Protocol I5B-MC-JGDM(c)

Title: A Phase 1b Trial to Assess the Modulation of Biological Markers in Patients with Potentially Resectable Soft Tissue Sarcoma Treated with Olaratumab Monotherapy Followed by Olaratumab plus Doxorubicin Combination Therapy

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A Phase 1b Trial to Assess the Modulation of Biological Markers in Patients with Potentially Resectable Soft Tissue Sarcoma Treated with Olaratumab Monotherapy Followed by Olaratumab plus Doxorubicin Combination Therapy

Olaratumab (LY3012207)

Study I5B-MC-JGDM is an open-label, single-arm, multicenter, multicountry Phase 1b study to enumerate whole blood circulating tumor cells and to characterize platelet-derived growth factor receptor alpha, platelet-derived growth factor receptor beta and canonical ligands (*PDGF-A, B, C,* and *D*) expression changes pre- and post-olaratumab monotherapy in tumor tissue in patients with potentially resectable soft tissue sarcoma.

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2. Synopsis

This Phase 1b study is an open-label, single-arm, multicenter, multicountry study to enumerate whole blood circulating tumor cells and to characterize platelet-derived growth factor receptor alpha, platelet-derived growth factor receptor beta, and canonical ligands (*PDGF-A, B, C,* and *D*) expression changes pre- and post-olaratumab monotherapy in tumor tissue in patients with potentially resectable 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 that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
$AUC_{(0\text{-}tlast)}$	area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
$AUC_{(0\text{-}\infty)}$	area under the plasma concentration-time curve from time zero to infinity
audit	A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-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).
BE1	biomarker evaluable 1
BE2	biomarker evaluable 2
C1D1	Cycle 1 Day 1
C1D8	Cycle 1 Day 8
C2D1	Cycle 2 Day 1
C2D8	Cycle 2 Day 8
C3D1	Cycle 3 Day 1
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	clearance

CLRM	clinical laboratory results modernization
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
collection database	A computer database where clinical trial data are entered and validated.
complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CR	complete response
CRu	complete response unconfirmed
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
CRS	clinical research scientist
CT	computed tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DCSI	Development Core Safety Information
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic

EMT	epithelial-mesenchymal transition
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least 1 dose of study treatment.
enter	Patients who are entered in the trial are those who have signed the informed consent form directly or through their legally acceptable representatives.
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 study are protected.
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factor
GIST	gastrointestinal stromal tumors
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IG	immunogenicity
IgG1	immunoglobulin G, subclass 1
IHC	immunohistochemistry
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.
interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for datalock.
IRR	infusion-related reaction

investigational product (IP)	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial. Investigational product 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 study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
ITT	intent-to-treat
IV	intravenous(ly)
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
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
monitor	A person responsible for ensuring the investigator site complies with the monitoring plan, applicable local standard operating procedures (if any), and global Medical standard operating procedures. Monitors are trained on the investigational product(s), the protocol, informed consent document, any other written information provided to subjects, relevant standard operating procedures, International Conference on Harmonisation Good Clinical Practice guidelines, and all applicable laws (for example, privacy and data protection) and regulations.
mOS	median overall survival
MRI	magnetic resonance imaging
MUGA	multi-gated acquisition
NCCN	National Comprehensive Cancer Network

NCI	National Cancer Institute
open-label	A study in which there are no restrictions on knowledge of treatment allocation; therefore, the investigator and the study participants are aware of the drug therapy received during the study.
ORR	objective response rate
patient	A subject with a defined disease.
PD	progressive disease
PDGF	platelet-derived growth factor
PDGFRα	platelet-derived growth factor receptor alpha
PDGFRβ	platelet-derived growth factor receptor beta
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PR	partial response
PS	performance status
QTc	corrected QT interval
QTcF	Fridericia's QT corrected interval
RECIST	Response Evaluation Criteria in Solid Tumors
Resectability	Evaluation of the resectability of a tumor is determined by the surgeon in consultation with the multi-disciplinary team, and depends on the tumor stage and the patient's co-morbidity. The primary aim of surgery is to completely excise the tumor with a margin of normal tissue.
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

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 trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	A patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
sponsor	The party who takes responsibility for the initiation, management and/or financing of a clinical study.
STS	soft tissue sarcoma
study completion	This study will be considered complete once Lilly determines that the evaluations of the primary objective and safety are sufficient and complete.
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TPO	third-party organization
ULN	upper limit of normal
V_d	volume of distribution

A Phase 1b Trial to Assess the Modulation of Biological Markers in Patients with Potentially Resectable Soft Tissue Sarcoma Treated with Olaratumab Monotherapy Followed by Olaratumab plus Doxorubicin Combination Therapy

5. Introduction

5.1. Rationale and Justification for the Study

Soft tissue sarcoma (STS) is a heterogeneous group of tumors that arise mainly from embryonic mesoderm, with some neuroectodermal contribution and differentiation to non-epithelial extraskeletal tissue including muscle, fat, and fibrous tissue (D'Angelo et al. 2014). There are approximately 50 tumor subtypes of STS (Sharma et al. 2013) and they can be located anywhere in the body. Soft tissue sarcoma is rare, comprising approximately 1% of adult cancers. The annual incidence of STS in the United Kingdom and United States is 3300 and 10,000, respectively (Jemal et al. 2009; NCIN [WWW]). Soft tissue sarcoma is best treated by multidisciplinary teams specialized in the management of these tumors (Linch et al. 2014). When the disease is localized, it is usually treated with curative intent using surgical resection with or without radiotherapy and/or chemotherapy. Unfortunately, STS recurs frequently as locally inoperable or metastatic disease, at which time systemic therapy plays a prominent role in the multidisciplinary management of this tumor. Single-agent doxorubicin is still considered the standard treatment option for many patients with metastatic STS (NCCN 2011; ESMO 2014; Schoffski et al. 2014) and has also been used in the pre-operative setting (NCCN 2016).

Previously reported data supported the advancement of olaratumab (IMC-3G3, LY3012207) in later phase human trials, including Eli Lilly and Company (Lilly)'s Phase 1b/2 randomized Phase 2 Study I5B-IE-JGDG (JGDG), which evaluated the efficacy and safety of doxorubicin with or without olaratumab in advanced STS. Patients treated with olaratumab and doxorubicin in the Phase 2 portion of this study, compared to those treated with single-agent doxorubicin, achieved a higher median progression-free survival (PFS; 6.6 vs. 4.1 months, respectively [stratified hazard ratio (HR) = 0.672 (95% confidence interval [CI]: 0.442, 1.021); p = 0.0615]), median overall survival (mOS; 26.5 vs. 14.7 months, respectively [stratified HR = 0.463 (95% CI: 0.301, 0.710); p = 0.0003]) and objective response rate (ORR; 18.2% vs. 11.9%, respectively; p = 0.3421), with an acceptable and monitorable safety profile.

The efficacy of olaratumab in this STS patient population provides an important opportunity to more fully characterize the mechanism of action (MOA) of olaratumab.

Olaratumab is a recombinant human immunoglobulin G, subclass 1 (IgG1) antagonist of the platelet-derived growth factor receptor alpha (PDGFRα), which has been demonstrated to play an important role in mesenchymal biology, and in modulating the tumor and stromal microenvironment. Preliminary analysis of tumor specimens from Study JGDG indicated that tumor expression of PDGFRα receptor by immunohistochemistry (IHC) did not predict improvement in mOS. Possible explanations for this finding include the highly variable and often lengthy time periods between tumor sampling and study entry, the analysis of primary

versus metastatic lesions, and incomplete understanding of the level of PDGFRα receptor and ligand expression in tumor and stroma needed for efficacy.

For these reasons, this study will enroll patients with potentially resectable STS, to allow pre- and post-olaratumab dosing tumor sampling of the same primary tumor lesion, while also providing the potential opportunity to examine a resected tumor specimen after combination treatment with olaratumab and doxorubicin.

