine or docetaxel 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 ≥10% (increase or decrease) from the weight used to calculate the prior dose, the olaratumab/placebo or gemcitabine or docetaxel dose will not need to be recalculated, unless deemed clinically meaningful. A ±5% variance in the calculated total dose (or for gemcitabine and/or docetaxel a variance according to local institutional guidelines is also allowed) will be allowed for ease of dose administration.

Day 8 administration of gemcitabine and docetaxel must not be given prior to Day 8.

Patients will receive treatment until evidence of progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria are met (as described in Section 7.3).

9.4.1. Special Treatment Considerations

9.4.1.1. Dose-Limiting Toxicity Determination (Phase 1b Part)

Bone marrow suppression occurs relatively frequently with the gemcitabine and docetaxel regimen and can lead to complications such as fever and neutropenia, infection, or bleeding, which are generally considered DLT-level toxicities and thus can confound DLT determination in the setting of combination with olaratumab. The criteria listed below will be used to determine the dose of olaratumab that can be added to gemcitabine and docetaxel without causing a significant increase in toxicity over that expected with gemcitabine/docetaxel alone.

In the Phase 1b part, DLT assessment will be performed. A DLT is defined as events such as the following, graded according to the NCI-CTCAE version 4.0, when the event occurs within Cycle 1, and is considered to be related to study treatment by the investigator in conjuncture with the Sponsor:

- febrile neutropenia with documented Grade ≥3 infection or sepsis
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia complicated by hemorrhage
- Grade 4 neutropenia lasting 7 days or longer
- nonhematologic Grade ≥3 toxicity, except for toxicities such as nausea, vomiting, transient electrolyte abnormalities, or diarrhea which can be controlled with optimal medical management within 48 hours)

In addition to the DLT assessment period in Cycle 1, safety data beyond Cycle 1 may also be taken into consideration prior to a decision to escalation or determination of the Phase 2 dose.

9.4.1.2. Dose Delays, Modifications, and Discontinuations

To begin dosing at each cycle (Day 1), the following criteria must be fulfilled:

- ANC ≥1.5 × 10^3 cells/μL (≥1500 cells/μL; ≥1.5 × 10^9/L), with no G-CSF in the prior 48 hours
- Platelets ≥100 × 10^3 cells/μL (≥100,000 cells/μL; ≥100 × 10^9 cells/L), with no platelet transfusion in the prior 72 hours
- Hemoglobin ≥8.0 g/dL. Note: For inclusion criteria, hemoglobin ≥ 9.0 g/dL.

- Total bilirubin below ULN. In patients with Gilbert's Syndrome, total bilirubin should be <3 mg/dL.
- Serum creatinine ≤1.5 times ULN. If creatinine is above ULN, the patient's creatinine clearance is ≥45 mL/min (refer to Attachment 8 for the Cockcroft-Gault formula for creatinine clearance).
- AST and ALT ≤3.0 x ULN, or ≤5 x ULN if the transaminase elevation is due to liver metastases
- Any treatment-related nonhematologic toxicity that is NCI-CTCAE, v4.0 Grade <2 or equivalent severity to baseline, unless toxicity consists of laboratory abnormalities (for example, potassium, magnesium, or phosphate) that are managed per institutional standards. (For Grade 4 nonhematologic toxicity deemed related to olaratumab/placebo, see Table JGDL.7.)

Delays:

In general, dose delays of one study drug (olaratumab/placebo, gemcitabine, or docetaxel) due to toxicity guidances outlined in Sections 9.4.1.2.1 and 9.4.1.2.2 will not necessitate delays of the other study drug. However, close consideration must be made by the investigator to administer all study treatments per the schedule outlined in Section 9.1.

Treatment may be delayed for up to 14 days to allow a patient sufficient time for recovery from study drug-related toxicity or non-study-drug-related events at the investigator's discretion (for example, an automobile accident).

Dose Modifications:

Any patient who requires a dose reduction for drug-related toxicity will continue to receive the reduced dose for the remainder of the study, except in the situation described in Table JGDL.2, footnote b. For gemcitabine or docetaxel, 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. For olaratumab, 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.

In the Phase 2 part, 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, gemcitabine or docetaxel need not be altered, and the planned gemcitabine or docetaxel schedule should be maintained.

Similarly, olaratumab/placebo therapy need not be altered for either gemcitabine- or docetaxel-related toxicity.

The dosing algorithm on Days 1 and 8 for gemcitabine, docetaxel, olaratumab and G-CSF use, based on ANC and platelet count, are shown in Table JGDL.2. Treatment should not begin on Day 1 of any cycle until the ANC is ≥ 1500 cells/µl and the platelet count is ≥100,000 cells/µl.

Dose adjustments required for hematologic and nonhematologic toxicity due to gemcitabine or docetaxel are presented in Table JGDL.4 and Table JGDL.5, respectively. Dose adjustments required for hematologic and nonhematologic toxicity due to olaratumab are presented in Table JGDL.6 and Table JGDL.7, respectively.

Table JGDL.2. Dosing Algorithm on Days 1 and 8 for Gemcitabine, Docetaxel, Olaratumab, and G-CSF Use Based on Absolute Neutrophil Count and Platelet Count

Treatment Day	Absolute Neutrophil Count (cells/µl)		Platelet Count cells/µl)	Gem Dose (mg/m^2)	Doc Dose (mg/m^2)	Olaratumab/Placebo	G-CSF Use[a]
Day 1 (Olaratumab /Placebo Gem)	≥1500	and	≥100,000	900[b]	Not Applicable	Administer	Not Applicable
Day 8 (Olaratumab /Placebo Gem, Doc)	≥ 1000	and	≥100,000	900[b]	75[b]	Administer	Not required
	500 to <1000		≥75000	675[c]	60[c]	Administer	Administer as outlined in Section 9.1.1.4.
	≥500		<100,000 to 75000	675[c]	60[c]	Administer	Not required unless ANC meets criteria
	<500		Any	Omit on Day 8[d]	Omit on Day 8[d]	Omit on Day 8 (also see Table JGDL.6)	Administer as outlined in Section 9.1.1.4.
	Any		<75000	Omit on Day 8[d]	Omit on Day 8[d]	Omit on Day 8 (also see Table JGDL.6)	Not required unless ANC meets criteria

Abbreviations: ANC = absolute neutrophil count; Doc = docetaxel; G-CSF = granulocyte colony-stimulating factor; Gem = gemcitabine; µl = microliter.

a Patients with a prior history of pelvic radiation should receive prophylactic G-CSF in all cycles. G-CSF use is recommended per the guidelines outlined in Section 9.1.1.4. Patients with a prior history of pelvic radiation who require chemotherapy dose reduction despite prophylactic G-CSF are not required to have prophylactic G-CSF in subsequent cycles if per investigator assessment such chemotherapy dose reductions adequately address the risk of further myelosuppression.

b If there has been 1 dose reduction for drug-related toxicity, the dose of gemcitabine is 675 mg/m^2 and the dose of docetaxel is 60 mg/m^2. If there have been 2 dose reductions for drug-related toxicity, the dose of gemcitabine is 500 mg/m^2 and the dose of docetaxel is 45 mg/m^2. A Day 8 dose reduction of gemcitabine or docetaxel because of Day 8 blood count parameters does not need to be continued on Day 1 of the subsequent cycle.

c If there has already been 1 dose reduction for drug-related toxicity, the dose of gemcitabine is 500 mg/m^2 and the dose of docetaxel is 45 mg/m^2. A Day 8 dose reduction of gemcitabine or docetaxel because of Day 8 blood count parameters does not need to be continued on Day 1 of the subsequent cycle.

d After omission of gemcitabine and docetaxel on Day 8 due to ANC <500 cells/µL and/or platelet count of <75,000 cells/µL, reduce dose of gemcitabine to the next appropriate dose level per Table JGDL.3 for subsequent cycles.

Discontinuations:

In the event of permanent discontinuation of olaratumab/placebo therapy due to an olaratumab/placebo-related toxicity, patients may continue on gemcitabine and docetaxel treatment per protocol. If either gemcitabine or docetaxel are permanently discontinued due to toxicity, the patient should discontinue active treatment with the gemcitabine/docetaxel combination if it is unclear which individual agent is the cause of the toxicity. If toxicity is clearly related to one agent or the other, for example neuropathy due to docetaxel, only that agent should be discontinued. The patient may continue treatment with olaratumab/placebo alone, at the discretion of the investigator, if gemcitabine and/or docetaxel are permanently discontinued. Any changes in treatments being added to or removed from patient care will be recorded on the eCRF.

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 gemcitabine and docetaxel therapy, including the following:

- Hematologic toxicity (see Section 9.4.1.2.1.2)
- Other nonhematologic toxicity (see Section 9.4.1.2.1.3)

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 olaratumab/placebo therapy, including the following:

- IRR (see Section 9.4.1.2.2.1)
- Hematologic toxicity (see Section 9.4.1.2.2.2)
- Nonhematologic toxicity (see Section 9.4.1.2.2.3)

9.4.1.2.1. Gemcitabine and Docetaxel

9.4.1.2.1.1. Dose Level Reductions

In the case of toxicity related to myelosuppression and its complications, the relative roles of gemcitabine and docetaxel are often impossible to separate, and thus it is expected such toxicity would result in dose reductions of both agents. In cases where AEs, in the opinion of the investigator, are more likely due to one drug than another, adjustment of one of the chemotherapy agents and not the other is permissible. Dose level reductions for gemcitabine and docetaxel are shown in Table JGDL.3.

The infusion time of gemcitabine after its dose reduction may be maintained at 90 minutes (±5 min) or may be shortened to keep a rate of approximately 10 mg/m^2/min according to discretion of the investigator. The infusion start and stop times must be recorded.

Table JGDL.3. Dose Level Reductions for Gemcitabine and Docetaxel

Study Drug	Starting Dose	Dose Reduction 1	Dose Reduction 2
Gemcitabine	900 mg/m^2	675 mg/m^2	500 mg/m^2
Docetaxel	75 mg/m^2	60 mg/m^2	45 mg/m^2

9.4.1.2.1.2. Hematologic Toxicity

The dosing algorithm on Days 1 and 8 for gemcitabine, docetaxel, olaratumab and G-CSF use, based on ANC and platelet count, are shown in Table JGDL.2.

General guidelines for dose modifications for other hematologic toxicities are shown in Table JGDL.4.

Table JGDL.4. General Guidelines for Gemcitabine and Docetaxel Dose Modification Due to Other Hematologic Toxicity

Toxicity	Required Dose Modification
Granulocyte nadirs lasting less than 7 days and with no complications	No dose modification needed
First occurrence of febrile neutropenia and/or documented Grade 4 neutropenia persisting ≥ 7 days	Reduce gemcitabine to 675 mg/m^2 and docetaxel to 60 mg/m^2. Prophylactic G-CSF recommended in subsequent cycles. If patient experiences of febrile neutropenia and/or documented Grade 4 neutropenia in a subsequent cycle despite dose reduction and prophylactic G-CSF, a second dose reduction (to gemcitabine 500 mg/m^2 and docetaxel 45 mg/m^2) is allowed. If febrile neutropenia or documented Grade 4 neutropenia occur in further cycles, the patient should be discontinued from the gemcitabine and docetaxel combination.
Grade 3 thrombocytopenia (platelet count 25,000/µL to <50,000/µL) associated with clinically significant bleeding	Reduce gemcitabine to 675 mg/m^2 and docetaxel to 60 mg/m^2 for all subsequent cycles. If the event recurs in a subsequent cycle despite dose reduction, a second dose reduction (to gemcitabine 500 mg/m^2 and docetaxel 45 mg/m^2) is allowed. If Grade 3 thrombocytopenia with clinically significant bleeding occurs in further cycles, the patient should be discontinued from the gemcitabine and docetaxel combination.
Grade 4 thrombocytopenia (platelet count < 25,000/µL)	Reduce gemcitabine to 675 mg/m^2 and docetaxel to 60 mg/m^2 for all subsequent cycles. If the event recurs in a subsequent cycle despite dose reduction, a second dose reduction (to gemcitabine 500 mg/m^2 and docetaxel 45 mg/m^2) is allowed. If Grade 4 thrombocytopenia occurs in further cycles, the patient should be discontinued from the gemcitabine and docetaxel combination.

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

9.4.1.2.1.3. Nonhematologic Toxicity

General guidelines for dose modification for hepatic toxicities related to gemcitabine and docetaxel are shown in Table JGDL.5.

Table JGDL.5. Dosage Reduction Guidelines for Docetaxel and Gemcitabine Due to Hepatic Toxicities

Toxicity	Required Dose Modification
On Day 1, bilirubin > ULN	Delay Day 1 (except for patients with Gilbert's Syndrome, who must have a total bilirubin <3 mg/dL. See Section 9.4.1.2).
On Day 8, if bilirubin is ≤ ULN	Administer docetaxel on Day 8.
On Day 8, if the bilirubin is > ULN	Omit docetaxel on Day 8. For subsequent cycles, omit docetaxel until bilirubin returns to ≤ ULN (except for patients with Gilbert's Syndrome, who must have a total bilirubin <3 mg/dL).
Grade ≥3 elevations in SGOT (AST), SGPT (ALT), or alkaline phosphatase	Reduce gemcitabine to 675 mg/m^2 and docetaxel to 60 mg/m^2 for all subsequent cycles. In subsequent treatments, delay gemcitabine and docetaxel for a maximum of 2 weeks, until recovery to Grade ≤1. If recovery to Grade ≤1 does not occur, discontinue gemcitabine and docetaxel. A second dose reduction (to gemcitabine 500 mg/m^2 and docetaxel 45 mg/m^2) is allowed if Grade ≥3 elevations recur.

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal.
Note: Bilirubin refers to total bilirubin.

For Grade ≥2 nonhematologic organ-related toxicities (excluding alopecia), delay treatment until recovery to Grade ≤1 or pre-therapy baseline. Treatment may be delayed for up to 14 days to allow a patient sufficient time to recover from study drug-related toxicity. If recovery to Grade ≤1 does not occur within this allowed time, discontinue gemcitabine and docetaxel. If the patient continues to experience the same toxicities, a second dose reduction (per Table JGDL.3) is allowed. Gemcitabine and docetaxel treatment should be discontinued if toxicities recur in spite of 2 dose reductions. In general, Grade 3 nonhematologic toxicities (excluding electrolyte toxicities that respond to supplemental treatment) require dose reduction. Permanent discontinuation of gemcitabine and docetaxel is indicated for Grade 3 organ-related toxicity that recurs despite up to 2 dose reductions. Docetaxel should be reduced for Grade 2 neurologic toxicity and permanently discontinued for Grade 3 neurologic toxicity. Gemcitabine and docetaxel should be permanently discontinued for Grade 4 nonhematologic toxicity unless previously discussed with the Lilly CRP/CRS.

Pulmonary toxicity has been reported with the use of gemcitabine. In cases of severe lung toxicity, gemcitabine therapy should be discontinued immediately and appropriate supportive care measures instituted.

Gemcitabine and docetaxel should be permanently discontinued for any of the following:

- unexplained new or worsening dyspnea or evidence of severe pulmonary toxicity
- severe hepatic toxicity

- Hemolytic Uremic Syndrome or severe renal impairment
- Capillary Leak Syndrome
- posterior reversible encephalopathy syndrome

9.4.1.2.2. Olaratumab/Placebo

9.4.1.2.2.1. Infusion-Related Reactions

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

A 1-hour observation period is required after the administration of olaratumab/placebo in the first and second cycles. 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 reinstituted for a minimum of 2 cycles. The reinstituted observation period may be suspended after 2 cycles if the patient shows no further signs or symptoms of an IRR. During the observation period, 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 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 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 intravenously: a histamine H1 antagonist (for example, diphenhydramine hydrochloride), glucocorticoid (for example, dexamethasone), 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. Patients who have experienced a prior Grade 1 or 2 IRR to olaratumab (or placebo), should be premedicated with the following (or equivalent) medications: a histamine H1 antagonist (for example, diphenhydramine) intravenously and glucocorticoid (for example, dexamethasone) intravenously, acetaminophen, and any other medications as appropriate for prophylaxis of IRR, approximately 30 to 60 minutes prior to all subsequent olaratumab/placebo infusions. In addition, the 1 hour post infusion observation period should be reinstated as per Section 9.2.1. If subsequent infusions are then tolerated with the use of premedications as above and a 50% decrease in infusion rate, the infusion rate may be increased to a rate deemed appropriate by the

investigator, as long as it does not exceed 25 mg/min. For olaratumab-pretreated patients who experienced a Grade 1 or 2 IRR during their prior treatment regimen (that is, prior to randomization in this study), the infusion rate that was last tolerated should be the infusion rate for both doses of olaratumab in Cycle 1. If tolerated, in subsequent cycles, the infusion rate may be increased to a rate deemed appropriate by the investigator, as long as it does not exceed 25 mg/min.

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 all study treatment 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 and olaratumab/placebo PK blood samples as close to the onset of the event as possible, at the resolution of the event, and 30 days (±3 days) following the event. The procedure for sample collection and handling is described in a separate procedural manual.

9.4.1.2.2.2. Hematologic Toxicity

Table JGDL.6 summarizes the olaratumab dose modifications required in case of hematologic toxicities.

Table JGDL.6. General Guidelines for Olaratumab/Placebo Dose Modification Due to Hematologic Toxicity Deemed Related to Olaratumab

Toxicity	Required Dose Modification
Neutropenia	
ANC Grade 1-3	No dose modification required
ANC <500 cells/µL (Grade ≥4)	No treatment administered; treatment cycle delayed
At retreatment:	
If ≥Grade 3 neutropenic fever/infection has occurred	Withhold dose until ANC is ≥ 1000 cells/µL; for a 15-mg/kg dose level, reduce dose to 12 mg/kg; for a 20-mg/kg dose level, reduce dose to 15 mg/kg.
If Grade 4 neutropenia lasting >1 week has occurred	Withhold dose until ANC is ≥ 1000 cells/µL; for a15-mg/kg dose level, reduce dose to 12 mg/kg; for a 20-mg/kg dose level, reduce dose to 15 mg/kg.
Grade 4 ANC without fever/infection lasting ≤ 1 week	Administer the next olaratumab/placebo at full dose at investigator's discretion with recommended use of prophylactic G-CSFs
Second incidence of either: 1) ≥Grade 3 neutropenic fever/infection 2) Grade 4 neutropenia lasting > 1 week	For a 15-mg/kg dose level, discontinue olaratumab/placebo; for the 20-mg/kg dose level, a second dose level reduction to 10 mg/kg. Modify/discontinue gemcitabine and docetaxel as per Table JGDL.4.