Platelet-derived growth factor receptor alpha activation leads to the activation of several well-characterized downstream signaling cascades including the Ras/mitogen-activated protein kinase (MAPK) pathway, the phosphatidylinositol 3-kinase pathway, and the phospholipase C-ɣ 1 pathway in sarcomas (Shah et al. 2010). Increased expression of PDGFRα has been described in epithelial malignancies as part of the epithelial-mesenchymal transition (EMT) (Jechlinger et al. 2006). The EMT state is associated with increased invasiveness and metastasis (Thiery et al. 2009). Autocrine signaling via PDGFRα in association with Ras oncogenic mutation is positively correlated with metastasis in a murine breast cancer line (Jechlinger et al. 2006). Non-canonical activation of PDGFRα promotes bone metastasis of prostate cancer cells, and inhibition of PDGFRα in prostate cancer suppresses tumor angiogenesis and growth of skeletal metastases (Doloff et al. 2007; Russell et al. 2009, 2010; Park et al. 2011). Given this growing body of literature, the ability of olaratumab to disrupt sarcoma metastasis will be investigated in Study I5B-MC-JGDM (JGDM).

The predilection for sarcomas to spread hematogenously provide rationale for using a whole blood "liquid biopsy" approach for enumeration and characterization of circulating sarcoma tumor cells pre- and posttreatment with olaratumab to investigate the role of olaratumab in disrupting the metastatic potential of sarcomas. Using serial pre- and posttreatment whole blood samples, the proposed study will investigate the effects of olaratumab (as monotherapy and in combination with doxorubicin) on circulating tumor cell (CTC) counts. The whole blood samples may also be used for exploratory analyses and further molecular characterization.

The sponsor (Lilly), monitor, and investigators will perform this study in compliance with the protocol, good clinical practice (GCP) and International Conference on Harmonisation (ICH) guidelines, and applicable regulatory requirements.

5.2. Objectives

5.2.1. Primary Objectives

The primary objectives of this study are:

- to enumerate CTCs changes pre- and post-olaratumab monotherapy in whole blood in patients with potentially resectable STS.
- to characterize PDGFRα and platelet-derived growth factor receptor beta (PDGFRβ) and canonical ligands (*PDGF-A, B, C*, and *D*) expression changes pre- and post-olaratumab monotherapy in tumor tissue in patients with potentially resectable STS.

5.2.2. Secondary Objectives

The secondary objectives of this study are:

- to evaluate any antitumor activity observed with olaratumab:
    - progression-free survival (PFS) and 3-month PFS
    - ORR (complete response [CR] + partial response [PR])
    - disease control rate (DCR) (CR+ PR + stable disease [SD])
    - rate of resectability.
- to evaluate the safety of olaratumab as assessed by reported AEs, clinical laboratory tests, vital signs, physical examinations, electrocardiograms (ECGs), and echocardiograms (ECHOs) or multi-gated acquisition (MUGA) scans.
- to evaluate the pharmacokinetics (PK) of olaratumab and immunogenicity (IG) parameters of olaratumab.

5.2.3. Exploratory Objectives

The exploratory objectives of this study are:

- to evaluate blood, CTCs, and tumor tissue pre- and post-therapy for biomarkers related to pathways associated with STS, the MOA of olaratumab, cancer-related conditions, and/or immune cells/immune and tumor microenvironment functioning within the disease state and/or cancer-related conditions.
- to assess the relationship between biomarker expression at baseline, and change from baseline, and clinical outcomes.

5.3. General Introduction to Olaratumab

Olaratumab is a recombinant human IgG1-type monoclonal antibody that binds to 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 MAPK (Loizos et al. 2005; Study Report IMC-3G3-01).

Platelet-derived growth factor/PDGFRα signaling has been implicated in the pathogenesis of multiple cancers, including sarcoma, 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. Platelet-derived growth factor receptor alpha can be expressed in both the tumor and stromal microenvironment. Furthermore, studies have shown that PDGF/PDGFRα signaling affects tumor vasculature through paracrine mediation of vascular endothelial growth factor production (Shah et al. 2010).

More information on the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of olaratumab may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to the investigational product (IP) may be found in Section 7 (Development Core Safety Information [DCSI]) 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.

More information about the known and expected benefits and risks of doxorubicin hydrochloride can be found in the approved doxorubicin package insert.

5.4. Rationale for Selection of Dose

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

In 2 Phase 1 dose-escalation trials (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 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. In Study JGDG, an increase in neutropenia and mucositis, but not in neutropenic sepsis or febrile neutropenia, was observed for olaratumab plus doxorubicin compared with single-agent doxorubicin. Overall, these toxicities are consistent with the toxicity profile of the combination agents used, and are considered monitorable and acceptable for the patient populations studied.

Based on an exposure-response analysis of data from Study JGDG, an olaratumab loading dose of 20 mg/kg on Day 1 and Day 8 of Cycle 1 was incorporated into Study I5B-MC-JGDJ (JGDJ), an ongoing randomized Phase 3 trial of doxorubicin plus olaratumab versus doxorubicin plus placebo in patients with advanced or metastatic STS. The goal of this dosing refinement was to decrease the time patients achieved steady state concentrations of olaratumab.

Study JGDM will consist of an initial cycle of olaratumab monotherapy (Cycle 1) administered on Day 1 and Day 8 of a 21-day cycle using a dose of 20 mg/kg. This dose is consistent with the loading dose used in Study JGDJ, and is anticipated to provide olaratumab concentrations optimal for testing olaratumab tumor and CTC biomarker effects during Cycle 1.

Because the patient population for Study JGDM consists of patients who have potentially resectable STS, early tumor reduction is an important therapeutic goal. Therefore, in Cycle 2, patients will receive additional 20 mg/kg doses of olaratumab on Day 1 and Day 8, in combination with 75 mg/m^2 doxorubicin on Day 1 of a 21-day cycle (totaling 2 cycles of olaratumab at a 20 mg/kg dose: 1 as monotherapy and 1 in combination with doxorubicin). This dosing schedule is intended to maximize the number of patients reaching potentially therapeutic

drug concentrations in the first 6 weeks, which is potentially important in this patient population. Pharmacokinetic model simulations indicate that this proposed dosing regimen may result in exposures slightly (approximately 15%) above previously studied steady-state serum levels of olaratumab. However, given the previously acceptable toxicity profile of olaratumab in combination with doxorubicin in Study JGDG, it is not anticipated that this will result in any additional safety risk to the patients enrolled in this study.

From Cycle 3 through Cycle 7, patients will receive olaratumab at a dose of 15 mg/kg on Day 1 and Day 8, in combination with doxorubicin 75 mg/m^2 on Day 1 of a 21-day cycle, the same doses studied in Study JGDG.

6. Investigational Plan

6.1. Study Population

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 enrollment. Individuals who do not meet the criteria for participation in this study within the 28-day screening period (screen failure) may be re-screened. Note that repeating laboratory tests during the 28-day screening period does not constitute re-screening. Screening laboratory tests may not be repeated more than once to meet eligibility during the 28-day screening period.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1.1. Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria during screening prior to first dose of study drug.

[1] Have a histologically confirmed diagnosis of STS for which olaratumab and doxorubicin would be appropriate therapy. Patients with a diagnosis of Grade 1 liposarcoma are eligible if there is histological or radiographic evidence of evolution to more aggressive disease. Patients with Kaposi's sarcoma and gastrointestinal stromal tumors (GIST) will be excluded. Patients must have potentially resectable disease (as assessed by the study investigator) and have a primary tumor lesion deemed amenable to serial biopsy.

[2] Have consented to undergo mandatory serial peripheral whole blood and tumor tissue sampling for pathology review and translational research. Refer to Sections 8.2.3.1 and 8.2.3.2 for details of biopsy and whole blood sample collection.

[3] Have signed an informed consent form (ICF) and authorization for release of health information for research prior to any study-specific procedures being performed.

[4] Are age ≥18 years at time of consent.

[5] Have measurable or nonmeasurable but evaluable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST v1.1, Eisenhauer et al. 2009). 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.

[6] Have a performance status (PS) of 0 to 1 on the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al. 1982). Attachment 6 provides the ECOG PS scale.

[7] Have had <2 prior systemic cytotoxic therapies for potentially resectable disease. All previous anticancer treatments must have been completed ≥3 weeks (21 days) prior to enrollment.

[8] Have had resolution of AEs and of all clinically significant toxic effects of prior locoregional therapy, surgery, radiotherapy, or systemic anticancer therapy to Grade ≤1, by National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

[9] Have adequate hematologic, organ, coagulation, and cardiac function within 2 weeks (14 days) prior to enrollment:

- 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.
- Platelet count ≥100 x 10^9/L.
- Hemoglobin ≥9.0 g/dL. No transfusions are allowed within 2 weeks (14 days) prior to enrollment.
- Creatinine clearance ≥45 mL/min (refer to Attachment 7 for the Cockcroft-Gault formula).
- Proteinuria ≤1000 mg in 24 hours (if routine urinalysis indicates ≥2+ proteinuria).
- Total bilirubin below upper limit of normal (ULN) (except for patients with Gilbert's Syndrome, who must have a total bilirubin <3 mg/dL).
- Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤3.0 × ULN; if the liver has tumor involvement, AST and ALT ≤5.0 × ULN are acceptable.
    - An adequate coagulation function as defined by International Normalized Ratio ≤1.5 x ULN or prothrombin time ≤1.5 x ULN, and partial thromboplastin time or activated partial thromboplastin time ≤1.5 x ULN if not receiving anticoagulation therapy. For patients receiving anticoagulants, exceptions to these coagulation parameters are allowed if they are within the intended or expected range for their therapeutic use. Patients must have no history of active bleeding (defined as within 14 days of first dose of study drug) or pathological condition that carries a high risk of bleeding (for example, tumor involving major vessels or known esophageal varices).

[10] Have left ventricular ejection fraction (LVEF) ≥50% assessed within 28 days prior to enrollment.

[11] Females of child-bearing potential must have a negative serum or urine pregnancy test within 7 days prior to enrollment.

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

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

- spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea that induced the amenorrhea (for example, oral contraceptives, hormones, gonadotropin releasing hormone, antiestrogens, selective estrogen receptor modulators, or chemotherapy)
- spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone level >40 mIU/mL

[12] Females of child-bearing potential must agree to use highly effective contraceptive precautions and men must agree to use effective contraceptive methods (for example, condom with spermicide) during the trial and up to 6 months following the last dose of study drug. A highly effective method of birth control is defined as one that results in a low failure rate (that is, <1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices, a vasectomized partner, or sexual abstinence that is in line with the preferred and usual lifestyle of the subject (periodic abstinence [for example, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception).

[13] Have, in the opinion of the investigator, a life expectancy of at least 3 months.

6.1.2. Exclusion Criteria

Potential study patients may not be included in the study if any of the following apply during screening.

[14] Have a diagnosis of GIST or Kaposi sarcoma.

[15] Have active central nervous system (CNS) or leptomeningeal metastasis (brain metastasis) at the time of enrollment. 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 to rule out brain metastasis.

[16] Have received prior treatment with doxorubicin, epirubicin, idarubicin, and/or other anthracyclines or anthracenediones; has received treatment with olaratumab or has participated in a prior olaratumab trial.

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

[18] Have unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction within 6 months of enrollment.

[19] Have a Bazett's corrected QT interval of >450 msec for males and >470 msec for females on screening ECG utilizing Bazett's correction. For bundle branch block patients, have a QTcF interval of >450 msec for males and >470 ms for females on screening ECG utilizing Fridericia's correction.

[20] Are females who are pregnant or breastfeeding.

[21] Are 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/randomized in this trial, or concurrent enrollment in any other type of medical research judged scientifically or medically incompatible with this trial. Patients participating in surveys or observational studies are eligible to participate in this study.

[22] Have serious pre-existing medical conditions that, in the opinion of the investigator, would exclude the patient as a candidate for this study.

[23] Have a known allergy to any of the treatment components including a history of allergic reactions attributed to compounds of chemical or biological composition similar to olaratumab.

6.2. Summary of Study Design

Study JGDM is an open-label, single-arm, multicenter, multicountry Phase 1b study to enumerate whole blood CTCs and to characterize PDGFRα and PDGFRβ and canonical ligands (*PDGF-A, B, C* and *D*) expression changes pre- and post-olaratumab monotherapy in tumor tissue in patients with potentially resectable STS.

Patients are to be treated with 20 mg/kg of olaratumab on Day 1 and Day 8 of Cycle 1, followed by up to 6 cycles (Cycle 2 – Cycle 7) of combination therapy with olaratumab plus doxorubicin. For Cycle 2, olaratumab is to be dosed at 20 mg/kg on Day 1 and Day 8 and doxorubicin is to be dosed at 75 mg/m^2 on Day 1. For Cycle 3 – Cycle 7, olaratumab is to be dosed at 15 mg/kg on Day 1 and Day 8 and doxorubicin is to be dosed at 75 mg/m^2 on Day 1. Each cycle of treatment is defined as an interval of 21 days. Approximately 35 patients are to be enrolled.

Starting with the first cycle of combination therapy (Cycle 2), the use of dexrazoxane (in a 10:1 ratio vs. doxorubicin dose) to mitigate cardiotoxicity during treatment with doxorubicin is allowed at the investigator's discretion and is recommended for all patients receiving 5 or more cycles of doxorubicin.

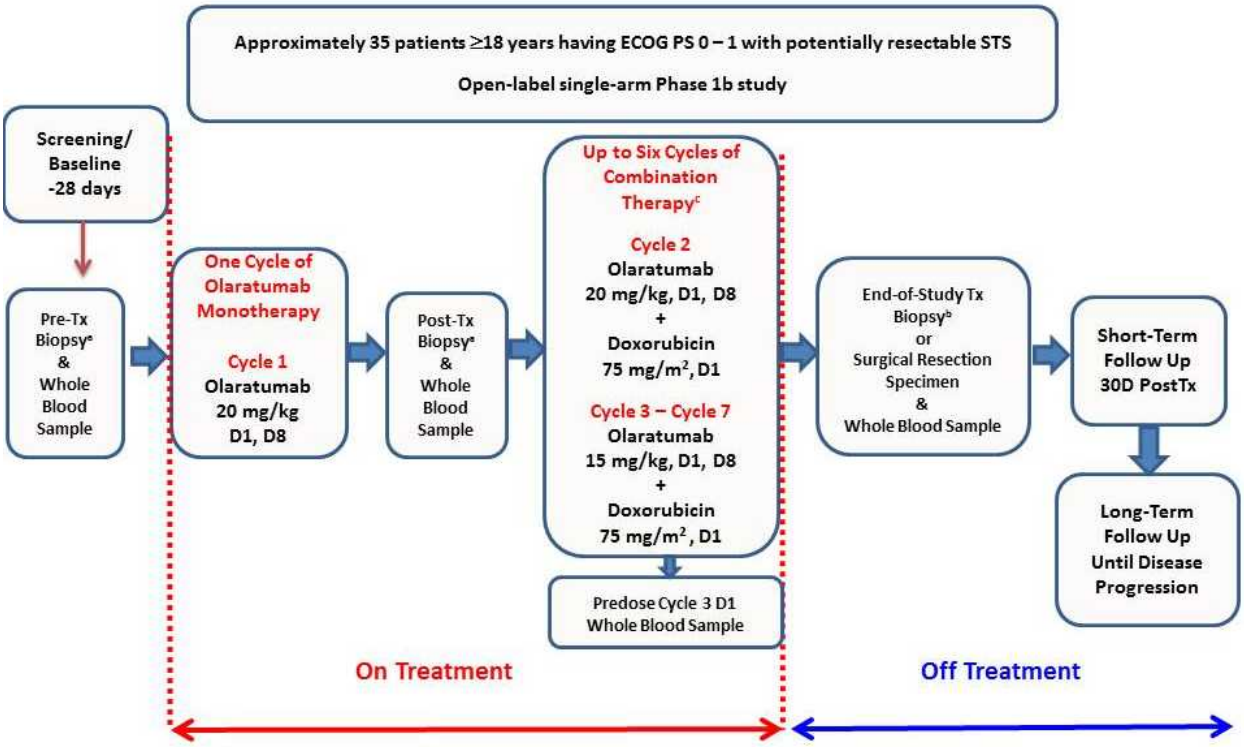
Tissue biopsies are required pre- and posttreatment with olaratumab monotherapy. The pretreatment tissue biopsy is to be performed within the screening period. The posttreatment tissue biopsy is to be performed after completion of the lead-in cycle of olaratumab monotherapy and prior to the initiation of combination therapy in Cycle 2. An optional third tissue biopsy (or tissue from a posttherapy surgical resection specimen) may be performed at the end of the patient's study treatment. If clinically feasible, the tissue biopsies should be taken from the same primary tumor lesion. If the patient has an additional surgical resection, tissue from this procedure is requested. Refer to Section 8.2.3.2 for details on tissue biopsies.