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

9.4.1.2.2.3. Nonhematologic Toxicity

Specific guidelines for dose adjustments in patients who experience olaratumab/placebo IRRs may be found in Section 9.4.1.2.2.1.

General guidelines for dose modification for other nonhematologic toxicities related to olaratumab/placebo are shown in Table JGDL.7.

Table JGDL.7. General Guidelines for Dose Modification Due to Nonhematologic Toxicities Deemed 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 organ toxicity is ≤ Grade 1 or has returned to pretreatment baseline; then treatment may resume at a reduced dose of 12 mg/kg for the 15-mg/kg dose level and reduced dose of 15 mg/kg for the 20-mg/kg dose level. If toxicity recurs after therapy resumes, a second dose reduction (second dose reduction of 10 mg/kg for the 15-mg/kg dose level and12 mg/kg for the 20-mg/kg dose level) is permitted.
Grade 4	The dose must be withheld until dose toxicity is ≤ Grade 1 or has returned to baseline. Permanent discontinuation should be considered for any patient experiencing Grade 4 nonhematologic 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 for the 15-mg/kg dose level; dose reduced to 15 mg/kg for the 20-mg/kg dose level. If Grade 4 toxicity recurs after therapy resumes, all study treatment will be discontinued.

9.5. Blinding

Phase 1b:

This part is an open-label study.

Phase 2:

This is the double-blinded part of the study.

During enrollment and prior to the interim efficacy analysis, only 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, 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 personnel until the study has been unblinded.

Upon final analyses of the study, 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 8.1.6). 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

Phase 2:

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/CRS 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 will 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/CRS 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.

Bisphosphonate osteoclast inhibitors (for example, 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.

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. Granulocyte-Colony Stimulating Factors

G-CSF use is recommended in all cycles for patients with a prior history of pelvic radiation. For all other patients, G-CSF use is recommended per the guidelines outlined in Table JGDL.2.

Patients with a prior history of pelvic radiation who require chemotherapy dose reduction despite prophylactic G-CSF are not required to have prophylactic G-CSF in subsequent cycles if per investigator assessment such chemotherapy dose reductions adequately address the risk of further myelosuppression.

Prophylactic use of G-CSF should consist of at least 5 days of G-CSF (5 micrograms/kg/day subcutaneously) beginning on Day 9, or a single dose of peg-GCSF (6 mg, subcutaneously) on Day 9 or 10.

9.6.1.2. 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 Criterion [9]).

9.6.1.3. Antiemetic Therapy

Both prophylactic and symptom-directed antiemetic therapies 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 Inhibitors and Inducers on Docetaxel

Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. Avoid concurrent use of docetaxel with inhibitors and inducers of CYP3A4. Refer to Attachment 7 for a list of common CYP3A4 inducers and inhibitors. Use of a drug that is listed in Attachment 7 when there is no appropriate clinical

substitute for that drug will not be considered a protocol violation. Close monitoring for toxicity and a docetaxel dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

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, Resource Utilization, 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, patient-reported outcomes, resource utilization 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 enrollment in Phase 1 b and randomization in Phase 2, baseline tumor measurements will be performed on each patient. Computed tomography (CT), including spiral CT scans and MRI are the preferred methods of measurement.

The CT portion of a positron emission tomography (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 date of enrollment for Phase 1b or randomization for Phase 2. Patients will be evaluated for response according to RECIST, v 1.1 guidelines (Eisenhauer et al. 2009), as outlined in Attachment 5.

A Lilly designated imaging core lab will collect and store all tumor assessment images on all enrolled patients throughout the study. An independent review of all or a randomly selected subset of patient scans may be performed by an independent panel of radiologists.

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 PD, the investigative sites will continue to monitor patients and periodically evaluate tumor response every 6 weeks (±7 days) as calculated from enrollment (Phase 1b) or randomization (Phase 2) by the same method used at baseline and throughout the study until the patient has objective disease progression, or until the final analysis of OS. After the patient has objective disease progression, radiologic tests are no longer required and the patient should be followed up approximately every 3 months (±7 days) for the first year, 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

In the Phase 2 part of the study, the primary efficacy measure is OS. 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

In the Phase 2 part of the study, 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. The secondary efficacy measures will be collected at the times shown in the Study Schedule (Attachment 1).

- 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
- 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 sustained 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 PS
- 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.

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, at least every effort should be made to administer at the same time point in each visit. Questionnaires should be administered to the patient prior to extensive interaction with site staff and 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 last 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 JGDL.8. 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 the baseline assessment (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).

Table JGDL.8. 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 the baseline assessment (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 the baseline assessment (Cycle 1 Day 1) followed by at least 1 EQ-5D-5L assessment after 1 dose of study drug (Cycle 2 Day 1 or later).

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 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 JGDL.9 presents a summary of AE and SAE reporting guidelines. Table JGDL.9 also shows which database or system is used to store AE and SAE data.

Table JGDL.9. 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 electrocardiograms (ECGs), 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 drugs 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 informed consent form (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, 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 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 (NCI 2009). 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 (AESIs) 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

Refer to Section 9.4.1.2 for special treatment considerations for dose delay, modifications, and discontinuations from olaratumab/placebo and gemcitabine/docetaxel, including adverse events of concern or special interest.

10.3.2. Other Safety Measures

10.3.2.1. Electrocardiograms

Twelve-lead ECGs will be collected according to the Study Schedule(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 JGDL.10 provides the Fridericia's QT correction formula.

Table JGDL.10. Fridericia's QT Correction Formula

Formula	**Fridericia** $QTcF = QT / (RR)^{1/3}$

Abbreviations: QT = ECG interval measured from the onset of the QRS complex to the offset of the T wave; QTcF = QT interval corrected for heart rate using Fridericia's formula; RR = time between corresponding points on 2 consecutive R waves on ECG.

After enrollment, if a clinically significant increase in the QT/corrected QT (QTc) interval from baseline (Table JGDL.10), 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.

For Phase 1b, all digital ECGs will be electronically transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will then conduct a full overread on the ECG (including all intervals); a report based on data from this analysis will be issued to the investigative site. All data from the overreads will be placed in the Lilly database for analytical and study report purposes.

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

Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes. The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

10.3.3. Safety Monitoring

The Lilly CRP/CRS will monitor safety data throughout the course of the Phase 1b part of the study and blinded safety data throughout the course of the Phase 2 part of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP/CRS 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
- AESI (as defined in Section 10.3.1.3)

If a patient experiences elevated ALT >5× ULN and elevated total bilirubin >2× ULN, clinical and laboratory monitoring should be initiated by the investigator. For patients entering the study with ALT >3× ULN, monitoring should be triggered at ALT >2× baseline. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See 0.

For the Phase 2 part of the study, 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 12.2.14) can conduct additional analyses of the safety data.

For the Phase 2 part 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.

10.3.4. Complaint Handling

Lilly collects product complaints on study treatment 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 docetaxel and/or gemcitabine are reported directly to the manufacturers of those drugs/devices 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 lists 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.

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. Biomarker Samples for Storage and Research

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including

deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

As part of Lilly's ongoing efforts to understand the relationship between cancer, genetics, and response to therapy, this study will analyze biomarkers relevant to olaratumab, gemcitabine, docetaxel, and/or STS. The study will analyze the correlation between biomarkers and clinical outcome and may be used for related research methods or validation of diagnostic tools or assays.

Samples for biomarker research will be collected at times specified in Attachment 6, where local regulations allow.

Where local regulations and ERBs allow, the following samples will be collected for biomarker research as summarized below, specified in the Study Schedule, and discussed in detail in the following subsections:

- whole blood sample for genetic research (see Section 10.4.2.1)
- tumor tissue (newly obtained or archived) (see Section 10.4.2.2)
- plasma for biomarkers (see Section 10.4.2.3)

10.4.2.1. Whole Blood Sample for Genetic Research

A blood sample will be collected for pharmacogenetic analysis as specified in the Sampling Schedule (Attachment 6), where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to study treatment and to investigate genetic variants thought to play a role in STS. Assessment of variable response may include evaluation of adverse events or differences in efficacy. These studies may include but are not limited to PDGFRα, PDGFRα ligands, and genes functional in the tumor microenvironment to evaluate their association with observed response to study treatment.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel. Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by the Sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies include whole genome or exome sequencing, genome wide association studies, candidate gene studies, and epigenetic analyses. Regardless of the technology utilized, data generated will be used only for the specific research scope described in this section.

10.4.2.2. Tumor Tissue for Biomarker Research

Previously obtained archived formalin-fixed paraffin-embedded tissue will be requested both for a central pathology review to confirm the diagnosis of STS and histologic subtype, and for exploratory biomarker research.

Collection of mandatory archived tumor tissue sample **or** newly obtained biopsy is required in order to participate in this study unless restricted by local regulations. If an archived specimen is not available, submission of a newly obtained biopsy (obtained at baseline) is required for participation in this study.

The availability of tumor tissues is important to better characterize the relationship of tumor biology and response evaluation in this study. As such, this study is requesting submission of tumor tissue (newly biopsied or archived) to support correlative studies.

Formalin-fixed paraffin-embedded tumor tissue should be provided as a block or unstained slides. Due diligence should be used to make sure that tumor specimen (not a normal adjacent or a tumor margin sample) is provided. Pathology notes accompanying archival tissue may also be requested. The report must be coded with the patient number. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission. Archival blocks will be sectioned and returned to the study site. Archival slides and tissue samples collected on-study will not be returned.

Tumor tissue will be examined for biomarkers that may include, but are not limited to, those related to STS, study treatment and/or the mechanism of action of olaratumab.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by the Sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

Technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches including mutation profiling, copy number variability, gene expression, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations with these biomarkers and clinical outcomes.

10.4.2.3. Plasma Samples for Biomarker Research

Plasma samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Sampling Schedule (Attachment 6), where local regulations allow.

Samples will be examined for biomarkers related to cancer, variable response to study treatment, the mechanism of action of study treatment, and/or for research-related methods, or validating diagnostic tools or assays.

Potential pharmacodynamics and/or circulating markers may include, but are not limited to, PDGF-AA, PDGF-BB, and PDGF-CC.

All biomarker samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs/IRBs impose shorter time limits, at a facility selected by the Sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

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 and PK 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 (± 3 days) after onset of the event (as noted in Attachment 6).

Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies (ADA) in the presence of the olaratumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of olaratumab. Immunogenicity may be further characterized by performing additional related assays. 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 and Immunogenicity Sampling Schedule (Attachment 6), venous blood samples will be collected to determine the serum concentrations of olaratumab and plasma concentrations of gemcitabine and docetaxel. A maximum of 5 samples may be collected at additional time points during the study, if warranted and agreed upon between both the investigator and Lilly. 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 diluted 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.

These samples will be analyzed at laboratories designated by the Sponsor. Serum concentrations of olaratumab will be assayed using a validated enzyme-linked immunosorbent assay (ELISA) method. Gemcitabine (with its major metabolite, dFdU) and docetaxel concentrations in plasma will be analyzed using validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) assays.

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

The PK samples will be stored at a facility designated by the Sponsor. The remaining serum and plasma from the samples collected for pharmacokinetics may be pooled and used for exploratory metabolism work and other exploratory PK/pharmacodynamic work as deemed appropriate.

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

10.5. Appropriateness of Measurements

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

11. Data Quality Assurance

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

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

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

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

11.1. Data Capture System

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

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

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect 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

Phase 1b

The primary objective of the Phase 1b part is to determine a recommended Phase 2 dose of olaratumab that may be safely administered in combination with gemcitabine (900 mg/m^2) and docetaxel (75 mg/ m^2) to patients with locally advanced or metastatic STS. Section 8.1.1 outlines the study design for the Phase 1b portion. Approximately, a total of 45 patients will ensure that at least 15 patients will be treated at the 15-mg/kg and 30 patients at the 20-mg/kg cohort (see also Section 8.1.1.).

Phase 2

Based on the outcome of the Phase 1b part, the dose selected for the Phase 2 part of Study JGDL will be either 15 mg/kg, 20 mg/kg, or 2 loading doses of 20 mg/kg during Cycle 1 followed by 15 mg/kg in every subsequent cycle. The dosing regimen for olaratumab will remain Days 1 and 8 of a 21-day cycle regardless of the dosing strategy adopted.

The primary objective of the Phase 2 part is to compare olaratumab plus gemcitabine and docetaxel (experimental arm) versus placebo plus gemcitabine/docetaxel (control arm) in terms of OS, in patients with locally advanced or metastatic STS, who have not previously been treated with olaratumab (the "olaratumab-naïve" cohort).

The Phase 2 part of the study will screen approximately 200 olaratumab-naïve patients to randomize 166 olaratumab-naïve patients in 1:1 randomization (83 patients in the experimental arm and 83 patients in the control arm). The primary ITT sample size of 166 was selected assuming the final analysis of OS will occur when at least 108 OS events in randomized olaratumab-naïve patients have been observed (35% censoring).

The final total of 108 OS events (deaths) in olaratumab-naïve patients provides 80% statistical power for a two-sided log-rank test at a 0.20 significance level (assuming the true OS HR is 0.665). An OS HR of 0.665 corresponds approximately to an increased median survival from 15 months (estimated from published clinical data in various types of patients with advanced or metastatic STS) in placebo plus gemcitabine and docetaxel to 22.5 months for olaratumab plus gemcitabine and docetaxel.

In the event that OS is statistically significant at the two-sided 0.20 alpha level, OS will also be compared to the more stringent two-sided 0.05 level. In the event that OS is statistically significant at a two-sided 0.05 alpha level, then PFS will also be formally tested at a two-sided 0.05 level. In the event that PFS is statistically significant at a two-sided 0.05 alpha level, then ORR will also be formally tested at a two-sided 0.05 level. This statistical "gate-keeping" among OS, PFS, and ORR ensures that an overall 0.05 alpha level is maintained, in the event that one or more endpoints are statistically significant at the 0.05 level.

A key secondary objective of the study will be to compare OS between the experimental arm and the control arm in patients with locally advanced or metastatic STS, who have previously been

treated with olaratumab (the "olaratumab-pretreated" cohort). The Phase 2 part of the study will screen approximately 114 olaratumab-pretreated patients to randomize 90 olaratumab-pretreated patients in 1:1 randomization.

The sample size of 90 patients in the secondary cohort of "olaratumab-pretreated" patients was selected based on both statistical and qualitative considerations. See Section 12.2.14 for further discussion of the rationale.

There will be an interim efficacy analysis planned for the Phase 2 part of the study. All available data on patient characteristics, efficacy, and safety outcomes will be included for consideration as part of the interim efficacy analysis. The primary efficacy hypothesis will be tested at the interim efficacy analysis using a nominal alpha level of 0.00001. The final analysis of the primary efficacy hypothesis will therefore be adjusted and tested at a nominal alpha level of 0.19999.

See Section 12.2.14 and the study's Statistical Analysis Plan (a separate document) for further details regarding the interim efficacy analysis.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly.

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.

Unless specifically described otherwise, all baseline, efficacy, safety, and health outcomes analyses will be performed separately for the olaratumab-naïve and olaratumab-pretreated cohorts.

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

12.2.2. Analysis Populations

Phase 1b

Safety population: All enrolled patients who receive any quantity of study treatment, regardless of their eligibility for the study, will be included in the safety analysis. Safety

evaluation will be performed based on the actual initial therapy a patient has received, regardless of any other cohort to which he or she was assigned.

Efficacy evaluation will be performed based on the cohort assigned, regardless of the actual dose level of therapy received.

DLT-evaluable Population: The DLT-evaluable population will include all enrolled patients who complete Cycle 1 or discontinue due to a DLT prior to completing Cycle 1 treatment.

Phase 2

The **Intent-to-Treat (ITT) population** includes all randomized patients. In ITT population, patients will be allocated to treatment groups as randomized, and not by actual treatment received. This population will be used for baseline, efficacy, and health outcome analyses.

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.

12.2.3. 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 important protocol deviations will be provided.

12.2.4. 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.

12.2.5. Concomitant Therapy

Concomitant medications will be summarized for the safety population.

12.2.5.1. 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.

12.2.6. Treatment Compliance

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

12.2.7. Primary Outcome and Methodology

Phase 1b

The Phase 1b is a dose-escalation study. The primary safety endpoint is DLT. For each dose cohort, the numbers of DLT will be assessed based on DLT-evaluable population.

Phase 2

The primary efficacy outcome for the Phase 2 part of the study is OS in the olaratumab-naïve cohort of the ITT population. The final analysis of OS will be based on the stratified log-rank test, stratified by 3 of the 4 randomization factors: number of prior systemic therapies for locally advanced or metastatic disease (0 versus ≥1), histological tumor type (leiomyosarcoma versus non-leiomyosarcoma), and ECOG PS (0 versus 1).

Overall survival curves, the median with 95% CI and survival rates at various time points for each treatment group will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). The HR will be estimated using a stratified Cox regression model (Cox 1972), stratified the same as the log-rank test described above.

12.2.8. Other Analyses of Efficacy

12.2.8.1. Progression-Free Survival

Phase 2

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.

PFS will be compared between the 2 treatment groups based on log-rank test, stratified by the same stratification factors used in the analysis of the primary endpoint OS. PFS survival curves, the median with 95% CI, and survival rates at various time points for each treatment group will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). The HR will be estimated using a stratified Cox regression model, stratified by randomization strata.

12.2.8.2. 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. In the event that efficacy is observed to be very similar between the olaratumab-naïve and olaratumab-pretreated cohorts, it may be reasonable to conclude a uniform efficacy across cohorts; in that case, additional efficacy analyses may be performed pooling these 2 populations, in order to obtain pooled estimates of efficacy parameters.

12.2.9. Pharmacokinetic and Immunogenicity Analyses

12.2.9.1. Pharmacokinetics

Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of the study drug and have had sufficient postdose samples collected to allow estimation of PK parameters.

In the Phase 1b part, PK parameter estimates will be computed by standard noncompartmental methods of analysis for olaratumab, and for gemcitabine, dFdU, and docetaxel. The maximum concentration (C_{max}), time of C_{max} (t_{max}), area under the concentration-time curve (AUC), half-life ($t_{1/2}$), volume of distribution at steady state (V_{ss}), clearance (CL), and other relevant parameters that can be calculated from the data will be reported from these noncompartmental analyses.

In the Phase 2 part, PK parameters for olaratumab (CL, exposure, V_{ss}, and $t_{1/2}$) and inter-individual PK variability will be computed using nonlinear mixed effect modeling implemented in NONMEM. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation. Gemcitabine, dFdU, and docetaxel plasma levels will be reported using descriptive methods.