Whole blood samples for CTC analyses are to be collected predose at Cycle 1 Day 1 (C1D1), at Cycle 1 Day 8 (C1D8), at Cycle 2 Day 1 (C2D1), at Cycle 2 Day 8 (C2D8), at Cycle 3 Day 1 (C3D1), and at the end of the patient's study treatment or at the time of surgical resection. Refer to Section 8.2.3.1 for details on blood samples.

After 1 cycle of monotherapy, patients will receive combination therapy for up to 6 cycles or until evidence of progressive disease (PD), unacceptable toxicity, surgical resection, death, or other withdrawal criteria are met. Patients who discontinue study treatment for reasons other than progression or surgical resection will be followed every 6 weeks (±7 days) until PD.

Refer to Attachment 1 for the Study Schedule.

Figure JGDM.1 illustrates the study design.



Abbreviations: C1D1 = Cycle 1 Day 1; C2D1 = Cycle 2 Day 1; C3D1 = Cycle 3 Day 1; CTC = circulating tumor cell; D = day(s); ECOG PS = Eastern Cooperative Oncology Group performance status; STS = soft tissue sarcoma, tx = treatment.

[a] The pre- and post-olaratumab monotherapy tissue biopsies and the whole blood sample collections pre-dose at C1D1, C1D8, C2D1, and C2D8 for CTC analyses are mandatory. The pre-olaratumab monotherapy biopsy is to be collected within the screening period. The post-olaratumab monotherapy biopsy is to be collected after completion of Cycle 1 and prior to initiation of Cycle 2 combination therapy. If clinically feasible, the biopsies should be taken from the same primary tumor lesion.

[b] An optional third tumor tissue biopsy is to be collected at the end of the patient's study treatment or when the patient undergoes a surgical resection through which a posttherapy tissue specimen can be collected. If clinically feasible, the biopsies should be taken from the same primary tumor lesion. Additionally, a whole blood sample for CTC analysis is to be collected at C3D1 and at the end of the patient's study treatment or at the time of surgical resection.

[c] See text in Section 6.2, Summary of Study Design.

Note: Each cycle of treatment is defined as an interval of 21 days.

Figure JGDM.1. Illustration of study design.

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

- **Baseline:** begins when the ICF is signed (study entry) and ends at the first study treatment (or at discontinuation, if no treatment is given).
- **Study Period:** begins at the first study treatment and ends at study completion.
    - **Study Treatment Period:** begins at the first study treatment and ends when the patient and the investigator agree that the patient will no longer continue study

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

- **Olaratumab Monotherapy Treatment Period:** begins at the first administration of olaratumab 20 mg/kg on Day 1 of Cycle 1 and ends on Day 21 of Cycle 1.
- **Combination Olaratumab plus Doxorubicin Therapy Treatment Period:** begins after the post Cycle 1 treatment biopsy is obtained, with the first administration of olaratumab 20 mg/kg and doxorubicin 75 mg/m^2 on Day 1 of Cycle 2, followed by the administration of olaratumab 20 mg/kg on Day 8 of Cycle 2. This treatment period continues from Cycle 3 through Cycle 7 with the administration of olaratumab at a dose of 15 mg/kg on Days 1 and 8 and doxorubicin 75 mg/m^2 on Day 1 of each 21-day cycle. Upon completion of the combination therapy treatment period, the patient will no longer receive study treatment.

- **Post-discontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.
  - **Short-term follow-up**: begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (±7 days). The short-term follow-up visit occurs at or near the end of the short-term follow-up period (±7 days).
    - Follow-up for safety - Patients who undergo surgical resection will be followed for safety for approximately 30 days (±7 days) after surgery.
  - **Long-term follow-up:** begins the day after short-term follow-up is completed.
    - Follow-up for progression - Patients who discontinue study treatment, or have completed 6 cycles of combination therapy, and have not progressed and have not initiated a new systemic treatment for their disease will be assessed for progression by imaging studies every 6 weeks (<7 days) until PD. Patients who have had surgical resection will not be followed for subsequent progression by imaging studies.

6.2.1. Study Completion and End of Trial

The study will be considered complete after all patients have progressed or undergone surgical resection and completed the follow-up period. The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed the 30-day follow-up period.

6.3. Discontinuations

The reason for discontinuation and the date of discontinuation will be collected for all patients. The date of discontinuation from study treatment for any of the reasons specified in Section 6.3.2

is to be reported on the eCRF. Patients who discontinue 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.

6.3.1. Discontinuation of Patients Inadvertently Enrolled

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) and the investigator to determine whether the patient may continue in the study, with or without IP. Inadvertently enrolled patients may be maintained in the study and on IP when the Lilly CRP agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without IP if the Lilly CRP does not agree with the investigator's determination that it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without IP.

6.3.2. Discontinuation of Patients from Study or Study Drug

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

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 IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- investigator/physician decision
    - the investigator/physician decides that the patient should be discontinued from the study or study drug(s)
    - 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 drug(s) occurs prior to introduction of the other agent
- patient decision

  - the patient or the patient's designee (for example, parents or legal guardian) requests to be discontinued from the study or study drug
- sponsor decision
  - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- evidence of PD
- unacceptable toxicity
- pregnancy
- surgical resection
- significant noncompliance with study procedures and/or treatment.

6.3.3. Patients 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. Study site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit, or with whom the site is otherwise unable to follow-up.

6.3.4. Discontinuation of Study Sites

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

6.3.5. Discontinuation of the Study

The study will be discontinued if Lilly, while considering the rights, safety, and well-being of the patient(s), judges discontinuation of the study necessary for any scientific, medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7. Treatment

7.1. Materials and Supplies

7.1.1. Packaging and Labelling

Olaratumab will be provided by Lilly.

Olaratumab 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).

Olaratumab 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 drug product are of pharmacopeial grade.

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

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

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

7.1.2. Olaratumab

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

Please refer to the Pharmacy Manual for information on preparing the olaratumab dosing solution for infusion.

CAUTION: Infusion-related reactions may occur during or following olaratumab administration (see Section 7.2.3.1.1.1 for a definition of Grade 3 and 4 IRRs). During the administration of olaratumab, patients should be in an area with resuscitation equipment and treatments necessary for advanced life support and cardiopulmonary resuscitation, such as bronchodilators, vasopressor agents (for example, epinephrine), oxygen, glucocorticoids, antihistamines, and IV fluids. A 1-hour Observation Period is required after the administration of the first and second cycles of olaratumab. If no evidence of an IRR manifests during the initial 2 cycles of olaratumab, 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.

7.1.3. Doxorubicin

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

Doxorubicin 75 mg/m^2 is administered IV. The dose of doxorubicin should be reconstituted in 100 mL of normal saline. Administer doxorubicin as an IV injection or as an infusion in less than 60 minutes. Decrease the rate of doxorubicin administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occurs.

Doxorubicin must be reconstituted prior to infusion. The reconstituted solution is stable for 7 days at room temperature and under normal room light and 15 days under refrigeration (2ºC-8ºC [36ºF-46ºF]). It should be protected from exposure to sunlight.

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

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

See Section 7.5.1.1 for dexrazoxane administration. Dexrazoxane should be started within 30 minutes prior to the doxorubicin infusion.

7.2. Study Drug Administration

The investigator or designee is responsible for:

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

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.

7.2.1. Treatments Administered

Table JGDM.1 shows the treatment regimens to be administered in this study.

Table JGDM.1. Treatment Regimens

Treatment	Cycle Length (Days)	Study Drug	Dose	Timing	Route
Monotherapy Cycle 1	21	Olaratumab[a]	20 mg/kg	approximately 1 hour infusion D1, D8	IV
		1-hour (±5 minutes) Observation Period[b]			
Combination Therapy Cycle 2	21	Olaratumab[a]	20 mg/kg	approximately 1 hour infusion D1, D8	IV
		1-hour (±5 minutes) Observation Period[b] followed by			
		Doxorubicin[c]	75 mg/m^2	IV injection on D1	IV
Combination Therapy Cycle 3 – Cycle 7	21	Olaratumab[a]	15 mg/kg	approximately 1 hour infusion D1, D8	IV
		Doxorubicin[c]	75 mg/m^2	IV injection on D1	IV

Abbreviations: D = day; eCRF = electronic case report form; IRR = infusion-related reaction; IV = intravenous; PO = orally.

a Premedicate all patients with the following (or equivalent) medications: a histamine H1 antagonist (for example, diphenhydramine) and dexamethasone intravenously 30–60 minutes prior to the olaratumab doses on Days 1 and 8 of Cycle 1. For subsequent cycles, premedicate all patients with a histamine H1 antagonist (for example, diphenhydramine) intravenously 30-60 minutes prior to each dose of olaratumab. Additional premedication may be provided at the investigator's discretion. Premedication **must be** provided in the setting of a prior Grade 1-2 IRR, as detailed in Section 7.2.2 and Section 7.2.3.1.1.1. All premedication administered must be adequately documented in the eCRF.

b A 1-hour (+5 minutes) Observation Period is required after the administration of the initial 2 cycles of olaratumab. During the Observation Period, collect vital signs 3 times: 1) within 15 minutes (+5 minutes) prior to olaratumab infusion, 2) within 1 hour (+5 minutes) after completion of the olaratumab infusion, and 3) within 1 hour (+5 minutes) after completion of the doxorubicin infusion. If no evidence of an IRR manifests during the initial 2 cycles of olaratumab, then no observation period is required for subsequent treatment cycles. In the event an IRR occurs thereafter, then the 1-hour Observation Period should be reinstituted; see Section 7.1.2. Thereafter (Cycles 3+), obtain vital signs 2 times: 1) within 15 minutes (+5 minutes) prior to olaratumab infusion and 2) within 1 hour (+5 minutes) after completion of the doxorubicin infusion.

c Administer doxorubicin according to institutional guidelines and/or clinical practice as an IV injection or as an infusion within 60 minutes. Decrease the rate of doxorubicin administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occurs. Infusion or injection start and end times will need to be recorded. Starting with Cycle 2, dexrazoxane may be administered at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion according to instructions provided in the pharmacy manual for this study, beginning within 30 minutes prior to the doxorubicin infusion for prevention of cardiotoxicity. It is recommended that all patients receiving 5 or more cycles of doxorubicin receive dexrazoxane.

7.2.2. Premedication

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

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

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

Premedication must be provided in the setting of a prior Grade 1 or 2 IRR, as detailed in Section 7.2.3.1.1.1. All premedication administered must be adequately documented in the eCRF.

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

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

Starting with Cycle 2, dexrazoxane may be administered IV at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion according to instructions provided in the pharmacy manual for this study, beginning no later than 30 minutes prior to each doxorubicin infusion for the prevention of cardiotoxicity. It is recommended that all patients receiving 5 or more cycles of doxorubicin receive dexrazoxane.

7.2.3. Dose Modifications

7.2.3.1. Dose Delays, Modifications, and Discontinuations

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

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

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

- Platelets $\geq 100 \times 10^3/\mu L$ ($100,000/\mu L$; $\geq 100 \times 10^9/L$)
- Hemoglobin ≥ 8 g/dL
- Creatinine clearance ≥ 45 mL/min (refer to Attachment 7 for the Cockcroft-Gault formula)
- Proteinuria ≤ 1000 mg in 24 hours (if routine urinalysis indicates $\geq 2+$ proteinuria) (to be performed every other cycle)

- Total bilirubin below ULN
- AST and ALT ≤3.0 x ULN, or ≤5 x ULN if the transaminase elevation is due to liver metastases
- Olaratumab-related AEs that are NCI-CTCAE Version 4.0 Grade <2 or equivalent severity to baseline

Delays:

In general, dose delays of 1 study drug (olaratumab or doxorubicin) due to toxicity guidances outlined in Sections 7.2.3.1.1 and 7.2.3.1.2 will not necessitate delays of the other study drug.

Treatment may be delayed for up to 21 days (1 equivalent cycle) to allow a patient sufficient time for recovery from study drug-related toxicity. If a patient does not recover from the toxicity within 42 days (2 equivalent cycles) from Day 1 of the previous treatment cycle, then the patient must be discontinued from study therapy.

Any procedure or sample collection whose timing is related to olaratumab dosing is to be completed according to when the olaratumab dose was actually administered, not when that dose was expected to occur. Samples whose adjusted timing would fall outside of the treatment cycle duration due to dose delay may be omitted.

Dose Modifications:

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

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

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

Discontinuations:

In general, discontinuation of olaratumab will not necessitate discontinuation of doxorubicin. In the event of discontinuation of olaratumab therapy due to an olaratumab-related toxicity or Grade 3 or 4 IRR, doxorubicin need not be altered, and the planned doxorubicin schedule may be maintained at the discretion of the investigator. Discontinuation of doxorubicin will necessitate discontinuation of olaratumab.

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 olaratumab therapy, including the following:

- IRR (see Section 7.2.3.1.1.1)
- Hematologic toxicity (see Section 7.2.3.1.1.2)
- Nonhematologic toxicity (see Section 7.2.3.1.1.3)

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

- Hematologic toxicity (see Section 7.2.3.1.2.1)
- Cardiovascular toxicity (see Section 7.2.3.1.2.2)
- Hepatic impairment (see Section 7.2.3.1.2.3)
- Nonhematologic toxicity (Section 7.2.3.1.2.4)

7.2.3.1.1. Olaratumab

7.2.3.1.1.1. Infusion-Related Reactions

As with other therapeutic protein products, hypersensitivity reactions may occur during or following olaratumab administration.

For the initial 2 cycles of olaratumab treatment, it is mandatory that patients be closely monitored by the medical staff for signs and symptoms indicative of an IRR from the start of the infusion until at least 1 hour after the end of the infusion (see Table JGDM.1) in an area where emergency medical resuscitation equipment and other agents (such as epinephrine or prednisolone equivalents) are available. If no evidence of an IRR manifests during the initial 2 cycles of olaratumab, then no observation period is required for subsequent treatment cycles. In the event an IRR occurs thereafter, then the 1-hour observation period should be reinstituted (see Section 7.1.2).