If warranted by the data, PK/pharmacodynamic analyses using OS, PFS, and/or other appropriate clinical endpoints will also be conducted to characterize the exposure-response relationship in this study.

12.2.9.2. Immunogenicity

Incidence of treatment-emergent (TE) anti-olaratumab antibodies and any related assays 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 TE ADA-negative and TE ADA-positive patients at correspondent visits, or before and after TE-ADA development for patients who developed TE-ADA. However, for patients who test positive for 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.

12.2.10. Exploratory Translational Research Analyses

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

12.2.11. 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 of compliance and reasons for non-compliance will be summarized by treatment arm and time point, for the ITT population. Percentage of compliance will be calculated as the number of completed assessments divided by the number of expected assessments.

Data will be separately summarized descriptively. Analyses will be performed separately by cohort (olaratumab naïve and olaratumab-pretreated). 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-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 post-baseline (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 sustained 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.

12.2.12. Safety Analyses

All safety summaries and analyses will be based upon the Safety Population as defined in Section 12.2.2. Analyses will be performed for olaratumab-naïve and olaratumab-pretreated cohorts separately as well as pooled between these cohorts.

All safety analyses are based on the Safety population unless specified otherwise.

- Adverse events (AEs), including TEAEs, 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 AEs will be determined and included in the listings.

- Study drug exposure will be summarized for each arm using the following variables: number of infusions, number of cycles, duration of study treatment, cumulative dose, dose intensity, and relative dose intensity.

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

- Hospitalizations due to AEs, transfusions, and concomitant drugs will be summarized.

- Vital signs

- ECG

In the Phase 1b part, DLTs will be summarized by cohort in the patients who are evaluable for DLT assessments and listed by patient. For Phase 1 b and Phase 2, the incidences of 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 will be summarized. Additionally, for Phase 1b and Phase 2 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 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.

12.2.13. Subgroup Analyses

Subgroup analyses of PFS and OS will be performed and will be detailed in the SAP.

12.2.14. Interim Analyses

There will be safety interim reviews for both Phase 1b and Phase 2 parts.

Phase 1b

The safety review for Phase 1b will be conducted by Lilly clinical research personnel. Patient safety will be assessed prior to dose escalation to ensure nothing precludes administration of a larger dose to future study patients. In addition to reviewing AEs and laboratory measurements, available PK/pharmacodynamic profiles of olaratumab will be reviewed per cohort. Based on these interim results, modifications (for example, reductions in dose increment or changes in dosing schedule) to the dose-escalation strategy or other design elements may be made to ensure patient safety. The study investigators and the Lilly CRP/CRS will make the determination regarding dose escalation based upon their review of the safety/tolerability data and the PK data from the previous cohorts.

In addition, an interim safety review will be conducted prior to proceeding to Phase 2 including safety, PK, and pharmacodynamics. All relevant data including data beyond Cycle 1 will be reviewed to determine the recommended Phase 2 dose of olaratumab. The decision to proceed to Phase 2 will be made following discussions between the investigators and Lilly clinical research personnel.

Phase 2

An independent data monitoring committee (iDMC) will be established to conduct safety interim 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.

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 first iDMC meeting to review interim data will occur when approximately 60 patients (approximately 30 patients from each arm) have received at least 2 cycles of treatment or discontinued all study treatment due to any reasons prior to Day 8 in Cycle 2. Pwill be provided

to the iDMC upon request. Subsequent iDMC meetings will occur approximately every 6 months thereafter until approximately 1 year after completing enrollment. 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.

As described in Section 12.1, an interim efficacy analysis is also planned for the Phase 2 part of the study. The iDMC will be responsible for initial conduct of the interim efficacy analysis according to the specifications of the iDMC charter and statistical analysis plan. If there is an evidence of interim efficacy to warrant a sponsor internal review of the data, results of this interim efficacy analysis may provide information to help inform the initiation of new studies, but will not be used to modify the design and conduct of this current trial.

The interim efficacy analysis will occur after observing approximately 40 OS events among the olaratumab-pretreated cohort of the ITT population. Due to the larger size of the olaratumab-naïve cohort, it is expected that there will be at least another 40 OS events in the olaratumab-naïve cohort at the time of this analysis. The decision to perform interim efficacy analyses after 40 OS events in each cohort was based on both statistical and qualitative considerations. An observation of a very strong efficacy in one of these cohorts, based on 40 events, should be sufficient to consider further development for that cohort. For example, an observed OS HR<0.60 would imply at least an 80% (Bayesian noninformative) probability that the true HR is less than 0.80. The evidence will be stronger if both cohorts show similar efficacy, allowing for pooling of the cohorts. With 80 pooled events, an observed pooled OS HR<0.67 would imply at least a 79% probability that the true pooled HR is less than 0.80. Other efficacy and safety outcomes will be evaluated, so these scenarios for the interim OS HR are included here merely as a reference, to illustrate the kind of evidence that might lead to the initiation of additional studies. For further details, refer to the study's Statistical Analysis Plan (a separate document).

A second interim efficacy analysis may optionally be performed depending on the expected timing of the final analysis and the results of the first interim efficacy analysis. If a second interim efficacy analysis is performed, it will be conducted applying a nominal alpha level of 0.00001 to the primary OS analysis in olaratumab-naïve patients.

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 drugs.

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the ERB may require the child to give documented assent, if capable.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

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

The ERB should include or consult with experts who are knowledgeable in pediatric ethical, clinical, and psychosocial issues.

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

- the current IB and updates during the course of the study
- the ICF
- the assent form
- 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 International Ethical Guidelines
- International Conference on Harmonisation (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 ERB(s).

Some of the obligations of Lilly will be assigned to a third-party organization.

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 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.

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Attachment 1. Protocol JGDL Study Schedule

Study Schedule, Protocol I5B-MC-JGDL

Perform procedures as indicated. All screening/baseline evaluations are performed within 14 days prior to enrollment in Phase 1b or randomization in Phase 2, unless otherwise specified. Upon signing the informed consent form, the site will register the patient in the Interactive Web Response System (IWRS). The patient will be enrolled in Phase 1b or randomized in Phase 2 via IWRS after meeting inclusion/exclusion criteria. After enrollment in Phase 1b or randomization in Phase 2, patients should receive their first dose of treatment within 72 hours (3 days) whenever possible.

Baseline Schedule (Phase 1b and Phase 2)

Study Period	Baseline	
Cycle	BL	
Visit	0	
Duration	Up to 14 days (except where noted)	
Relative Day from Enrollment in Phase 1b/ Randomization in Phase 2	≤14	≤7

Procedure Category	Protocol Sections	Procedure			Comments
Study Entry/ Enrollment	7, 13.1	Informed Consent/Assent (if applicable)	X (within 28 days of enrollment in Phase 1b or randomization in Phase2, unless otherwise specified)		Written informed consent (or assent, if applicable) 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	Upon signing the informed consent form, the site will register the patient in the IWRS. The patient will be enrolled in Phase 1b or randomized in Phase 2 via IWRS after meeting inclusion/exclusion criteria. After enrollment in Phase 1b or randomization in Phase 2, 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 ≥ 3 weeks (21 days) prior to first dose of study drug.
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.
		Vital signs		X	Vital signs include blood pressure, pulse, respiratory rate 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.

Baseline Schedule (Phase 1b and Phase 2)

Study Period	Baseline		
Cycle	BL		
Visit	0		
Duration	Up to 14 days (except where noted)		
Relative Day from Enrollment in Phase 1b/ Randomization in Phase 2	≤14	≤7	

Procedure Category	Protocol Sections	Procedure			Comments
Lab/ Diagnostic Tests	7.1 Att. 2	Hematology	X		Screening evaluations done within 7 days prior to enrollment in Phase 1b or randomization in Phase 2, do not have to be repeated.
	7.1 Att. 2	Serum Chemistry	X		Screening evaluations done within 7 days prior to enrollment in Phase 1b or randomization in Phase 2, do not have to be repeated.
	7.1 Att. 2	Coagulation Profile	X		Screening evaluations done within 7 days prior to enrollment in Phase 1b or randomization in Phase 2 do not have to be repeated.
	Att. 2	Urinalysis	X		Screening evaluations done within 7 days prior to enrollment in Phase 1b or randomization in Phase 2 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 the patient must have ≤ 1000 mg of protein in 24-hour urine or urine protein/creatinine ratio ≤ 1 on spot urine (up to 3 business days is allowed if the weekend).
	7.1 Att. 2	Pregnancy Test		X	Serum β-HCG pregnancy test (women of childbearing potential only) within 7 days prior to enrollment in Phase 1b or randomization in Phase 2. 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.
	10.4.2.2 Att. 6	Mandatory Tumor Tissue	X		Mandatory archived tumor tissue or tumor tissue from biopsy (if adequate archived samples are unavailable) for biomarkers and tumor type (refer to Section 10.4.2.2 for details).
	10.3.2.1	ECG	X (within 28 days of enrollment in Phase 1b or randomization in Phase 2)		A single 12-lead ECG is to be obtained within 28 days prior to enrollment in Phase 1b or randomization in Phase 2 (refer to Section 10.3.2.1 for details).
Efficacy Assessment	10.1.1 Att. 5	Imaging Studies (CT/MRI) Tumor Assessments (according to RECIST v1.1)	X (within 28 days of enrollment in Phase 1b and randomization in Phase 2)		Within 28 days prior to enrollment in Phase 1b or randomization in Phase 2 (refer to Section 10.1.1 for details). Scans performed prior to the date of consent may be used provided they are within 28 days of enrollment (Phase 1b) and randomization (Phase 2).
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; FSH = follicle-stimulating hormone; IWRS = interactive web-response system; MRI = magnetic resonance imaging; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria In Solid Tumors; v = version.

Study Schedule, Protocol I5B-MC-JGDL

Perform procedures as indicated. Please refer to appropriate protocol sections for more detailed instructions.

Treatment Period Schedule (Phase 1 b and Phase 2)

		Study Period	Treatment Period		
Procedure Category	**Protocol Sections**	**Relative Day within Cycle** (21 day cycle − 3 days)	1[a]	8[a]	**Comment**
Physical Examination	9.4, 10.3.1	Physical Examination	X	X	Physical examination during treatment period includes weight and BSA measurement. Patients should be weighed at D1 and D8 of each cycle and BSA calculated.
	Att. 4	ECOG Performance Status	X		Complete prior to treatment infusion.
	10.3.1	Vital signs	X	X	Vital signs include blood pressure, pulse, respiratory rate, and temperature. Please refer to Table JGDL.1 footnote b for the times when vital signs should be collected.
Lab/ Diagnostic Tests	Att. 2	Hematology	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 and D8 of each cycle. See Attachment 2 for details.
	Att. 2	Coagulation Profile	X		Perform within 3 days prior to D1 of every other cycle or as clinically indicated. See Attachment 2 for details.
	Att. 2	Pregnancy Test	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 6 for specific time points		Whole blood samples collected and processed into serum (olaratumab) or plasma (gemcitabine/docetaxel). If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 (± 3 days) days after onset of the IRR event.
	10.4.3	Immunogenicity Samples	See Attachment 6 for specific time points		Whole blood samples collected and processed into serum. If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 (± 3 days) days after onset of the IRR event.
	10.4.2.1	Pharmacogenetic (DNA) Whole Blood Sample	See Attachment 6 for specific time point.		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.
	10.4.2.3	Plasma sample for biomarkers	See Attachment 6 for time points.		Whole blood samples collected and processed into plasma.
	10.3.2.1	ECG	X		In Phase 1b, twelve-lead ECGs are to be performed as single ECGs within 3 days prior to Day 1 of every cycle, until PD or treatment discontinuation, whichever comes first.
Patient reported outcomes	10.2	PRO Assessments (mBPI-sf, EORTC QLQ C30, EQ-5D-5L)	X		The Patient Reported Outcome (PRO) measures will be collected on Day 1 of every cycle (Phase 2 only).
Efficacy Assessment	10.1.1 Att. 5	Imaging Studies (CT/MRI) Tumor Assessments (according to RECIST v1.1)	X		Imaging studies and tumor assessments are be obtained every 6 weeks (±7 days), irrespective of treatment cycles as calculated from enrollment in Phase 1b or randomization in Phase 2, 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 for details.

Procedure Category	Protocol Sections	Study Period: Relative Day within Cycle (21 day cycle − 3 days)	Treatment Period: 1[a]	Treatment Period: 8[a]	Comment
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.
Concomitant Therapy	9.6	Concomitant Medications	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.
Premedication	9.1.1.1, 9.1.1	Administer premedication prior to olaratumab or placebo.	X	X	Premedicate all patients with the following (or equivalent) medications intravenously: a histamine H1 antagonist (e.g., diphenhydramine) and dexamethasone 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 (e.g., diphenhydramine) intravenously 30-60 minutes prior to each dose of olaratumab or placebo.
Study Treatment	9.2.1	Administer olaratumab or placebo.	X	X	Administer until progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria are met. No crossover will be permitted in the Phase 2 part.
	9.2.2	Administer gemcitabine.	X	X	Administer until progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria are met.
	9.2.3	Administer docetaxel.		X	Administer until progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria are met.
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-JGDL

Perform procedures as indicated.

Post-Treatment Discontinuation Schedule

			Study Period	Post-discontinuation Follow-Up		
				Short-Term Follow-Up	Long-Term Follow-Up	
			Visit	801	802-8XX	
			Duration	30 ± 7 days	See footnote for duration	
Procedure Category	**Protocol Section**	**Procedure**				**Comments**
Physical Examination	9.4, 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, respiratory rate, 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+, obtain urine protein/creatinine ratio on spot urine or a 24-hour urine collection (to assess protein) must be obtained (up to 3 business days is allowed if the weekend).
	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			In Phase 1b only, twelve-lead ECGs are to be performed as single ECGs for all patients at the short–term follow-up.
	10.4.4	PK sample	X			See Attachment 6. 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.
	10.4.3	Immunogenicity sample	X			See Attachment 6. 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.
	10.4.2.3	Plasma sample for biomarkers	X			See Attachment 6.
Patient Reported Outcomes	10.2	PRO Assessments (mBPI-sf, EORTC QLQ C30, EQ-5D-5L)	X			The Patient Reported Outcome (PRO) measures will be collected at the 30-day short-term follow-up visit.
Efficacy Assessments	10.1.1, Att. 5	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 be obtained every 6 weeks (±7 days), irrespective of treatment cycles as calculated from enrollment in Phase 1b or from randomization for Phase 2, until documented progression.

Post-Treatment Discontinuation Schedule

Procedure Category	Protocol Section	Procedure	Post-discontinuation Follow-Up: Short-Term Follow-Up (Visit 801, 30 ± 7 days)	Post-discontinuation Follow-Up: Long-Term Follow-Up (Visit 802-8XX, See footnote for duration)	Comments
	8.1.3	Survival Information, All Subsequent Anti-Cancer Treatments, and Associated Disease Progression Date		X	For patients enrolled in Phase 1 b and randomized in the Phase 2 part that discontinue study treatment after objectively measured PD the following information will be collected every 3 months (±7 days) for the first year, 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		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; ECOG = Eastern Cooperative Oncology Group; LCSS = Lung Cancer Symptom Scale; 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 date of this agreement is to be reported on the CRF as the date of Discontinuation from study treatment.

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 followed every 6 weeks (±7 days) until PD.
- Follow-up for survival: Patients will be followed every 3 months (±7 days) for the first year, then every 6 months (±14 days) until the patient's death or overall study completion.

Study Schedule, Protocol I5B-MC-JGDL

Perform procedures as indicated.

Continued Access Period Schedule

		Study Period	Continued Access Treatment Period	Continued Access Follow-Up Period	
		Cycle	X-Y	Follow-Up	
		Visit	501-5XX	901	
		Duration	1 day	30 ± 7 days	
Procedure Category	**Protocol Section**	**Procedure**			**Comments**
Physical Examination	9.4	Physical examination	X		Weight.
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	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. 6	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	9.1.1.1	Administer premedication prior to olaratumab treatment.	X		Premedicate all patients with a histamine H1 antagonist (e.g., diphenhydramine) intravenously 30-60 minutes prior to each dose of olaratumab.
Study Treatment	9.2.1	Administer olaratumab.	X		Administer on Days 1 and 8, until evidence of progressive disease, unacceptable toxicity, death, or other withdrawal criteria are met.
	9.2.2	Administer gemcitabine.	X		Administer on Days 1 and 8, until evidence of progressive disease, unacceptable toxicity, death, or other withdrawal criteria are met.
	9.2.3	Administer docetaxel.	X		Administer on Day 8, until evidence of progressive disease, unacceptable toxicity, death, or other withdrawal criteria are met.

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

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

Abbreviations: CRP = clinical research physician; D = Day; INR = international normalized ratio; LDH = lactate dehydrogenase; PK = pharmacokinetics; 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 ≥2+ at evaluations, a 24-hour urine collection (to assess protein) must be collected, or alternatively, a urine protein/creatinine ratio on spot urine. Note: UPC 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:

- [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
- [(urine protein) x 0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L.

d Assayed by a Sponsored-designated (central) laboratory. Refer to Attachment 6.

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

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

g Performed locally at screening only, repeat not required but should be obtained if clinically appropriate.

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

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

Hepatic Monitoring Tests

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

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

a Assayed by Lilly-designated laboratory.