Olaratumab IRRs will be defined according to the NCI-CTCAE Version 4.0 definition of IRRs.

Symptoms occurring during or following infusion of investigational therapy may also be defined according to AE terms such as allergic reaction, anaphylaxis, or cytokine release syndrome (NCI-CTCAE Version 4.0 section “Immune system disorders”). In the setting of symptoms occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE term “IRR” and any additional terms (including those not listed here) that best describe the event.

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

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

If a patient experiences an IRR to olaratumab, all attempts should be made to obtain an anti-olaratumab antibody blood sample as close to the onset of the event as possible, at the resolution of the event, and 30 days (±3 days) following the event. In addition, these same samples may be assessed for levels of olaratumab and for pharmacodynamic markers to provide information on the nature of the IRR. The procedure for sample collection and handling is described in a separate procedural manual.

Section 7.1.3 provides information on doxorubicin and IRRs.

7.2.3.1.1.2. Hematologic Toxicity

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

Table JGDM.2. General Guidelines for Olaratumab 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 or higher; reduce dose to 12 mg/kg (15 mg/kg if toxicity occurs during Cycle 1 or Cycle 2).
If Grade 4 neutropenia lasting longer than 1 week has occurred	Withhold dose until ANC is 1000 cells/μL or higher; reduce dose to 12 mg/kg (15 mg/kg if toxicity occurs during Cycle 1 or Cycle 2).
Grade 4 ANC without fever/infection	Retreatment with olaratumab at full dose at investigator's discretion with recommended use of prophylactic G-CSFs.
Second incidence of either: 1) Grade ≥3 neutropenic fever/infection 2) Grade 4 neutropenia lasting longer than 1 week	Second dose reduction to 10 mg/kg.
Thrombocytopenia	
Platelets <75,000 cells/μL (Grade 1)	No treatment administered; treatment delayed until resolved to ≥100,000 cells/μL.
Anemia	
Hemoglobin <9 gm/dL (Grade 2)	No treatment administered; treatment delayed until resolved to ≤Grade 1.

Abbreviations: ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor.

7.2.3.1.1.3. Nonhematologic Toxicity

Specific guidelines for dose adjustments in patients who experience olaratumab IRRs may be found in Section 7.2.3.1.1.1.

Table JGDM.3 provides general guidelines for dose modification for other nonhematologic toxicities related to olaratumab. If more than 2 toxicity-related olaratumab dose reductions are required, treatment with this agent will be permanently discontinued.

Table JGDM.3. General Guidelines for Olaratumab Dose Modification Due to Nonhematologic Toxicity Deemed Related to Olaratumab

Reaction Grade	Required Dose Modification
Grade 1	No dose modification is required.
Grade 2	At the investigator's discretion, the patient may continue to receive olaratumab per protocol, provided that the event does not pose a serious health risk or is easily treated.
Grade 3	For a Grade 3 toxicity not adequately controlled with appropriate supportive care, the dose must be withheld until toxicity is Grade ≤1 or has returned to pretreatment baseline; then treatment may resume at a reduced dose of 12 mg/kg (15 mg/kg if the toxicity occurs during Cycle 1 or Cycle 2). If toxicity recurs after therapy resumes, a second dose reduction (to 10 mg/kg) is permitted.
Grade 4	The dose must be withheld until dose toxicity is ≤Grade 1 or has returned to baseline. Permanent discontinuation should be considered for any patient experiencing Grade 4 nonhematological toxicity assessed as related to olaratumab. However, if resumption of dosing is deemed appropriate by the investigator, treatment may resume only after consultation with the Lilly study physician, with the dose reduced to 10 mg/kg (15 mg/kg if the toxicity occurs during Cycle 1 or Cycle 2). If Grade 4 toxicity recurs after therapy resumes, olaratumab treatment will be discontinued.

7.2.3.1.2. Doxorubicin

7.2.3.1.2.1. Hematologic Toxicity

Doxorubicin will not be administered after the initial dose if the patient's ANC is <1000 cells/μL or if the platelet count is <100,000 cells/μL. When necessary, the next treatment cycle should be delayed until the ANC is ≥1000 cells/μL and the platelet count is ≥100,000 cells/μL and nonhematologic toxicities have resolved. For patients who experience ≥Grade 3 neutropenic fever or infection or Grade 4 neutropenia without fever lasting more than 1 week, doxorubicin should be reduced to 75% of the starting dose (that is, to approximately 60 mg/m^2). If a patient experiences a second incidence of neutropenic fever/infection or has another episode of Grade 4 neutropenia lasting >1 week, then a second dose reduction to 45 mg/m^2 will be necessary. Therapeutic and prophylactic use of pegfilgrastim (Neulasta®) or other G-CSFs will be allowed per current American Society of Clinical Oncology (ASCO; Smith et al. 2006) and National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2014). For patients with Grade 4 ANC without fever/infection lasting less than 1 week, retreatment will be allowed at the investigator's discretion with the full dose of doxorubicin (75 mg/m^2) with recommended use of

G-CSFs per current ASCO guidelines (Smith et al. 2006). See Table JGDM.4 for doxorubicin dose modification for neutropenia.

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

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

Abbreviations: ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor.

7.2.3.1.2.2. Cardiovascular Toxicity

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

Electrocardiogram changes, arrhythmias, tachycardia, and/or chest pain should be managed according to clinical practice based on the specific findings.

Patients will undergo baseline LVEF determination by ECHO or MUGA scan. This evaluation may be repeated at any time during the study if clinically indicated. If there is a decrease in LVEF of ≥10% and below the lower limit of normal, if there is an absolute decrease of 20%, or if the absolute LVEF decreases to or below 40%, then doxorubicin will be discontinued. Doxorubicin should also be discontinued if the patient develops Grade 3 or 4 left ventricular systolic dysfunction (symptomatic congestive heart failure). All such changes should be reported as AEs. If doxorubicin is discontinued for the above changes in LVEF, then olaratumab must be discontinued as well (see Section 7.2.3.1).

The diagnostic method used at baseline for cardiovascular assessments (for example, ECHO or MUGA scans) should be the same method used throughout the study, unless there is clinical or instrumental evidence that further investigations are needed.

7.2.3.1.2.3. Hepatic Impairment

Doxorubicin is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C or total serum bilirubin >5.0 mg/dL). Refer to Section 7.2.3.1 for additional information.

7.2.3.1.2.4. Nonhematologic Toxicity

Permanent discontinuation of doxorubicin should be considered for any patient experiencing Grade 4 nonhematologic toxicity assessed as related to doxorubicin. If the investigator feels re-dosing of doxorubicin is appropriate (except for Grade 4 cardiotoxicities and Grade 4 bilirubin increase which require mandatory discontinuation [see Section 7.2.3.1.2.2 and Section 7.2.3.1.2.3]), treatment may only resume after consultation with the Lilly study physician, with the dose reduced to 60 mg/m² (or less if agreed by the investigator and Lilly physician). If Grade 4 toxicity recurs after therapy resumes, doxorubicin treatment will be permanently discontinued.

For appropriate management of cardiac toxicities and hepatic impairment, refer to Section 7.2.3.1.2.2 and Section 7.2.3.1.2.3.

7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive treatment. After the patient signs the 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. Once the patient is registered through the IWRS, he/she is considered to be enrolled in the study.

7.3.1. Selection and Timing of Doses

A cycle is defined as an interval of 21 days (a cycle may be delayed up to 3 days due to holidays, weekends, bad weather, or other unforeseen circumstances without being counted as a protocol deviation).

The dose of olaratumab to be administered will be determined by measuring the patient's weight in kilograms on Day 1 and Day 8 of each cycle. The dose of doxorubicin to be administered will be determined by calculating the patient's body surface area 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 dose will not need to be recalculated. A ±5% variance in the calculated total dose will be allowed for ease of dose administration.

A patient may continue to receive study treatment until he or she has received a maximum of 6 cycles of olaratumab in combination with doxorubicin, or until he or she meets 1 or more of the specified reasons for discontinuation (as described in Section 6.3.2).

7.4. Blinding

This is an open-label study.

7.5. 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 therapy, 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, or erythropoietin; procedures such as paracentesis, or thoracentesis; or blood products such as blood cells, platelets, or fresh frozen plasma transfusions) must be captured on the eCRF.

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

7.5.1. 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 with the Lilly CRP. Use of any supportive care therapy must be captured on the eCRFs.

7.5.1.1. Dexrazoxane

Starting with the first cycle of combination therapy (that is, Cycle 2), dexrazoxane may be administered IV at the investigator's discretion according to instructions provided in the pharmacy manual for this study, beginning within 30 minutes prior to each doxorubicin infusion for the prevention of cardiotoxicity. It is recommended that all patients receiving 5 or more cycles of doxorubicin receive dexrazoxane. Investigators should consult the dexrazoxane information provided in the pharmacy manual for this study for administration information (including warnings, precautions, contraindications, adverse reactions, and dose modifications).

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

7.5.1.2. Granulocyte-Colony Stimulating Factors and Erythroid Growth Factors

Following the first dose of doxorubicin treatment, the use of G-CSFs such as pegfilgrastim and erythroid stimulating factors (for example, erythropoietin) are permitted, including prophylactic use, during investigational therapy at the discretion of the investigator, according to ASCO guidelines (Smith et al. 2006) and NCCN guidelines (NCCN 2014).

7.5.1.3. Transfusion of Blood Products

Transfusions of red blood cells, platelets, or other blood products are permitted at the investigator's discretion, but may not be used to meet hematologic criteria for inclusion in the study (refer to Section 6.1.1, inclusion criterion #9).

7.5.1.4. Anti-emetic Therapy

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

7.5.2. 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 to symptomatic sites of disease will not be permitted while on study.

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

Doxorubicin is a major substrate of cytochrome P450 (CYP)3A4 and CYP2D6, and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4, CYP2D6, and/or P-gp (for example, verapamil), resulting in increased concentration and clinical effect of doxorubicin. Inducers of CYP3A4 (for example, phenobarbital, phenytoin, St. John's Wort) and P-gp inducers may decrease the concentration of doxorubicin. Avoid concurrent use of doxorubicin with inhibitors and inducers of CYP3A4, CYP2D6, or P-gp. Attachment 9 provides a list of these inhibitors and inducers.

7.6. Treatment Compliance

The study medication will be administered only at the investigational sites by the authorized study site 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.

7.6.1. Evaluable Patients

Evaluable patients are those with adequate biomarker samples who have a baseline (pre-monotherapy) and at least 1 postbaseline measurement. Patients who withdraw from the study before receiving study drug will be replaced and will not be included in the safety or primary objective assessments. Safety analyses will be conducted on all patients who have received at least 1 dose of study drug.

If the patient is noncompliant during olaratumab monotherapy (Cycle 1) and does not undergo the post-olaratumab monotherapy biopsy or the C1D1 pre-dose and C2D1 predose whole blood sample collection due to reasons other than drug-related toxicity, he or she will be considered nonevaluable for the primary objective. These patients may be replaced to ensure that 35

patients complete the pre-treatment tissue biopsy, the C1D1 pre-dose whole blood sample collection, 1 cycle of olaratumab monotherapy, and the post-olaratumab monotherapy biopsy, and the associated C2D1 predose whole blood sample collection.

8. Safety, Pharmacokinetic, Pharmacodynamic, and Efficacy Data Collection

8.1. Safety Evaluations

8.1.1. Safety Data Collection and Review

Investigators are responsible for monitoring the safety of patients who have entered into 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 the patient during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE 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). Section 8.1.2.4 presents a summary of AE and SAE reporting guidelines. Table JGDM.5 shows the database or system used to store AE and SAE data.

8.1.2. 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 occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any clinically significant findings from labs, vital sign measurements, and so on that occur should also be reported to Lilly or its designee as an AE. Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

The investigator, monitor, and sponsor will review the collected data regularly for evidence of AEs. All patients will be assessed routinely for AEs as outlined in the Study Schedule (Attachment 1). The NCI-CTCAE Version 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. All AEs observed will be graded using CTCAE Version 4.0. For AEs without matching terminology within the NCI-CTCAE Version 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. Note that both CTCAE term (actual or coded) and severity grade must be selected

by study site personnel and collected on the case report form (CRF). This collection is in addition to verbatim text used to describe the AE.

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

Cases of pregnancy that occur during maternal or paternal exposures to study should be reported. Data on fetal outcome and breastfeeding should be collected, if feasible, for regulatory reporting and drug safety evaluation.

Upon documentation of pregnancy, the patient must be removed from the study and treatment with study drugs must be stopped immediately.

For all enrolled patients, 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. While the patient is on study, site personnel will record any change in these preexisting condition(s) and the occurrence and nature of any AEs. In addition, all AEs related to protocol procedures will be reported to Lilly or designee.

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.

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

The investigator decides whether he or she interprets the observed AEs as either related to disease, study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terminologies are defined:

- **Related**: a direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Unrelated**: without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures, all "related" and "possibly related" AEs and SAEs will be defined as related to study drug.

8.1.2.1. Serious Adverse Events

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

An SAE is any AE during this study that results in one of the following outcomes:

- death

- initial or prolonged inpatient hospitalization (except for study drug administration)
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- 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 SAEs when, based on 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 events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study drug.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Attachment 5 provides recommendations for reporting SAEs.

When a condition related to study treatment necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

If an investigator becomes aware of SAEs 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 drug, the investigator should report the SAEs to the sponsor and the SAEs 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.

8.1.2.2. Adverse Event and Serious Adverse Event Reporting

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

8.1.2.2.1. Prior to Administration of Study Drugs

Although all AEs after signing the ICF are recorded in the CRF, SAE reporting begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

8.1.2.2.2. On Study Treatment

All AEs and SAEs, regardless of relatedness to study drugs or protocol procedures, occurring while the patient is receiving study drug must be reported to Lilly or its designee. A patient is

considered to be receiving study drug from the time he/she receives the first dose of study drug to when he/she receives the last dose of study drug.

8.1.2.2.3. Follow-Up Visit

All AEs and SAEs, regardless of relatedness to study drugs or protocol procedures, occurring during the follow-up visit (Visit 801) must be reported to Lilly or its designee. The follow-up visit begins the day after the patient and the investigator agree that the patient will no longer continue study treatment. At the end of the follow-up visit, the patient will be required to have specific safety assessments (Attachment 1). The timing of these safety assessments is 30 ± 7 days after the last dose of study drug.

Following the safety assessments, which mark the end of the follow-up visit (Visit 801), the patient will continue into long-term follow-up until disease progression. Any ongoing AE or SAE considered possibly related to study drug should be followed during the long-term follow-up. In this instance, the patient should be followed in subsequent follow-up visits (Visit 802, Visit 8XX) until the event is resolved, or is no longer considered to be drug-related, or becomes stable, or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up.

If it is deemed to be in the best interest of the patient to start a new anticancer treatment prior to the scheduled end of the follow-up visit, the follow-up visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

After the follow-up visit (Visit 801), AEs are not required to be reported unless the investigator feels the AEs were related to either study drug, drug delivery system, or a protocol procedure. If an investigator becomes aware of any SAEs believed to be related to protocol procedures or study drug, the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

8.1.2.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are not listed in the DCSI and that the investigator identifies as related to study drug or procedure. The United States 21 CFR 312.32, the 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 regulatory regulations and the associated detailed guidances.