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

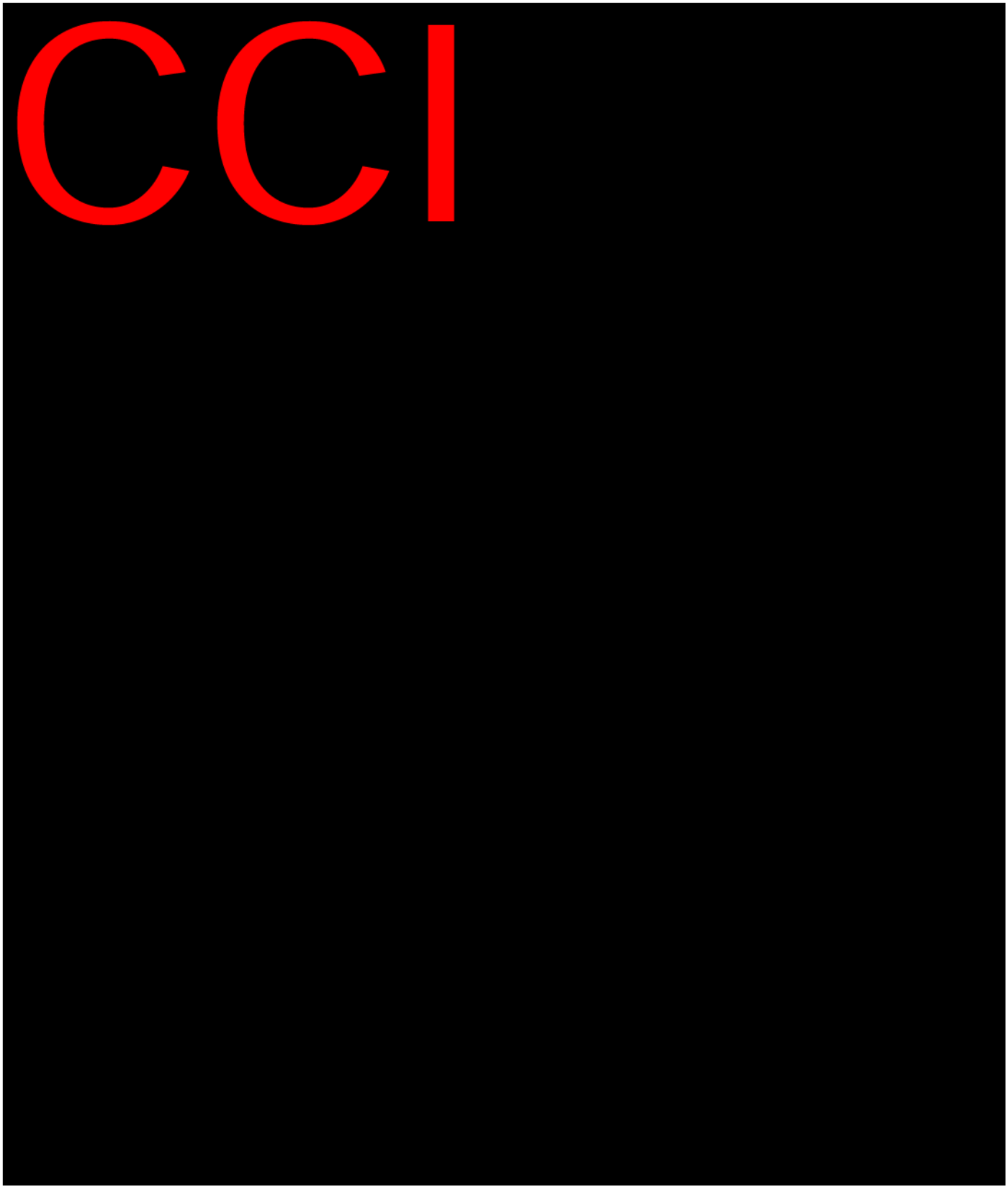
Attachment 4. Protocol JGDL ECOG Performance Status

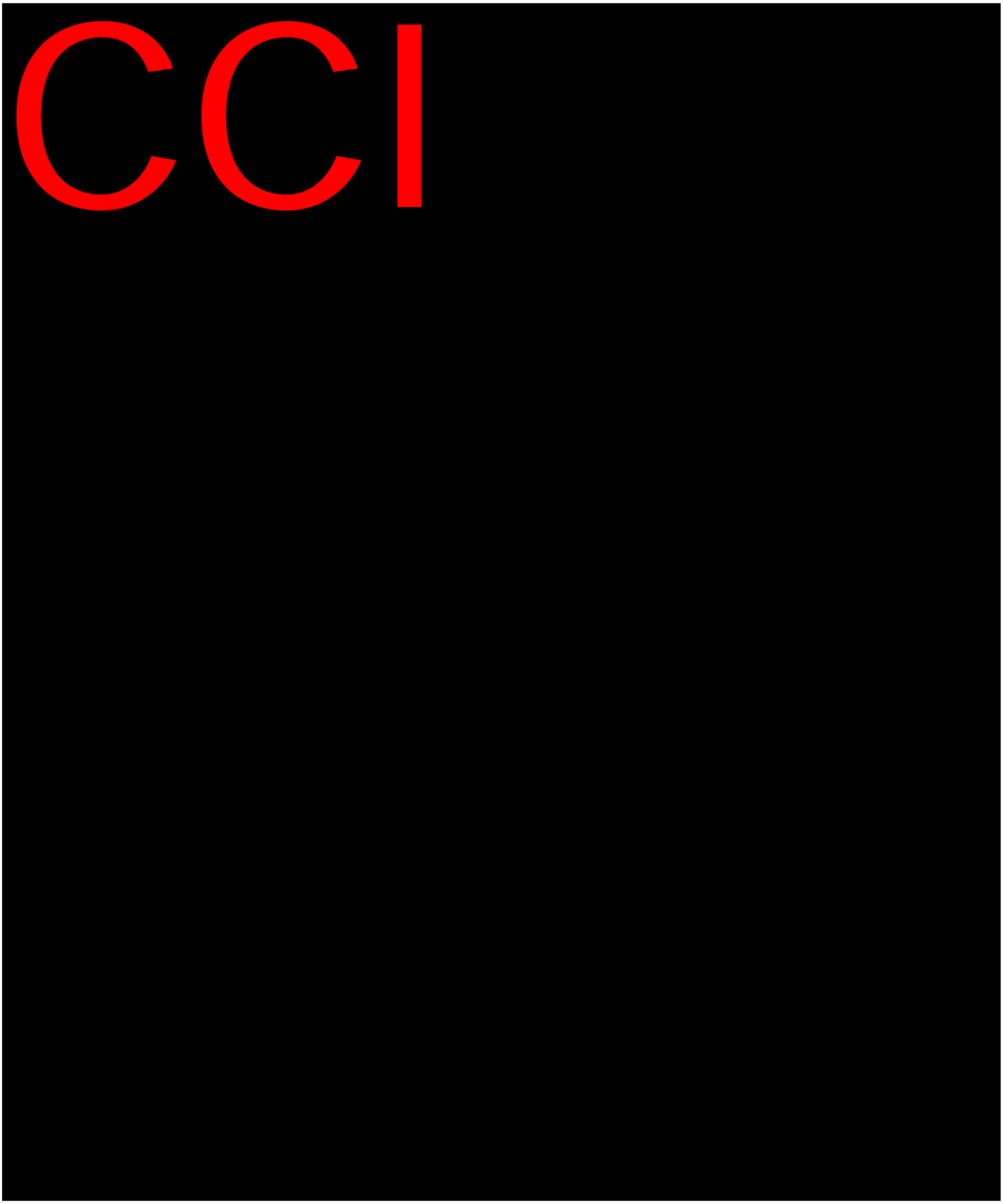
ECOG Performance Status

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 JGDL RECIST Criteria 1.1

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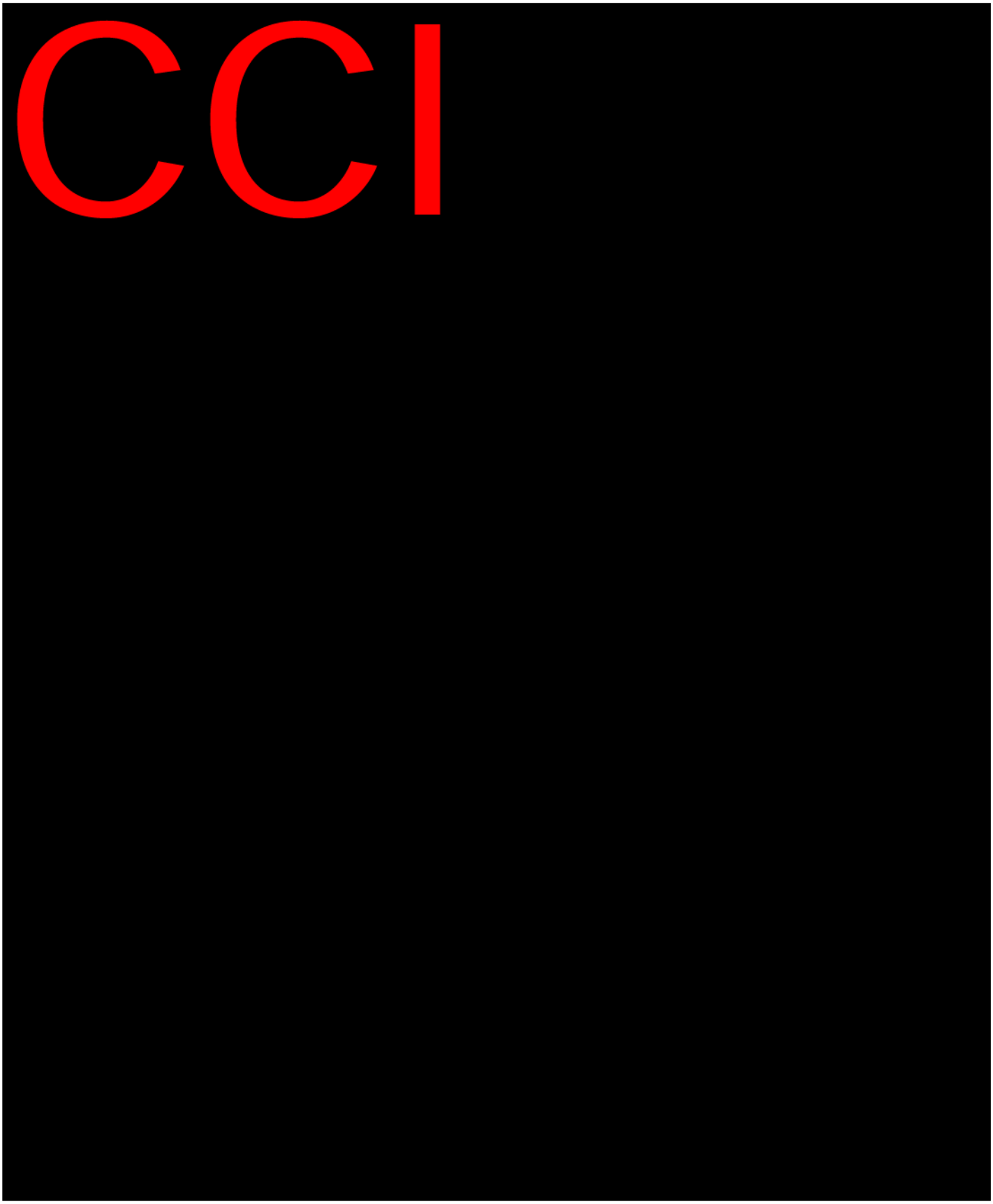
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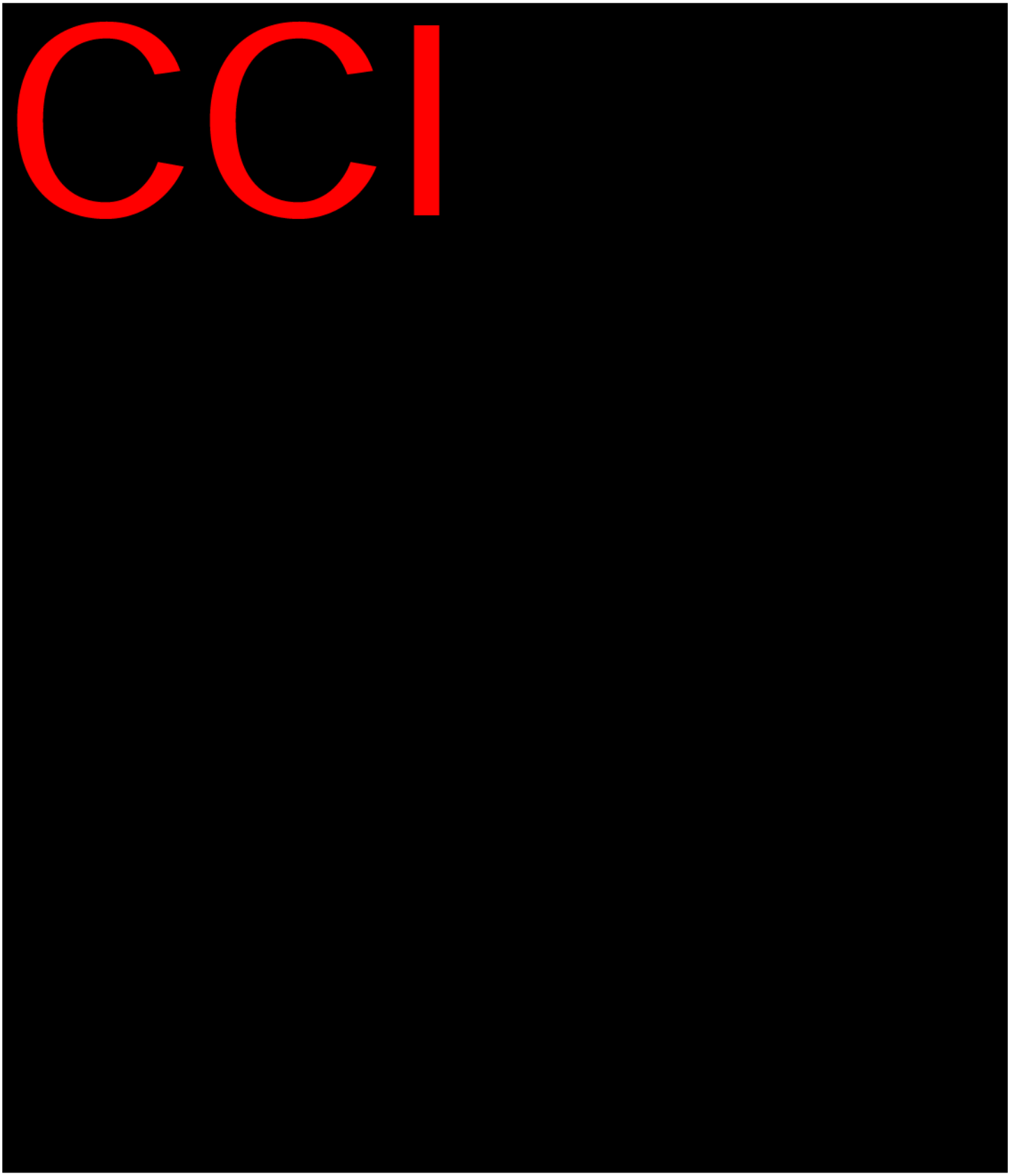
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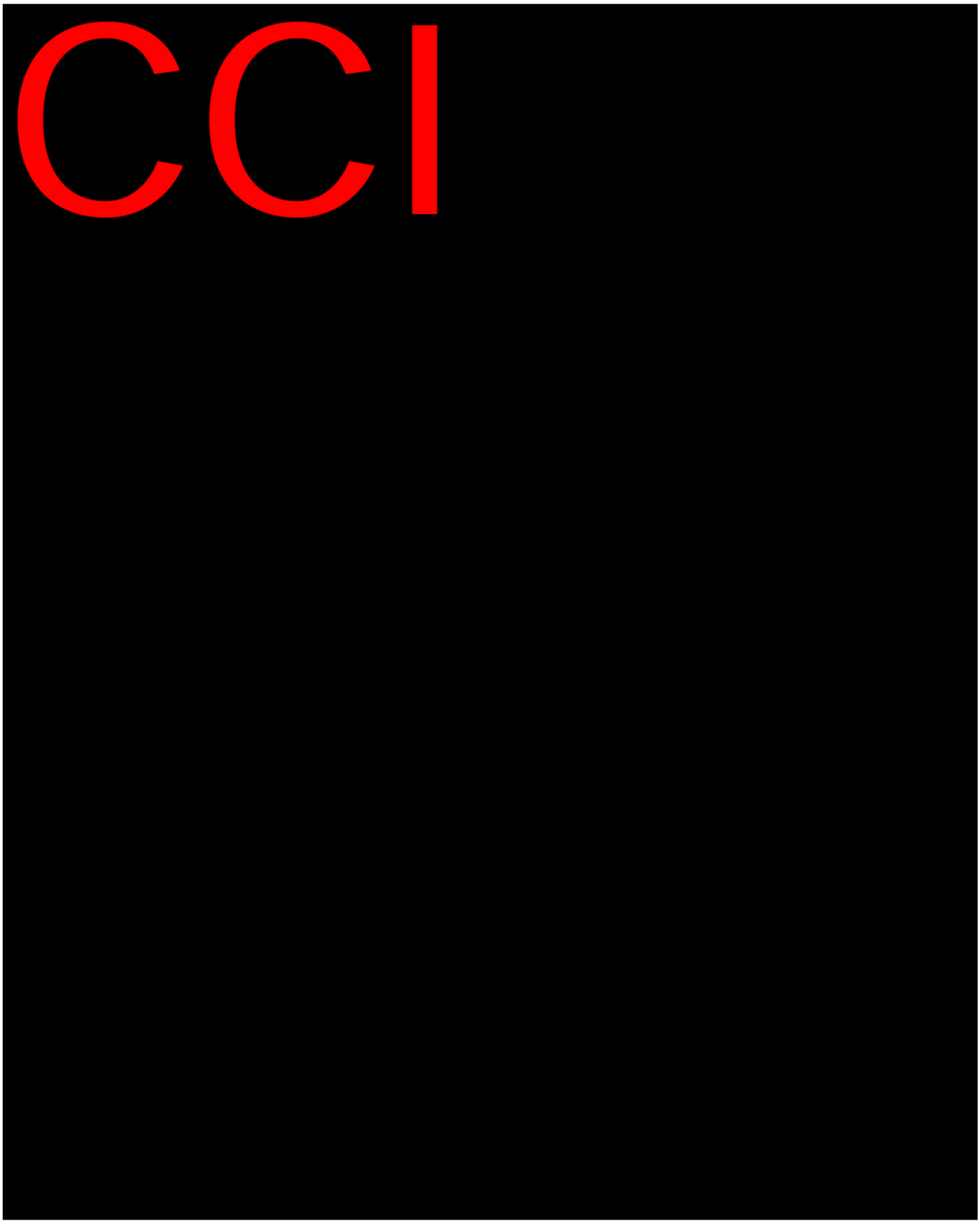
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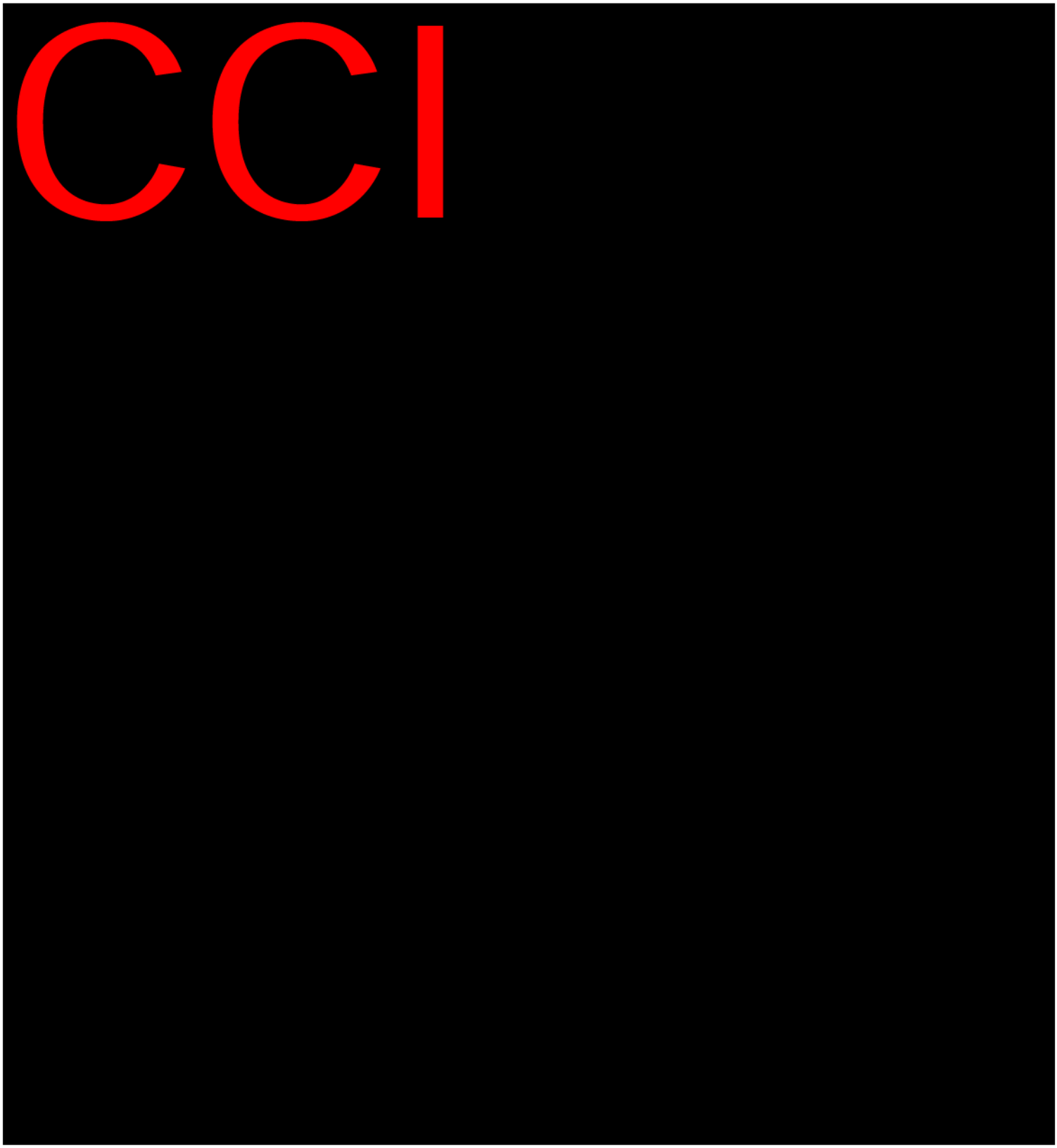
CCI

Attachment 6. Protocol JGDL Pharmacokinetic, Immunogenicity, and Translational Research Sampling Schedule

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

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

Pharmacokinetic Sampling Schedule – Phase 1b

Sample Number	Cycle	Day	Dosing	Sampling Time	Olaratumab PK[a, e]	Gem PK[b]	Doce PK[c]	IK[d, e]
1	1	1		Prior to olaratumab[f]	X			X
			Olaratumab (1 hr)					
2				≤ 5 min post-olaratumab	X			
			Obs (1 hr)					
3				60 ± 10 min post-olaratumab	X			
4				4 hr ± 25 min post-olaratumab	X			
5		2		24 ± 3 hr post-olaratumab	X			
6		5		Anytime	X			
7		8		Prior to olaratumab[f]	X			X
			Olaratumab (1 hr)					
8				≤ 5 min post-inf	X			
			Obs (1 hr)					
9				60 ± 10 min post-olaratumab	X			
			Gem (1.5 hr)					
10				≤ 5 min post-gem		X		
			Docetaxel (1 hr)					
11				≤ 5 min post-doce		X	X	
12				60 ± 10 min post doce	X	X	X	
13				3 hr ± 15 min post-doce		X	X	
14		9		24 ± 3 hr post-olaratumab[f]	X	X	X	
15		10		Anytime			X	
16		12		Anytime	X			
17		15		Anytime	X			
18	2	1		Prior to olaratumab[f]	X			X
			Olaratumab (1 hr)					
19				≤ 5 min post-inf	X			
20		8		Prior to olaratumab[f]				
			Olaratumab (1 hr)					
21				≤ 5 min post-inf	X			
22	3	1		Prior to olaratumab[f]	X			X
			Olaratumab (1 hr)					
23				≤ 5 min post-olaratumab	X			
24				60 ± 10 min post-olaratumab	X			
25				4 hr ± 25 min post-olaratumab	X			
26		2		24 ± 3 hr post-olaratumab	X			
27		5		Anytime	X			
28		8		Prior to olaratumab[f]	X			
			Olaratumab (1 hr)					
29				≤ 5 min post-olaratumab	X			
30				60 ± 10 min post-olaratumab	X			
31				4 hr ± 25 min post-olaratumab	X			
32		9		24 ± 3 hr post-olaratumab	X			
33		12		Anytime	X			
34		15		Anytime	X			
35-	5 and then every other cycle	1		Prior to olaratumab[f]	X			X
801	30-day follow-up visit			Anytime	X			X

Abbreviations: Doce = docetaxel; Gem = gemcitabine; IK = immunogenicity; IRR = Infusion related reaction; PK = pharmacokinetic; Obs = observation.

a Samples of approx. 3 mL of whole blood will be drawn without anticoagulant for measurement of olaratumab in serum.

b Samples of approx. 2 mL of whole blood will be drawn into plastic tubes with anticoagulant for measurement of gemcitabine in plasma.

c Samples of approx. 3 mL of whole blood will be drawn into plastic tubes with anticoagulant for measurement of docetaxel in plasma.

d For the immunogenicity assay, approx. 10 mL of whole blood will be drawn.

e 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.

f Pretreatment PK samples may be collected up to 60 minutes prior to the olaratumab infusion and must be prior to administering any premedication.

Pharmacokinetic Sampling Schedule – Phase 2

Sample Number	Cycle	Day	Dosing	Sampling Time	Olaratumab PK[a, e]	Gem PK[b]	Doce PK[c]	IK[d, e]
1	1	1		Prior to olaratumab/placebo[f]	X			X
			Olaratumab (1 hr)					
2				≤ 5 min post-olaratumab/placebo	X			
3		8		Prior to olaratumab dose/placebo[f]	X			X
			Olaratumab (1 hr)					
4				≤ 5 min post-olaratumab/placebo	X			
			Obs (1 hr)					
			Gem (1.5 hr)					
5				≤ 5 min post-gem		X		
			Docetaxel (1 hr)					
6				≤ 5 min. post-docetaxel	X		X	
7	2	1		Prior to olaratumab/placebo[f]	X			X
			Olaratumab (1 hr)					
8				≤ 5 min post-olaratumab/placebo	X			
9		8		Prior to olaratumab/placebo[f]	X			
			Olaratumab (1 hr)					
10				≤ 5 min post-olaratumab/placebo	X			
11	3	1		Prior to olaratumab/placebo[f]	X			X
			Olaratumab (1 hr)					
12				≤ 5 min post-olaratumab/placebo	X			
13		8		≤ Prior to olaratumab/placebo[f]	X			
			Olaratumab (1 hr)					
14				≤ 5 min post-olaratumab/placebo	X			
15-	5 and then every other cycle	1		Prior to olaratumab/placebo[f]	X			X
801	30-day follow-up visit			Anytime	X			X

Abbreviations: Gem = gemcitabine; IK = immunogenicity; IRR = Infusion related reaction; PK = pharmacokinetic; Obs = observation.

a Samples of approx. 3 mL of whole blood will be drawn without anticoagulant for measurement of olaratumab in serum.

b Samples of approx. 2 mL of whole blood will be drawn into plastic tubes with anticoagulant for measurement of gemcitabine in plasma.

c Samples of approx. 3 mL of whole blood will be drawn into plastic tubes with anticoagulant for measurement of docetaxel in plasma.

d For the immunogenicity assay, approx. 10 mL of whole blood will be drawn.

e 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.

f Pretreatment PK samples may be collected up to 60 minutes prior to the olaratumab infusion and must be prior to administering any premedication.

Biomarker 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
	3	1	Prior to olaratumab/placebo infusion[d]	X		
801	30-day follow-up visit		Anytime	X		

a Refer to Section 10.4.2.3 for details on whole blood for plasma collection.

b Refer to Section 10.4.2.1 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 10.4.2.2 for details on tumor tissue collection.

d Pretreatment samples may be collected up to 60 minutes prior to the olaratumab/placebo infusion.

Attachment 7. Protocol JGDL List of Common CYP3A4 Inhibitors and Inducers of Docetaxel

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	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	Norfloxacin
	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 antiemetic is recommended.

Attachment 8. Protocol JGDL 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:

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

For serum creatinine concentration in μmol/L:

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

a Age in years, weight (wt) in kilograms.

Reference: Cockcroft and Gault 1976.

Attachment 9. Protocol JGDL Amendment (c) Summary A Phase 1b (Open-Label) / Phase 2 (Randomized, Double-Blinded) Study Evaluating Gemcitabine and Docetaxel With or Without Olaratumab in the Treatment of Advanced Soft Tissue Sarcoma

Overview

Protocol I5B-MC-JGDL (b) "A Phase 1b (Open-Label) / Phase 2 (Randomized, Double-Blinded) Study Evaluating Gemcitabine and Docetaxel With or Without Olaratumab in the Treatment of Advanced Soft Tissue Sarcoma" has been amended. The new protocol is indicated by amendment (c) 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:

- The protocol synopsis, definitions, Figure JGDL.1 and Sections 7.1 and 8.1.2 were modified to allow for expansion of olaratumab of inclusion criteria by enrolling 90 additional patients that have previously received olaratumab (olaratumab pre-treated) in the Phase 2 part of the study. Section 6.2 is updated with a secondary objective regarding this patient population. The rationale for adding these patients is to evaluate for a signal for strategic planning of future studies including this patient subset (refer to section 5.2 and 5.5.3).
- The protocol synopsis, Sections 8.1.8 and 12.2.14, and SAP have been modified to add an interim efficacy analysis to the Phase 2 part of the study. This analysis will be triggered after 40 OS events in the olaratumab pre-treated patients.
- In Section 5.4 the number of patients previously treated with olaratumab in clinical trials is updated per the most recent IB.
- Inclusion criterion [9] regarding patients receiving anti-coagulant therapy was updated for consistency across clinical trials with olaratumab.
- Exclusion criterion [23] was added regarding the olaratumab pre-treated population for safety.
- Criteria to begin subsequent treatment cycles was clarified in Section 9.4.1.2. In this same section, clarification was added to allowable treatment delays.
- A second dose reduction in gemcitabine and docetaxel will be allowed with this amendment. Clarifications are also made on dose alterations for toxicities of gemcitabine and docetaxel. These changes are noted in Tables JGDL.2, JGDL.3, JGDL.4, and JGDL.5 and Section 9.4.1.2. In addition, in this same section it is clarified that treatment may continue with one chemotherapy agent if the other is discontinued for toxicity.
- Section 9.4.1.2.2 is updated with information on modification of infusion rates for patients with Grade 1 and 2 IRRs. It is also updated for instructions on olaratumab pre-treated patients with prior IRR.

- Tables JGDL.6 and JGDL.7 are updated for dose modifications of olaratumab for toxicities. These changes are for consistency across all olaratumab protocols.
- In Table JGDL.10 the criteria for QT interval assessment is changed to the Fridericia's QT correction formula, for consistency across olaratumab protocols.
- Alterations in LDH, gammaglutamyl transferase, and TSH have not been found to be related to olaratumab. Accordingly, in Attachment 2, these labs are no longer required subsequent to baseline evaluation.
- PROs are not needed to be done in long-term follow-up period (Visit 802-8XXX) for Phase 1b/2. Accordingly, the Post-Treatment Discontinuation Schedule has been updated.
- 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 double underscore.

2. Synopsis

Study Rationale:

~~Recently, t~~The platelet-derived growth factor receptor alpha (PDGFRα) antibody olaratumab in combination with doxorubicin demonstrated a significant improvement in ~~an interim analysis of~~ overall survival (OS) over doxorubicin alone in patients with advanced soft tissue sarcoma (STS) (Tap et al. 2016~~5~~). Since some patients may not be appropriate candidates for doxorubicin-based chemotherapy, or have received prior anthracycline treatment, exploring olaratumab combinations with other chemotherapeutic agents that are often used in STS treatment is of considerable interest. Study I5B-MC-JGDL is a multicenter Phase 1b/2 study of olaratumab in combination with gemcitabine and docetaxel in patients with advanced or metastatic STS, not amenable to treatment with surgical resection or radiotherapy with curative intent. The first part (Phase 1b) of the study will consist of an open-label, single-arm, dose-escalation assessment of the safety and tolerability of olaratumab administered at 15 mg/kg (Days 1 and 8) or 20 mg/kg (Days 1 and 8) with gemcitabine (900 mg/m^2 [fixed dose rate: 10 mg/m^2/minute] Days 1 and 8) and docetaxel (75 mg/m^2 Day 8), of a 21-day cycle. After the dose of olaratumab in combination with gemcitabine and docetaxel has been determined from the analysis of the Phase 1b part, the Phase 2, randomized, double-blinded, placebo-controlled part of the study will open to enrollment. Approximately ~~166~~ 256 patients will be randomized in Phase 2 in a 1:1 ratio to Arm A (olaratumab plus gemcitabine and docetaxel) or Arm B (placebo plus gemcitabine and docetaxel).

Clinical Protocol Synopsis: Study I5B-MC-JGDL

Number of Planned Patients:
Phase 1b:
Enrolled: Approximately ~~45~~ 55 patients
Phase 2:
Entered: Approximately ~~200~~ 314
Randomized: 256 ~~166~~ **Length of Study:** approximately ~~44~~ 47 months
Planned last patient visit: ~~August~~ November 2020
Planned interim safety analyses ~~are performed to monitor the safety data~~ in the Phase 2 part of the study:~~-~~

1. Approximately 60 patients in Phase 2 have completed at least 2 cycles of treatment: required safety, ~~and~~ PK data if needed.
2. Every 6 months thereafter until approximately 1 year after completing enrollment: required safety ~~and~~ PK data if needed.

Planned interim efficacy analyses in the Phase 2 part of the study:

1. After 40 OS events in olaratumab-pretreated patients.

Objectives:
The primary objective of the Phase 2 part is to compare the OS in olaratumab-naïve patients with locally advanced or metastatic STS treated with olaratumab plus gemcitabine and docetaxel versus placebo plus gemcitabine and docetaxel.

A secondary objective of the Phase 2 part is to compare OS in olaratumab-pretreated patients with locally advanced or metastatic STS treated with olaratumab plus gemcitabine and docetaxel versus placebo plus gemcitabine and docetaxel.

The secondary objectives of the Phase 2 part are to compare olaratumab plus gemcitabine and docetaxel versus placebo plus gemcitabine and docetaxel in both olaratumab-naïve and olaratumab-pretreated groups, for the following:

The exploratory objectives for both Phase 1b and Phase 2 ~~is~~ are:

Study Design: This trial is a Phase 1b open-label, dose-escalation part followed by a randomized, double-blind, placebo-controlled Phase 2 study of olaratumab plus gemcitabine and docetaxel in patients with locally advanced or metastatic STS, not amenable to treatment with surgical resection or radiotherapy with curative intent. In the Phase 1b part, 2 cohorts (15 mg/kg or 20 mg/kg) will be studied to determine the olaratumab dose that may be safely administered in combination with gemcitabine and docetaxel. After the dose of olaratumab in combination with gemcitabine and docetaxel has been determined from the Phase 1b part, the Phase 2 part of the study will open to enrollment. In Phase 2, approximately ~~166~~ 256 patients will be randomized 1:1, in a double-blinded manner, to Arm A (olaratumab plus gemcitabine and docetaxel) or Arm B (placebo plus gemcitabine and docetaxel). Randomization will be stratified by prior treatment with olaratumab (yes versus no), number of prior systemic therapies for locally advanced or metastatic disease (0 versus ≥1), histological tumor type (leiomyosarcoma versus non-leiomyosarcoma), Eastern Cooperative Oncology Group performance status (ECOG PS) (0 versus 1), and prior pelvic radiation (yes versus no). Patients will continue treatment until there is documented disease progression, unacceptable toxicity, death, or other discontinuation criteria are met.

Diagnosis and Main Criteria for Inclusion and Exclusions: Patients at least 16 years of age, ECOG PS 0 to 1, gemcitabine~~,~~ and docetaxel~~, and olaratumab~~ naïve, with histologically confirmed, locally advanced, unresectable or metastatic STS, and not amenable to curative treatment with surgery or radiotherapy. Patients with gastrointestinal stromal tumor or Kaposi's sarcoma will be excluded. Patients previously enrolled in Study I5B-MC-JGDJ or any other blinded study with olaratumab are not eligible to participate in this trial.

Reference Therapy, Dose, and Mode of Administration:
For the Phase 1b and 2 parts:
Gemcitabine is a commercially available product and should be stored, reconstituted, and discarded per manufacturer's instructions. Gemcitabine is administered at a dose of 900 mg/m2 over approximately 90 minutes (fixed dose rate: 10 mg/m^2/minute) on Days 1 and 8 of each 21-day cycle.
Docetaxel: is a commercially available product ~~A commercial preparation of docetaxel will be used~~ and should be prepared and administered according to the manufacturer's instructions. ~~In the Phase 1b and Phase 2 parts,~~ ~~d~~Docetaxel ~~will be~~ is administered at a dose of 75 mg/m^2 (IV) over approximately 60 minutes on Day 8 of each 21-day cycle.
For the Phase 2 part:
Placebo: injection for IV use, supplied in single-use vials, administered to patients as an IV infusion over approximately 60 minutes on Days 1 and 8 of each 21-day cycle

Planned Duration of Treatment:

Long-term follow-up (postdiscontinuation): Patients that discontinue study treatment for reasons other than progression will be followed every 6 weeks (±7 days) until progressive disease (PD), thereafter every ~~2~~ 3 months (±7 days) for the first ~~2~~ year~~s~~, then every 6 months (±14 days) until the patient's death or overall study completion.

Statistical Methods:

Statistical:

Efficacy: Phase 2: The primary objective is to compare OS in olaratumab-naïve patients with locally advanced or metastatic STS treated with olaratumab plus gemcitabine and docetaxel versus placebo plus gemcitabine and docetaxel. ~~Investigative sites will screen approximately 200 patients to randomize 166~~ Patients will be randomized ~~in~~ 1:1 ~~randomization~~ to the two treatment arms.~~(83 patients in the experimental arm and 83 patients in the control arm)~~. The intention-to-treat (ITT) sample size of 166 for olaratumab-naïve patients (83 in the experimental arm and 83 in the control arm) was selected assuming the final analysis of OS will occur after 108 OS events have been observed (35% censoring).

The final total of 108 OS events in the olaratumab-naïve patients (deaths) provides 80% statistical power for a two-sided log-rank test at a 0.20 significance level (assuming the true OS hazard ratio [HR] is 0.665). An OS HR of 0.665 corresponds approximately to an increased median survival from 15 months (estimated from published clinical data in various types of patients with locally advanced or metastatic STS) in placebo plus gemcitabine and docetaxel to 22.5 months for olaratumab plus gemcitabine and docetaxel.

An additional 90 olaratumab-pretreated patients (45 in the experimental arm and 45 in the control arm) will be randomized to compare the same regimens as a secondary objective.

The primary efficacy outcome for the Phase 2 part of the study is OS in the olaratumab-naïve cohort of the ITT population. Analysis of OS will be based on the stratified log rank test, stratified by the 3 of the 4 randomization strata; that is, number of prior systemic therapies for locally advanced or metastatic disease (0 versus ≥1), histological tumor type (leiomyosarcoma versus non–leiomyosarcoma), and ECOG PS (0 versus 1).

Overall survival curves, the median with 95% confidence interval (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 the aforementioned 3 randomization strata. All ITT population will be included in the analysis of this endpoint. ~~There is no interim efficacy analysis planned for the Phase 2 part.~~ The same OS analyses will also be performed separately for the olaratumab-pretreated cohort of the ITT population.

Interim analysis

There will be safety interim reviews for both Phase 1b and Phase 2 parts. In addition, an interim efficacy analysis is planned for the Phase 2 part of the study.

The safety review for Phase 1b will be conducted by Lilly clinical research personnel. The study investigators and the Lilly clinical research physician/clinical research scientist (CRP/CRS) will make the determination regarding dose escalation based upon their review of the safety/tolerability data and the PK data from the previous cohorts. In addition, an interim safety review will be conducted prior to proceeding to Phase 2 including safety and PK.

An independent data monitoring committee (iDMC) will be established to conduct Phase 2 safety interim reviews. The first iDMC meeting to review interim data will occur when approximately 60 patients (approximately 30 patients from each arm) have received at least 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 regularly thereafter.

An interim efficacy analysis is planned for the Phase 2 part of the study. After observing 40 OS events among the olaratumab-pretreated cohort of the ITT population, interim analysis will occur. Any positive interim efficacy results may be used for planning of additional separate clinical studies, but will not be used to modify the design and conduct of this current trial.

4. Abbreviations and Definitions

Term	Definition
Olaratumab naïve	A study participant who has never received olaratumab prior to enrollment or randomization
Olaratumab pretreated	A study participant who has previously received commercially available olaratumab, as defined by the inclusion criteria

5.2 Olaratumab Background

In normal mesenchymal biology, PDGF/PDGFR signaling has a significant role in mesenchymal stem cell differentiation, growth of mesenchymal cells, angiogenesis, and wound healing (Andrae et al. 2008; Ng et al. 2008; Li et al. 2014). PDGF/PDGFRα signaling has been implicated in the pathogenesis of multiple cancers, including osteosarcoma, chondrosarcoma, prostate cancer, breast cancer, ovarian cancer, and others. In malignant disease, the PDGF/PDGFRα axis promotes tumor growth and proliferation through both autocrine and paracrine mechanisms. PDGFRα is expressed on stromal cells, as well as the cancer cells themselves, within certain tumors. Furthermore, studies have shown that PDGF/PDGFRα signaling affects tumor vasculature through paracrine mediation of vascular endothelial growth factor production (Shah et al. 2010). Additional information is available in the olaratumab investigator's brochure (IB).

5.3 Study Rationale

The positive efficacy results seen with olaratumab in combination with doxorubicin in Study JGDG (Tap et al. 2016~~5~~) warrant further study of olaratumab with gemcitabine plus docetaxel, another active treatment regimen, for patients with advanced or metastatic STS.

Study I5B-MC-JGDL will evaluate the efficacy and safety of olaratumab, in combination with docetaxel and gemcitabine (fixed dose rate: 10 mg/m^2/minute) in patients with locally advanced or metastatic STS. The study will allow this evaluation in both olaratumab-naïve and olaratumab-pretreated populations. Olaratumab-naïve patients are those who may be ineligible for treatment with doxorubicin or for whom gemcitabine/docetaxel is more appropriate as initial chemotherapy than doxorubicin.

5.4 Rationale for Selection of Dose

Olaratumab:

The current dose-selection strategy for this study is based on the integrated safety, efficacy, and pharmacokinetics (PK) data for olaratumab across previous Phase 1 and Phase 2 studies. In 2 Phase 1 dose-escalation trials (Studies I5B-IE-JGDC and I5B-IE-JGDF) and in the 2 Phase 2 monotherapy studies (Studies I5B-IE-JGDE and I5B-IE-JGDH), single-agent olaratumab has consistently been well tolerated, with no dose-limiting toxicities (DLTs) observed up to a dose of 20 mg/kg administered every 2 weeks and up to a dose of 15 mg/kg administered on Days 1 and 8 of a 21-day cycle. When used in combination with liposomal doxorubicin in Study I5B-IE-JGDA (olaratumab dose of 20 mg/kg every 2 weeks), and with paclitaxel plus carboplatin in

Study I5B-IE-JGDB (olaratumab dose of 15 mg/kg Days 1 and 8 every 3 weeks), a higher rate of toxicities such as neutropenia and infections was observed versus the comparator agents. As of 30 June ~~2015~~2016, ~~691 patients have been enrolled into the olaratumab clinical program and 497~~ 790 patients have received olaratumab through Phase 1, Phase 2, and Phase 3 studies . In Study JGDG, although there was a higher incidence of some known doxorubicin toxicities such as mucositis, nausea/vomiting, and diarrhea, these were monitorable, predominantly Grade ≤ 2, and did not lead to a higher incidence of treatment discontinuation. 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.

Gemcitabine and Docetaxel:

Fixed-dose rate gemcitabine (900 mg/m^2 over 90 minutes [fixed dose rate of 10 mg/m^2/min], Days 1 and 8, plus docetaxel 100 mg/m^2 on ~~d~~ Day ~~eight~~8) yielded high objective response rates among patients with advanced leiomyosarcoma in both the second-line, and first-line setting (Hensley et al. 2008a, 2008b). However, to increase the tolerability of this chemotherapy regimen a docetaxel dose of 75 mg/m^2, which is lower than 100 mg/m^2, has been selected for this study. Some of the toxicity seen in previous clinical experience (fatigue, asthenia, and fluid retention) was more typical of the docetaxel counterpart, suggesting that this docetaxel dose modification could improve the tolerability of this regimen. This is consistent with the 75-mg/m^2 docetaxel dose chosen in recent Phase 3 GeDDiS trial (Seddon et al. 2015b). Therefore, this Phase 1b/2 trial investigates the efficacy and safety of olaratumab in combination with gemcitabine (900 mg/m^2 over 90 minutes [fixed-dose rate of 10 mg/m^2/min]) and docetaxel (75 mg/m^2) for the treatment of locally advanced or metastatic STS that is not amenable to treatment with surgical resection or radiotherapy with curative intent.

5.5.3 Rationale for Amendment (c)

As doxorubicin in combination with olaratumab becomes more common in clinical practice for advanced or metastatic STS, additional evaluation in olaratumab-pretreated patients is warranted in order to understand the effect of olaratumab as continuation therapy with regimens such as gemcitabine/docetaxel that are customarily administered after maximal doxorubicin dosing. Additionally, the concept of continuing a biologic treatment with a change in chemotherapy backbone is supported by evidence of on-going treatment effect of trastuzumab and bevacizumab in multiple lines of therapy in HER2 positive breast cancer and metastatic colon cancer, respectively. Furthermore, resistance to antibody therapy in cancer is via separate mechanisms than chemotherapy resistance, supporting the theory that continued benefit from olaratumab is possible after progressive disease on other chemotherapy regimens. Finally, due to potential effect on PDGFRα expressing stromal cells, continued olaratumab exposure may lead to favorable changes in the tumor microenvironment irrespective of change in chemotherapy regimen. The evaluation of olaratumab in combination with gemcitabine and docetaxel in olaratumab pre-treated patients will be a secondary objective. Ninety patients will be added as this is deemed to be an adequate number to observe a signal for strategic planning of future studies. The protocol amendment also adds an interim efficacy analysis of all study outcomes to allow for timely Phase 3 development strategies.

6.1 Primary Objective

Phase 1b
The primary objective of the Phase 1b part is to determine a recommended Phase 2 dose of olaratumab that may be safely administered in combination with gemcitabine and docetaxel to patients with locally advanced or metastatic STS.

Phase 2
The primary objective of the Phase 2 part is to compare the OS in olaratumab-naive patients with locally advanced or metastatic STS treated with olaratumab plus gemcitabine and docetaxel versus placebo plus gemcitabine and docetaxel.

6.2 Secondary Objectives

Phase 2
A secondary objective of the Phase 2 part is to compare OS in olaratumab-pretreated patients with locally advanced or metastatic STS treated with olaratumab plus gemcitabine and docetaxel versus placebo plus gemcitabine and docetaxel.

The secondary objectives of the Phase 2 part are to compare olaratumab plus gemcitabine and docetaxel versus placebo plus gemcitabine and docetaxel in both olaratumab-naïve and olaratumab pre-treated groups, for the following:

7. Study Population

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

7.1 Inclusion Criteria

[6] The patient may have no more than 2 prior lines of systemic therapies (neoadjuvant and adjuvant therapies will not be considered as a prior line of therapy) for locally advanced or metastatic disease and is suitable to receive gemcitabine and docetaxel therapy. All previous anticancer treatments must have completed ≥ 3 weeks (21 days) prior to first dose of study drug.

- In the Phase 2 part, prior olaratumab/doxorubicin combination therapy in 1 prior treatment line is allowed.
    - Prior olaratumab therapy must have been received with doxorubicin as indicated on the olaratumab label.
    - Prior olaratumab therapy must have included at least 2 full cycles of olaratumab/doxorubicin (that is, a minimum of 4 doses of olaratumab).

- Patients, who completed at least 2 cycles of combination olaratumab/doxorubicin therapy then discontinued doxorubicin due to toxicity or maximum dosing and proceeded to olaratumab monotherapy, are eligible.
- The most recent dose of olaratumab must have been received within 180 days of randomization in this study.

[9] The patient has adequate hematologic, organ, and coagulation function within 2 weeks (14 days) prior to enrollment (Phase 1b) or randomization (Phase 2):

- The patient has an adequate coagulation function as defined by International Normalized Ratio (INR) ≤1.5 × ULN or prothrombin time (PT) ≤1.5 × ULN, and partial thromboplastin time (PTT or aPTT) ≤1.5 × ULN ~~(unless receiving anticoagulation therapy). Patients receiving oral anticoagulants are recommended to switch to low molecular weight heparin and have achieved stable coagulation status prior to first dose of protocol therapy.~~ if not on anticoagulant 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).

7.2 Exclusion Criteria

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

[15] The patient has received prior treatment with gemcitabine or docetaxel~~, and/or olaratumab.~~

[16] The patient has history of another primary malignancy, with the exception of

- ~~a) c~~Curatively treated non-melanomatous skin cancer~~, b)~~ or
- C~~e~~uratively treated cervical carcinoma in situ~~,~~ or
- ~~c)n~~Non-metastatic prostate cancer, treated only with observation or
- ~~d) o~~Other primary nonhematologic malignancies or solid tumors treated with curative intent, no known active disease, and no treatment administered during the last 3 years prior to enrollment (Phase 1 b) or randomization (Phase 2).

[23] The patient has a history of Grade 3 or 4 infusion-related reaction (IRR) to olaratumab or discontinued olaratumab due to other significant toxicity.

8.1 Summary of Study Design

Study I5B-MC-JGDL is a multicenter Phase 1b/2 study of olaratumab in combination with gemcitabine and docetaxel in patients with locally advanced or metastatic STS, not amenable to

treatment with surgical resection or radiotherapy with curative intent. The first part (Phase 1b) of the study will consist of an open-label, single-arm, dose-escalation assessment of the safety and tolerability of olaratumab administered at 15 mg/kg (Days 1 and 8) or 20 mg/kg (Days 1 and 8) with gemcitabine (900 mg/m^2 [fixed dose rate: 10 mg/m^2/minute], Days 1 and 8) and docetaxel (75 mg/ m^2, Day 8), on a 21-day cycle (Figure JGDL.1). After the dose of olaratumab in combination with gemcitabine and docetaxel has been determined from the analysis of the Phase 1b part, the Phase 2, randomized, double-blinded, placebo-controlled part of the study will open to enrollment. Patients will be randomized in a 1:1 ratio in a double-blinded manner to Arm A (olaratumab plus gemcitabine and docetaxel) or Arm B (placebo plus gemcitabine and docetaxel). Figure JGDL.1 illustrates the study design.

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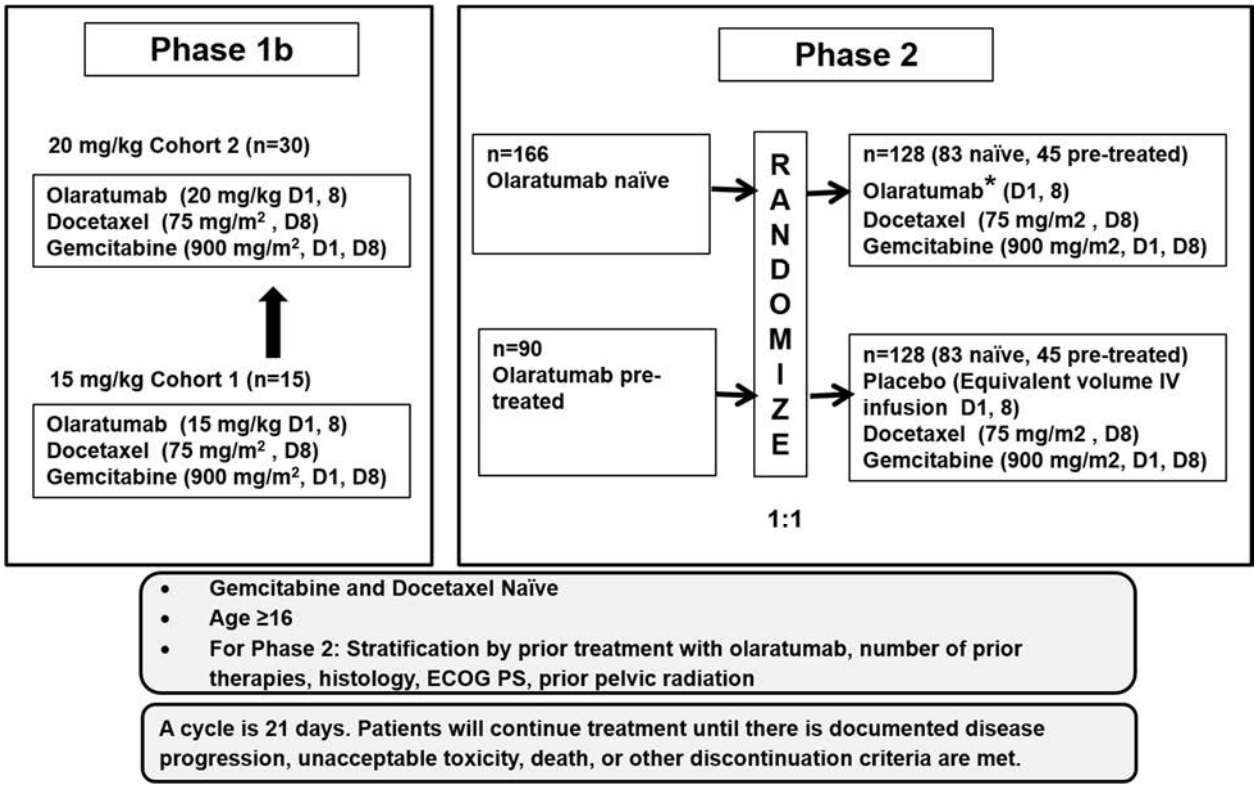

Abbreviations: D = Day 1; IV = intravenous; n= number of patients.
* Based on the outcome of the Phase 1b part, the dose selected for the Phase 2 part of JGDL will be either 15 mg/kg or 20 mg/kg. Depending on the safety and pharmacokinetic profile of these dose levels, it is possible that an intermediate dosing regimen of 2 loading doses of 20 mg/kg during Cycle 1 followed by 15 mg/kg in every subsequent cycle could be utilized in Phase 2, as is being studied in the Phase 3 Study JGDJ.

Figure JGDL.1. Illustration of study design.

8.1.1 Phase 1b Dose Escalation

The Phase 1b part is a single-arm dose escalation to determine the recommended dose of olaratumab for the Phase 2 part that may be safely administered in combination with gemcitabine (900 mg/m^2) and docetaxel (75 mg/m^2) in patients with locally advanced or metastatic STS. This dose escalation has a starting olaratumab dose of 15 mg/kg and the highest olaratumab dose of 20 mg/kg. No intrapatient dose escalation is permitted. Patients in any cohort who do not complete Cycle 1 treatment for reasons other than a DLT will be replaced.

8.1.2 Phase 2

After the dose of olaratumab in combination with gemcitabine and docetaxel has been determined from the Phase 1b part, the Phase 2 randomized, double-blinded part of the study will open to enrollment. In the Phase 2 part, approximately ~~166~~ 256 patients will be randomized 1:1 to receive either olaratumab plus gemcitabine and docetaxel (Arm A) or placebo plus gemcitabine and docetaxel (Arm B). Out of the 256 patients, 166 patients will be olaratumab naïve and 90 patients will be olaratumab pretreated. Randomization will be stratified by prior treatment with olaratumab (yes versus no), number of prior systemic therapies for locally advanced or metastatic disease (0 versus ≥1), histological tumor type (leiomyosarcoma versus non-leiomyosarcoma), ECOG performance status (PS) (0 versus 1), and prior pelvic radiation (yes versus no).

8.1.3 Definitions of Study Periods

- ***Follow-up for survival*** - Patients will be followed every ~~2~~ 3 months (±7 days) for the first ~~2~~ years, then every 6 months (±14 days) until the patient's death or overall study completion.

8.1.4 Baseline and Study Treatment Period Assessments

Phase 2:

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

- Olaratumab ~~(15 or 20 mg/kg IV infusion)~~ on Days 1 and 8 of every 21-day cycle over 60 minutes, followed by a 1-hour observation period for the first 2 cycles. If there is no evidence of an IRR after the Day 1 and Day 8 infusions 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 reinstituted for a minimum of 2 cycles. The reinstituted observation period may be suspended after 2 cycles if the patient shows no further signs or symptoms of an IRR. The dose of olaratumab will be determined from the Phase 1b part of the study. Depending on the safety and PK profile of the Phase 1b dose levels, it is possible that an intermediate dosing regimen of 2 loading doses of 20 mg/kg during Cycle 1 followed by 15 mg/kg in every subsequent cycle could be utilized in Phase 2, as is being studied in the Phase 3 Study JGDJ.

8.1.5 Postdiscontinuation Follow-Up Period Assessments

For patients that discontinue study treatment after objectively measured PD, the following information will be collected every ~~2~~ 3 months (±7 days) for the first ~~2 years~~, then every 6 months (±14 days) until the patient's death, or overall study completion:

8.1.6 Study Completion and End of Trial

Phase 1b

The Phase 1b part of the study will be considered complete following determination of the recommended Phase 2 dose of olaratumab that may be safely administered in combination with gemcitabine plus docetaxel to patients with locally advanced or metastatic STS (Figure JGDL.2).

Phase 2

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following final analysis of the OS endpoint (at least 108 OS events in the olaratumab-naïve cohort) has been performed and evaluated, as determined by Lilly (Figure JGDL.3). Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred.

Abbreviations: iDMC = independent Data Monitoring Committee; OS = overall survival; PK = pharmacokinetic.
The iDMC safety reviews will occur when approximately 60 patients (approximately 30 patients from each arm) have received at least 2 cycles of treatment or discontinued all study treatment due to any reasons prior to Day 8 in Cycle 2. An interim PK analysis will accompany the iDMC safety review. Subsequent iDMC meetings will occur approximately every 6 months thereafter until approximately 1 year after completing enrollment.

Figure JGDL.3. Phase 2: Study period and continued access diagram.

8.1.8 Committees

Independent Data Monitoring Committee (iDMC)

Phase 2:

Additionally, the iDMC will perform the interim efficacy analysis according to specifications in iDMC charter and study statistical analysis plan.

8.1.9 Study Duration

From first patient visit in the Phase 1b part to last patient visit in the Phase 2 part, the estimated study duration is ~~44~~ 47 months.

Table JGDL.1 Treatment Regimens/Dosing Schedule

a Administer olaratumab as an infusion over 60 minutes **(± 5 minutes)**, not to exceed 25 mg/min. Note exceptions when the infusion times of olaratumab are longer than 60 minutes (Section 9.4.1.2.2.1 ~~9.2.1~~). Premedicate all patients with the following medications (or equivalent) intravenously: a histamine H1 antagonist (for example, diphenhydramine) and dexamethasone 30 to 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 (for example, diphenhydramine) intravenously 30 to 60 minutes prior to each dose of olaratumab. See also Section 9.2.1 for more details. 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 9.4.1.2.2.1. All premedication administered must be adequately documented in the eCRF.

Treatment Regimens/Dosing Schedule (concluded)

d Administer docetaxel as an infusion over 60 minutes (± 5 minutes) after gemcitabine. Premedication for docetaxel may be administered according to institutional guidelines and/or clinical practice. All premedication administered must be adequately documented in the eCRF. Docetaxel premedication~~, if needed,~~ must not be administered before the end of olaratumab/placebo infusion or before completion of the observation period (if applicable). Exception is given to dexamethasone premedication that is started 1 day prior to docetaxel per package insert.

9.2.1 Olaratumab/Placebo

CAUTION: Infusion-related reactions may occur during or following olaratumab/placebo administration (see Section 9.4.1.2.2.1 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 (for example, 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 reinstituted for a minimum of 2 cycles. The reinstituted

observation period may be suspended after 2 cycles if the patient shows no further signs or symptoms of an IRR. See Section 9.4.1.2.2.1 for management of infusion rate with Grades 1 and 2 IRRs.

9.3 Method of Assignment to Treatment

Phase 2:

The IWRS will assign patients to treatment arms according to a stratified method of randomization (that is, independent randomization within each ~~of 16~~ stratu~~a~~m ~~or cells~~), defined by the following ~~4~~ 5 ~~prognostic~~ factors:

- Prior treatment with olaratumab (yes versus no)
- Number of prior systemic therapies for locally advanced/metastatic disease (0 versus ≥1)

9.4.1.2 Dose Delays, Modifications, and Discontinuations

To begin dosing at each cycle (Day 1), the following criteria must be fulfilled:

- ANC ≥1.5 × 10^3 cells/µL (≥1500 cells/µL; ≥1.5 × 10^9/L), with no G-CSF in the prior 48 hours
- Platelets ≥100 × 10^3 cells/µL (≥100,000 cells/µL; ≥100 × 10^9 cells/L), with no platelet transfusion in the prior 72 hours

Delays:

Treatment may be delayed for up to 14 days to allow a patient sufficient time for recovery from study drug-related toxicity or non-study-drug-related events at the investigator's discretion (for example, an automobile accident).

Dose Modifications:

Any patient who requires a dose reduction for drug-related toxicity will continue to receive the reduced dose for the remainder of the study, except in the situation described in Table JGDL.2, footnote b. For gemcitabine or docetaxel, any patient who has had ~~1~~ 2 dose reductions and who experiences a toxicity that would cause a third~~second~~ dose reduction must be discontinued from study treatment. For olaratumab, 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.

Table JGDL.2. Dosing Algorithm on Days 1 and 8 for Gemcitabine, Docetaxel, Olaratumab, and G-CSF Use Based on Absolute Neutrophil Count and Platelet Count

Treatment Day	Absolute Neutrophil Count (cells/µl)		Platelet Count cells/µl)	Gem Dose (mg/m^2)	Doc Dose (mg/m^2)	Olaratumab/Placebo	G-CSF Use[a]
Day 1 (Olaratumab /Placebo Gem)	≥1500	and	≥100,000	900[b]	Not Applicable	Administer	Not Applicable
Day 8 (Olaratumab /Placebo Gem, Doc)	≥ 1000	and	≥100,000	900[b]	75[b]	Administer	Not required
	500 to <1000		≥75000	675[c]	60[c]	Administer	Administer as outlined in Section 9.1.1.4.
	≥500		<100,000 to 75000	675[c]	60[c~~e~~]	Administer	Not required unless ANC meets criteria
	<500		Any	Omit on Day ~~8~~[e]8[d]	Omit on Day ~~8~~[e]8[d]	Omit on Day 8 (also see Table JGDL.6)	Administer as outlined in Section 9.1.1.4.
	Any		<75000	Omit on Day ~~8~~[e]8[d]	Omit on Day ~~8~~[e]8[d]	Omit on Day 8 (also see Table JGDL.6)	Not required unless ANC meets criteria

Abbreviations: ANC = absolute neutrophil count; Doc = docetaxel; G-CSF = granulocyte colony-stimulating factor; Gem = gemcitabine; µl = microliter.

a Patients with a prior history of pelvic radiation should receive prophylactic G-CSF in all cycles. G-CSF use is recommended per the guidelines outlined in Section 9.1.1.4. Patients with a prior history of pelvic radiation who require chemotherapy dose reduction despite prophylactic G-CSF are not required to have prophylactic G-CSF in subsequent cycles if per investigator assessment such chemotherapy dose reductions adequately address the risk of further myelosuppression.

b If there has been ~~a previous~~ 1 dose reduction for drug-related toxicity, the dose of gemcitabine is 675 mg/m^2 and the dose of docetaxel is 60 mg/m^2. If there have been 2 dose reductions for drug-related toxicity, the dose of gemcitabine is 500 mg/m^2 and the dose of docetaxel is 45 mg/m^2. A Day 8 dose reduction of gemcitabine or docetaxel because of Day 8 blood count parameters does not need to be continued on Day 1 of the subsequent cycle.

c If there has already been 1 dose reduction for drug-related toxicity, the dose of gemcitabine is 500 mg/m^2 and the dose of docetaxel is 45 mg/m^2. A Day 8 dose reduction of gemcitabine or docetaxel because of Day 8 blood count parameters does not need to be continued on Day 1 of the subsequent cycle.

~~c~~d After omission of gemcitabine and docetaxel on Day 8 due to ANC <500 cells/µL and/or platelet count of <75,000 cells/ µL, reduce dose of gemcitabine to the next appropriate dose level per ~~Table~~ Table JGDL.3 ~~JGDL-3 675 mg/m^2 and docetaxel to 60 mg/m^2~~ for subsequent cycles.

Discontinuations:

In the event of permanent discontinuation of olaratumab/placebo therapy due to an olaratumab/placebo-related toxicity, patients may continue on gemcitabine and docetaxel treatment per protocol. If either gemcitabine or docetaxel are permanently discontinued due to toxicity, the patient should discontinue active treatment with the gemcitabine/docetaxel combination if it is unclear which individual agent is the cause of the toxicity. If toxicity is clearly related to 1 agent or the other, for example neuropathy due to docetaxel, only that agent should be discontinued. ~~However,~~ T~~t~~he patient may continue treatment with olaratumab/placebo alone, at the discretion of the investigator, if gemcitabine and/or docetaxel are permanently discontinued. Any changes in treatments being added to or removed from patient care will be recorded on the eCRF.

9.4.1.2.1 Gemcitabine and Docetaxel

9.4.1.2.1.1 Dose Level Reductions

The infusion time of gemcitabine after its dose reduction may be maintained at 90 minutes (±5 min) or ~~70 minutes (±5 min)~~ may be shortened to keep a rate of approximately 10 mg/m^2/min according to discretion of the investigator. The infusion start and stop times must be recorded.

Table JGDL.3. Dose Level Reductions for Gemcitabine and Docetaxel

Study Drug	Starting Dose	Dose Reduction 1	Dose Reduction 2
Gemcitabine	900 mg/m^2	675 mg/m^2	500 mg/m^2
Docetaxel	75 mg/m^2	60 mg/m^2	45 mg/m^2

Table JGDL.4 General Guidelines for Gemcitabine and Docetaxel Dose Modification Due to Other Hematologic Toxicity

Toxicity	Required Dose Modification
Granulocyte nadirs lasting less than 7 days and with no complications	No dose modification needed

First occurrence of febrile neutropenia and/or documented Grade 4 neutropenia persisting ≥ 7 days	Reduce gemcitabine to 675 mg/m^2 and docetaxel to 60 mg/m^2. Prophylactic G-CSF recommended in subsequent cycles. If patient experiences of febrile neutropenia and/or documented Grade 4 neutropenia in a subsequent cycle despite dose reduction and prophylactic G-CSF, a second dose reduction (to gemcitabine 500 mg/m^2 and docetaxel 45 mg/m^2) is allowed. If febrile neutropenia or documented Grade 4 neutropenia occur in further cycles, the patient should be discontinued from the gemcitabine and docetaxel combination.
Grade 3 thrombocytopenia (platelet count 25,000/μL to <50,000/μL) associated with clinically significant bleeding	Reduce gemcitabine to 675 mg/m^2 and docetaxel to 60 mg/m^2 for all subsequent cycles. If the event recurs in a subsequent cycle despite dose reduction, a second dose reduction (to gemcitabine 500 mg/m^2 and docetaxel 45 mg/m^2) is allowed. If Grade 3 thrombocytopenia with clinically significant bleeding occurs in further cycles, the patient should be discontinued from the gemcitabine and docetaxel combination.
Grade 4 thrombocytopenia (platelet count < 25,000/μL)	Reduce gemcitabine to 675 mg/m^2 and docetaxel to 60 mg/m^2 for all subsequent cycles. If the event recurs in a subsequent cycle despite dose reduction, a second dose reduction (to gemcitabine 500 mg/m^2 and docetaxel 45 mg/m^2) is allowed. If Grade 4 thrombocytopenia occurs in further cycles, the patient should be discontinued from the gemcitabine and docetaxel combination.

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

Table JGDL.5 Dosage Reduction Guidelines for Docetaxel and Gemcitabine Due to Hepatic Toxicities

Toxicity	Required Dose Modification
On Day 1, bilirubin > ULN	Delay Day 1 (except for patients with Gilbert's Syndrome, who must have a total bilirubin <3 mg/dL. See Section 9.4.1.2).
On Day 8, if bilirubin is ≤ ULN	Administer docetaxel on Day 8.
On Day 8, if the bilirubin is > ULN	Omit docetaxel on Day 8. For subsequent cycles, omit docetaxel until bilirubin returns to ≤ ULN (except for patients with Gilbert's Syndrome, who must have a total bilirubin <3 mg/dL).

Grade ≥3 elevations in SGOT (AST), SGPT (ALT), or alkaline phosphatase	Reduce gemcitabine to 675 mg/m^2 and docetaxel to 60 mg/m^2 for all subsequent cycles. In subsequent treatments, delay gemcitabine and docetaxel for a maximum of 2 weeks, until recovery to Grade ≤1. If recovery to Grade ≤1 does not occur, discontinue gemcitabine and docetaxel. A second dose reduction (to gemcitabine 500 mg/m^2 and docetaxel 45 mg/m^2) is allowed if Grade ≥3 elevations recur.

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal.
Note: Bilirubin refers to total bilirubin.

For Grade ≥2 nonhematologic organ-related toxicities (excluding alopecia), delay treatment until recovery to Grade ≤1 or pre-therapy baseline. Treatment may be delayed for up to 14 days to allow a patient sufficient time to recover from study drug-related toxicity. If recovery to Grade ≤1 does not occur within this allowed time, discontinue gemcitabine and docetaxel. If the patient continues to experience the same toxicities, a second dose reduction (per Table JGDL.3) is allowed. ~~at the reduced dose, the g~~Gemcitabine and docetaxel treatment should be discontinued if toxicities recur in spite of 2 dose reductions. In general, Grade 3 nonhematologic toxicities (excluding electrolyte toxicities that respond to supplemental treatment) require dose reduction ~~of gemcitabine to 675 mg/m^2 and/or docetaxel to 60 mg/m^2~~. Permanent discontinuation of gemcitabine and docetaxel is indicated for Grade 3 organ-related toxicity that recurs despite ~~prior~~up to 2 dose reductions. Docetaxel should be reduced ~~to 60 mg/m^2~~ for Grade 2 neurologic toxicity and permanently discontinued for Grade 3 neurologic toxicity. Gemcitabine and docetaxel should be permanently discontinued for Grade 4 nonhematologic toxicity unless previously discussed with the Lilly CRP/CRS.

9.4.1.2.2.1 Infusion-Related Reactions

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 intravenously: a histamine H1 antagonist (for example, diphenhydramine hydrochloride), glucocorticoid (for example, dexamethasone), 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. ~~For~~Patients who have experienced a prior Grade 1 or 2 IRR to olaratumab (or placebo), ~~patients~~should be premedicated with the following (or equivalent) medications: a histamine H1 antagonist (for example, diphenhydramine) intravenously and glucocorticoid (for example, dexamethasone) intravenously, acetaminophen, and any other medications as appropriate for prophylaxis of IRR, approximately 30 to 60 minutes prior to all subsequent olaratumab/placebo infusions. In addition, the 1 hour post infusion observation period should be reinstated as per Section 9.2.1. If subsequent infusions are then tolerated with the use of premedications as above and a 50% decrease in infusion rate, the infusion rate may be increased to a rate deemed appropriate by the investigator, as long as it does not exceed 25 mg/min. For olaratumab-

pretreated patients who experienced a Grade 1 or 2 IRR during their prior treatment regimen (that is, prior to randomization in this study), the infusion rate that was last tolerated should be the infusion rate for both doses of olaratumab in Cycle 1. If tolerated, in subsequent cycles, the infusion rate may be increased to a rate deemed appropriate by the investigator, as long as it does not exceed 25 mg/min.

Table JGDL.6 General Guidelines for Olaratumab/Placebo Dose Modification Due to Hematologic Toxicity Deemed Related to Olaratumab

Toxicity	Required Dose Modification
Neutropenia	
ANC Grade 1-3	No dose modification required
ANC <500 cells/μL (Grade ≥4)	No treatment administered; treatment cycle delayed
At retreatment:	
If ≥Grade 3 neutropenic fever/infection has occurred	Withhold dose until ANC is ≥ 1000 cells/μL; for ~~the~~ a 15-mg/kg dose level ~~cohort~~, reduce dose to 12 mg/kg; for ~~the~~ a 20-mg/kg ~~cohort~~ dose level, reduce dose to 15 mg/kg.
If Grade 4 neutropenia lasting >1 week has occurred	Withhold dose until ANC is ≥ 1000 cells/μL; for ~~the~~ a 15-mg/kg ~~cohort~~ dose level, reduce dose to 12 mg/kg; for ~~the~~a 20-mg/kg ~~cohort~~ dose level, reduce dose to 15 mg/kg.
Grade 4 ANC without fever/infection lasting ≤ 1 week	Administer the next olaratumab/placebo at full dose at investigator's discretion with recommended use of prophylactic G-CSFs
Second incidence of either: 1) ≥Grade 3 neutropenic fever/infection 2) Grade 4 neutropenia lasting > 1 week	For ~~the~~ a 15-mg/kg ~~cohort~~ dose level, discontinue olaratumab/placebo~~, gemcitabine, and docetaxel~~; for the 20-mg/kg ~~cohort~~ dose level, a second dose level reduction to 10 mg/kg. Modify/discontinue gemcitabine and docetaxel as per Table JGDL.4.

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

9.4.1.2.2.3 Nonhematologic Toxicity

General guidelines for dose modification for other nonhematologic toxicities related to olaratumab/placebo are shown in Table JGDL.7. ~~If more than 2 toxicity-related olaratumab/placebo dose reductions are required, all study treatment will be permanently discontinued.~~

Table JGDL.7 General Guidelines for Dose Modification Due to Nonhematologic Toxicities Deemed Related to Olaratumab/Placebo

Reaction Grade	Required Dose Modification
Grade 1	No dose modification is required.

Reaction Grade	Required Dose Modification
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 organ toxicity is ≤ Grade 1 or has returned to pretreatment baseline; then treatment may resume at a reduced dose of 12 mg/kg for the 15-mg/kg ~~cohort (Phase 1b)~~ dose level and reduced dose of 15-mg/kg for the 20-mg/kg ~~cohort~~ dose level. If toxicity recurs after therapy resumes, a second dose reduction (second dose reduction of 10 mg/kg for the 15 mg/kg ~~cohort~~ dose level and12 mg/kg for the 20-mg/kg dose level ~~cohort)~~) is permitted.
Grade 4	The dose must be withheld until dose toxicity is ≤ Grade 1 or has returned to baseline. Permanent discontinuation should be considered for any patient experiencing Grade 4 nonhematologic 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 for the 15-mg/kg dose level ~~cohort~~; dose reduced to 15 mg/kg for the 20-mg/kg ~~cohort~~ dose level. If Grade 4 toxicity recurs after therapy resumes, all study treatment will be discontinued.

9.5 Blinding

Phase 2:

This is the double-blinded part of the study.

During enrollment and prior to the interim efficacy analysis~~To preserve the blinding of the study~~, only 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, 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 personnel until the study has been unblinded.

Upon final analyses of the ~~overall~~ study ~~completion (see Section 8.1.6)~~, investigators may unblind patients to study treatment assignment.

10.1.2 Radiographic Assessments during the Study Period Postdiscontinuation Follow Up

For those patients who discontinue study treatment without objectively measured PD, the investigative sites will continue to monitor patients and periodically evaluate tumor response every 6 weeks (±7 days) as calculated from enrollment (Phase 1b) or randomization (Phase 2) by the same method used at baseline and throughout the study until the patient has objective disease progression, or until the final analysis of OS. After the patient has objective disease progression, radiologic tests are no longer required and the patient ~~will~~ should be followed up approximately every ~~2~~ 3 months (±7 days) for the first ~~2~~ years, then every 6 months (±14 days) until the patient's death or overall study completion.

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. ~~For those patients who discontinued for reasons other than PD, a full due diligence will be taken to collect PRO measures during long-term follow-up, every 6 weeks (±7 days) until PD.~~

Table JGDL.10 provides the Fridericia's ~~Bazett's~~QT ~~heart rate~~ correction formula.

Table JGDL.10 Fridericia's ~~Bazett's~~ QT ~~Heart Rate~~Correction Formula

Formula	Fridericia ~~Bazett~~ QTcF = QT ~~(HR/60)$^{1/2}$ = QT~~/ (RR)$^{1/2\ 1/3}$
~~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 = ECG interval measured from the onset of the QRS complex to the offset of the T wave; ~~QTc = corrected QT interval~~; QTcF = QT interval corrected for heart rate using Fridericia's formula; ~~HR = heart rate;~~ RR = time between corresponding points on 2 consecutive R waves on ECG. ~~RR = duration of ventricular cardiac cycle; TdP = torsade de pointes (a polymorphic ventricular tachycardia).~~

12.1 Determination of Sample Size

Phase 1b

The primary objective of the Phase 1b part is to determine a recommended Phase 2 dose of olaratumab that may be safely administered in combination with gemcitabine (900 mg/m^2) and docetaxel (75 mg/ m^2) to patients with locally advanced or metastatic STS. Section 8.1.1 outlines the study design for the Phase 1b portion. Approximately, a total of 45 patients will ensure that at least 15 patients will be treated at the 15-mg/kg and 30 patients at the 20-mg/kg cohort (see also Section 8.1.1.).

Phase 2

The primary objective of the Phase 2 part is to compare olaratumab plus gemcitabine and docetaxel (experimental arm) versus placebo plus gemcitabine/docetaxel (control arm) in terms of OS, in patients with locally advanced or metastatic STS, who have not previously been treated with olaratumab (the "olaratumab-naïve" cohort).

The Phase 2 part of the study will screen approximately 200 olaratumab-naïve patients to randomize 166 olaratumab-naïve patients in 1:1 randomization (83 patients in the experimental arm and 83 patients in the control arm). The primary ITT sample size of 166 was selected assuming the final analysis of OS will occur when at least 108 OS events in randomized olaratumab-naïve patients have been observed (35% censoring).

The final total of 108 OS events (deaths) in olaratumab-naïve patients provides 80% statistical power for a two-sided log-rank test at a 0.20 significance level (assuming the true OS HR is 0.665). An OS HR of 0.665 corresponds approximately to an increased median survival from 15 months (estimated from published clinical data in various types of patients with advanced or metastatic STS) in placebo plus gemcitabine and docetaxel to 22.5 months for olaratumab plus gemcitabine and docetaxel.

A key secondary objective of the study will be to compare OS between the experimental arm and the control arm in patients with locally advanced or metastatic STS, who have previously been treated with olaratumab (the "olaratumab-pretreated" cohort). The Phase 2 part of the study will screen approximately 114 olaratumab-pretreated patients to randomize 90 olaratumab-pretreated patients in 1:1 randomization.

The sample size of 90 patients in the secondary cohort of "olaratumab-pretreated" patients was selected based on both statistical and qualitative considerations. See Section 12.2.14 for further discussion of the rationale.

There ~~is no~~ will be an interim efficacy analysis planned for the Phase 2 part of the study. All available data on patient characteristics, efficacy, and safety outcomes will be included for consideration as part of the interim efficacy analysis. The primary efficacy hypothesis will be tested at the interim efficacy analysis using a nominal alpha level of 0.00001. The final analysis of the primary efficacy hypothesis will therefore be adjusted and tested at a nominal alpha level of 0.19999.

See Section 12.2.14 and the study's Statistical Analysis Plan (a separate document) for further details regarding the interim efficacy analysis.

12.2.1 General Considerations

Unless specifically described otherwise, all baseline, efficacy, safety, and health outcomes analyses will be performed separately for the olaratumab-naïve and olaratumab-pretreated cohorts.

12.2.2 Analysis Populations

Phase 2

The **Intent-to-Treat (ITT) population:** ~~will~~ includes all randomized patients. In ~~The~~ ITT ~~analysis of efficacy data will consider~~ population, ~~allocation of~~ patients will be allocated 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.~~

12.2.7 Primary Outcome and Methodology

Phase 2

The primary efficacy outcome for the Phase 2 part of the study is OS in the olaratumab-naïve cohort of the ITT population. The final analysis of OS will be based on the stratified log-rank test, stratified by 3 of the 4 randomization factors: number of prior systemic therapies for locally advanced or metastatic disease (0 versus ≥1), histological tumor type (leiomyosarcoma versus non-leiomyosarcoma), and ECOG PS (0 versus 1).

Overall survival curves, the median with 95% CI and survival rates at various time points for each treatment group will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). The HR will be estimated using a stratified Cox regression model (Cox 1972), stratified the same as the log-rank test described above. ~~by the 3 randomization strata (number of prior systemic therapies for advanced or metastatic disease [0 versus ≥1], histological tumor type [leiomyosarcoma versus non-leiomyosarcoma], and ECOG PS [0 versus 1]). All ITT population will be included in the analysis of this endpoint.~~

12.2.8.2 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. In the event that efficacy is observed to be very similar between the olaratumab-naïve and olaratumab-pretreated cohorts, it may be reasonable to conclude a uniform efficacy across cohorts; in that case, additional efficacy analyses may be performed pooling these 2 populations, in order to obtain pooled estimates of efficacy parameters.

12.2.11 Analyses of Patient-Reported Outcomes (PROs)

Data will be separately summarized descriptively. Analyses will be performed separately by cohort (olaratumab naïve and olaratumab- pretreated). 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-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 post-baseline (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.

12.2.12 Safety Analyses

All safety summaries and analyses will be based upon the Safety Population as defined in Section 12.2.2. Analyses will be performed for olaratumab-naïve and olaratumab-pretreated cohorts separately as well as pooled between these cohorts.

12.2.14 Interim Analysis

There will be ~~a~~ safety interim ~~analysis~~ reviews for both Phase 1b and Phase 2 parts.

Phase 2

~~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 60 patients (approximately 30 patients from each arm) have received at least 2 cycles of treatment or discontinued all study treatment due to any reasons prior to Day 8 in Cycle 2. ~~An interim PK analyses will accompany the iDMC safety review and the PK analyses will be performed by a Lilly PK scientist independent from the study team.~~ These data will be provided to the iDMC upon request. Subsequent iDMC meetings will occur approximately every 6 months ~~thereafter~~ until approximately 1 year after completing enrollment. 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.

As described in Section 12.1, an interim efficacy analysis is also planned for the Phase 2 part of the study. The iDMC will be responsible for initial conduct of the interim efficacy analysis according to the specifications of the iDMC charter and statistical analysis plan. If there is an evidence of interim efficacy to warrant a sponsor internal review of the data, results of this interim efficacy analysis may provide information to help inform the initiation of new studies, but will not be used to modify the design and conduct of this current trial.

The interim efficacy analysis will occur after observing approximately 40 OS events among the olaratumab-pretreated cohort of the ITT population. Due to the larger size of the olaratumab-naïve cohort, it is expected that there will be at least another 40 OS events in the olaratumab-naïve cohort at the time of this analysis. The decision to perform interim efficacy analyses after 40 OS events in each cohort was based on both statistical and qualitative considerations. An observation of a very strong efficacy in one of these cohorts, based on 40 events, should be sufficient to consider further development for that cohort. For example, an observed OS HR<0.60 would imply at least an 80% (Bayesian noninformative) probability that the true HR is less than 0.80. The evidence will be stronger if both cohorts show similar efficacy, allowing for pooling of the cohorts. With 80 pooled events, an observed pooled OS HR<0.67 would imply at least a 79% probability that the true pooled HR is less than 0.80. Other efficacy and safety outcomes will be evaluated, so these scenarios for the interim OS HR are included here merely as a reference, to illustrate the kind of evidence that might lead to the initiation of additional studies. For further details, refer to the study's Statistical Analysis Plan (a separate document).

A second interim efficacy analysis may optionally be performed depending on the expected timing of the final analysis and the results of the first interim efficacy analysis. If a second

interim efficacy analysis is performed, it will be conducted applying a nominal alpha level of 0.00001 to the primary OS analysis in olaratumab-naïve patients.

~~A limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the interim or final database lock, in order to initiate the final population PK/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.~~

~~Unblinding details are specified in the blinding section of the protocol (Section 9.5). If changes to the unblinding plan occurred after protocol approval, they may be described in either a protocol amendment, the unblinding plan section of the SAP, or in separate unblinding plan document.~~

14. References

Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D, ~~Van Tine BA,~~ Agulnik M, Cooney MM, Livingston MB, Pennock GK, Hameed MR, Shah GD, Qin A, Shahir A, Cronier DM, Ilaria RL, Conti I, Cosaert J, Schwartz GK. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomized phase 2 trial.

~~A randomized phase Ib/II study evaluating the safety and efficacy of olaratumab (IMC-3G3), a human anti-platelet-derived growth factor α (PDGFRα) monoclonal antibody, with or without doxorubicin (Dox), in advanced soft tissue sarcoma (STS). *J Clin Oncol.* 2016;33 388:488-497.suppl; Presented at American Society of Clinical Oncology annual meeting, 2015b. Associated with Abstract 10501).~~

Attachment 1 Protocol JGDL Study Schedule

Treatment Period Schedule (Phase 1b and Phase 2)

		Study Period	Treatment Period		
Procedure Category	**Protocol Sections**	**Relative Day within Cycle** (21 day cycle ≙ – 3 days)	1[a]	8[a]	
Physical Examination	9.4, 10.3.1	Physical Examination	X	X	Physical examination during treatment period includes weight and BSA measurement. Patients should be weighed at D1 and D8 of each cycle and BSA calculated.
	Att. 4	ECOG Performance Status	X		Complete prior to treatment infusion.
	10.3.1	Vital signs	X	X	Vital signs include blood pressure, pulse, respiratory rate, and temperature. Please refer to Table JGDL.1 footnote b for the times when vital signs should be collected.
Lab/ Diagnostic Tests	Att. 2	Hematology	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 and D8 of each cycle. See Attachment 2 for details.
	Att. 2	Coagulation Profile	X		Perform within 3 days prior to D1 of every other cycle or as clinically indicated. See Attachment 2 for details.
	Att. 2	Pregnancy Test	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 6 for specific time points		Whole blood samples collected and processed into serum (olaratumab) or plasma (gemcitabine/docetaxel). If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 (± 3 days) days after onset of the IRR event.
	10.4.3	Immunogenicity Samples	See Attachment 6 for specific time points		Whole blood samples collected and processed into serum. If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 (± 3 days) days after onset of the IRR event.
	10.4.2.1	Pharmacogenetic (DNA) Whole Blood Sample	See Attachment 6 for specific time point.		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.
	10.4.2.3	Plasma sample for biomarkers	See Attachment 6 for time points.		Whole blood samples collected and processed into plasma.
	10.3.2.1	ECG	X		In Phase 1b, twelve-lead ECGs are to be performed as single ECGs within 3 days prior to Day 1 of every cycle, until PD or treatment discontinuation, whichever comes first.
Patient reported outcomes	10.2	PRO Assessments (mBPI-sf, EORTC QLQ C30, EQ-5D-5L)	X		The Patient Reported Outcome (PRO) measures will be collected on Day 1 of every cycle (Phase 2 only).
Efficacy Assessment	10.1.1 Att. 5	Imaging Studies (CT/MRI) Tumor Assessments (according to RECIST v1.1)	X		Imaging studies and tumor assessments are be obtained every 6 weeks (±7 days), irrespective of treatment cycles as calculated from enrollment in Phase 1b or randomization in Phase 2, 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 for details.

Procedure Category	Protocol Sections	Study Period Relative Day within Cycle (21 day cycle ≒ – 3 days)	Treatment Period 1[a]	 8[a]	
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.
Concomitant Therapy	9.6	Concomitant Medications	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.
Premedication	9.1.1.1, 9.1.1	Administer premedication prior to olaratumab or placebo.	X	X	Premedicate all patients with the following (or equivalent) medications intravenously: a histamine H1 antagonist (e.g., diphenhydramine) and dexamethasone 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 (e.g., diphenhydramine) intravenously 30-60 minutes prior to each dose of olaratumab or placebo.
Study Treatment	9.2.1	Administer olaratumab or placebo.	X	X	Administer until progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria are met. No crossover will be permitted in the Phase 2 part.
	9.2.2	Administer gemcitabine.	X	X	Administer until progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria are met.
	9.2.3	Administer docetaxel.		X	Administer until progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria are met.
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.

Post-Treatment Discontinuation Schedule

		Study Period	Post-discontinuation Follow-Up		
			Short-Term Follow-Up	Long-Term Follow-Up	
		Visit	801	802-8XX	
		Duration	30 ± 7 days	See footnote for duration	
Procedure Category	**Protocol Section**	**Procedure**			**Comments**
Physical Examination	9.4, 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, respiratory rate, 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+, obtain urine protein/creatinine ratio on spot urine or a 24-hour urine collection (to assess protein) must be obtained (up to 3 business days is allowed if the weekend).
	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		In Phase 1b only, twelve-lead ECGs are to be performed as single ECGs for all patients at the short–term follow-up.
	10.4.4	PK sample	X		See Attachment 6. 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.
	10.4.3	Immunogenicity sample	X		See Tap WD. 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.
	10.4.2.3	Plasma sample for biomarkers	X		See Attachment 6.
Patient Reported 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. ~~For those patients who discontinued for reasons other than PD, a full due diligence will be taken to collect PRO measures during long-term follow-up every 6 weeks [±7 days] until PD~~.
Efficacy Assessments	10.1.1, Att. 5	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 be obtained every 6 weeks (±7 days), irrespective of treatment cycles as calculated from enrollment in Phase 1b or from randomization for Phase 2, until documented progression.
	8.1.3	Survival Information, All Subsequent Anti-Cancer Treatments, and Associated		X	For patients enrolled in Phase 1 b and randomized in the Phase 2 part that discontinue study treatment after objectively measured PD the following information will be collected every ~~2~~ 3 months (±7 days) for the first year,

Post-Treatment Discontinuation Schedule

		Study Period	Post-discontinuation Follow-Up		
			Short-Term Follow-Up	Long-Term Follow-Up	
		Visit	801	802-8XX	
		Duration	30 ± 7 days	See footnote for duration	
Procedure Category	**Protocol Section**	**Procedure**			**Comments**
		Disease Progression Date			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		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; ECOG = Eastern Cooperative Oncology Group; LCSS = Lung Cancer Symptom Scale; 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 date of this agreement is to be reported on the CRF as the date of Discontinuation from study treatment.

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 followed every 6 weeks (±7 days) until PD.
- Follow-up for survival: Patients will be followed every ~~2~~3 months (±7 days) for the first ~~2~~years, then every 6 months (±14 days) until the patient's death or overall study completion.

Attachment 2. Protocol JGDL Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b]	Clinical Chemistry[a,b]
Hemoglobin	**Serum Concentrations of the following:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT)
Neutrophils	Aspartate aminotransferase (AST)
Lymphocytes	Gammaglutamyl transferase[g]

Monocytes
Eosinophils
Basophils
Platelets

Coagulation Test[a]
Partial thromboplastin time (PTT or aPTT)
Prothrombin time (PT or INR)

Urinalysis[a,c]

Specific gravity
pH
Protein
Glucose
Ketones
Blood

Urine leukocyte esterase

Other[d]
Immunogenicity samples
PK samples

Blood urea nitrogen (BUN)
Creatinine
Uric acid[g]
Calcium
Glucose, random
Albumin
Total protein

Chloride
Thyroid-stimulating hormone[g]
Direct bilirubin
LDH

Pregnancy test[a,e]

Follicle-stimulating hormone (FSH)[a,f]

Exploratory Biomarker Tests[d]

Refer to Section 10.4.2.

Abbreviations: CRP = clinical research physician; D = Day; INR = international normalized ratio; LDH = lactate dehydrogenase; PK = pharmacokinetics; 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 ≥2+ at evaluations, a 24-hour urine collection (to assess protein) must be collected, or alternatively, a urine protein/creatinine ratio on spot urine. Note: UPC 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:

- [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
- [(urine protein) x 0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L.

d Assayed by a Sponsored-designated (central) laboratory. Refer to Attachment 6.

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

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

g Performed locally at screening only, repeat not required but should be obtained if clinically appropriate.

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