8.1.2.4. Summary of AE/SAE Reporting Guidelines

Table JGDM.5 summarizes the AE and SAE reporting guidelines.

Table JGDM.5. 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 All AEs SAEs related to protocol procedures	x x x	 x
Study treatment period	All AEs All SAEs	x x	 x
30-day short-term postdiscontinuation follow-up	All AEs All SAEs	x x	 x
Long-term postdiscontinuation follow-up	All SAEs related to protocol procedures or study treatment	x	x
After the patient is no longer participating in the study (that is, no longer receiving study treatment and no longer in long-term postdiscontinuation follow-up)	All SAEs related to protocol procedures or study treatment that the investigator becomes aware of		x

Abbreviations: AE = adverse event; SAE = serious adverse event.

8.1.3. Other Safety Measures

8.1.3.1. Electrocardiograms

For each patient, 12-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. Section 9.2.2 provides additional information on ECG collection and storage.

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

Table JGDM.6 provides Bazett's QT heart rate correction formula. Table JGDM.8.7 provides Fridericia's QT correction formula for patients with bundle branch block.

Table JGDM.6. Bazett's QT Heart Rate Correction Formula

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

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

Table JGDM.8.3 Fridericia's QT Correction Formula

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

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.

8.1.3.2. Echocardiograms/MUGA Scans

An ECHO or MUGA scan is required within 28 days prior to enrollment for all patients. Thereafter, ECHO or MUGA scans, whichever technique was used initially (as described in Section 7.2.3.1.2.2), must be performed at the end of Cycles 5 and 7, and when clinically indicated. For patients with LVEF <50% or other cardiac dysfunction, perform more frequently, if clinically indicated. After Cycle 7 (for patients with resting LVEF ≥50%), an ECHO or MUGA scan should be obtained at the 30-day follow-up visit (refer to the Study Schedule [Attachment 1]).

Patients who stop doxorubicin prior to Cycle 7 will undergo cardiac monitoring assessment at the 30-day follow-up visit (refer to the Study Schedule [Attachment 1]) with whichever technique (ECHO or MUGA scan) was used initially (as described in Section 7.2.3.1.2.2).

8.1.4. Safety Monitoring

The Lilly CRP/clinical research scientist (CRS) will monitor safety data throughout the course of the study, including a safety review conducted after the first 5 patients have completed Cycle 2 of treatment.

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

- trends in safety data
- laboratory analytes
- AEs, including cardiac events such as:
  - myocardial failure or dysfunction
  - myocardial ischemia or infarction
  - arrhythmias
  - cardiovascular insufficiency
- adverse events of special interest (AESIs; as defined in Section 8.1.4.1)
- If a study patient experiences elevated ALT ≥5× ULN and elevated total bilirubin ≥2× ULN, clinical and laboratory monitoring should be initiated by the investigator.

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/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3).

8.1.4.1. Adverse Events of Special Interest

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

AESI for olaratumab

IRRs

AESI for combination of olaratumab and doxorubicin

Cardiac arrhythmias and cardiac dysfunction

Refer to Section 7.2.3 for special treatment considerations for dose delay, modifications, and discontinuations from olaratumab and/or doxorubicin, including AEs of concern or AESIs.

8.1.5. Complaint Handling

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

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP so that the situation can be assessed.

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

The investigator or his/her designee is responsible for handling the following aspects of the 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.

8.2. 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.

Attachment 4 provides details on and timing for the collection of biomarker, PK, and immunogenicity blood samples.

8.2.1. Samples for Study Qualification and Health Monitoring

Blood, urine, and tissue samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health.

Investigators must document their review of each laboratory safety report.

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.

Section 8.2.3.1 specifies blood sample requirements for study qualification.

Section 8.2.3.2 specifies tumor tissue sample requirements for study qualification.

8.2.2. Samples for Drug Concentration Measurements Pharmacokinetics

Pharmacokinetic samples will be collected as specified in the Biomarker, PK, and Immunogenicity Blood Sampling Schedule (Attachment 4).

8.2.2.1. Pharmacokinetic Samples

At the visits and times specified in the Study Schedule (Attachment 1) and in the Biomarker, PK, and Immunogenicity Blood Sampling Schedule (Attachment 4), samples of approximately 3 mL of whole blood will be drawn into tubes to perform olaratumab serum PK measurements. A maximum of 3 samples per drug 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 Lilly. 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 method.

Bioanalytical samples collected to measure IP concentration will be retained for a maximum of 1 year following last patient visit for the study and will be stored at facilities designated by Lilly.

8.2.3. Samples for Biomarkers

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 drug targets, disease process, pathways associated with STS and/or cancer-related conditions, immune cells/immune and tumor microenvironment functioning within the disease state and MOA of olaratumab or doxorubicin.

The primary objectives of this study are to enumerate whole blood CTCs and to characterize PDGFRα, PDGFRβ, and canonical ligands (*PDGF-A, B, C,* and *D*) expression changes pre- and post-olaratumab monotherapy in tumor tissue in patients with potentially resectable STS.

There will be mandatory collection of tumor tissue samples pre- and post-olaratumab monotherapy and an optional collection of tumor tissue at the end of the patient's study treatment, or when the patient undergoes a surgical resection, for study objectives relating to PDGFRα expression and related pathways, and to the biomarkers in the primary objective and clinical outcomes. The study may be used for related research methods or validation of diagnostic tools or assays.

Collection of samples for biomarker research is a mandatory part of this study. Blood and tissue samples will be collected.

Required samples for biomarker research to be collected from all patients in this study are the following:

- blood (see Section 8.2.3.1 and Section 8.2.4)
- tumor tissue (see Section 8.2.3.2)

Sample collection including blood and tumor tissue will occur at specified time points as indicated in the Study Schedule (Attachment 1). These samples are also described in the following sections.

It is possible that biomarker data has already been generated from samples that were collected and analyzed prior to enrolling in this trial. This may include data generated from genetic analyses. If available, this data may be requested from medical records for use in the research described in the following sections.

Samples may be stored for a maximum of 15 years following last patient visit for the study.

8.2.3.1. Blood Samples

Whole blood samples are required for all patients in order to participate in this study for biomarker research:

- newly obtained peripheral whole blood specimens will be collected specifically to enumerate CTCs. These specimens will be collected at C1D1 (predose), C1D8 (predose), C2D1 (predose), C2D8 (predose), C3D1 (predose), and at the end of the patient's study treatment or at the time of surgical resection. Refer to Attachment 4 for details.
- blood (ethylenediaminetetraacetic [EDTA] plasma, serum) samples for nonpharmacogenetic biomarker research will be collected. Refer to Attachment 4 for details.

Newly obtained peripheral whole blood specimens are to be collected specifically to enumerate CTCs. Sequentially collected blood specimens will be used for CTC detection and enumeration. The primary analysis of these samples will be focused on the relationship between pre-olaratumab monotherapy and on-treatment (post-olaratumab monotherapy treatment) CTC counts. These samples may be used for other exploratory analyses and further molecular characterization.

Additional blood (EDTA plasma, serum) samples for nonpharmacogenetic biomarker research will be collected. These samples will be examined for biomarkers related to STS, immune cells/immune and tumor microenvironment functioning within the disease state and/or cancer-related conditions, variable response to olaratumab and/or doxorubicin, and the MOA of olaratumab or doxorubicin. Potential pharmacodynamics and/or circulating markers may include, but are not limited to, PDGF receptors, canonical ligands (*PDGF-A, B, C,* and *D*), and downstream signaling pathways. Biomarker assays may be performed on these samples to evaluate systemic immune modulation and changes in immune cell infiltration, activation, modulation, microenvironment, and changes in stromal and tumor biology in 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 at a facility selected by the sponsor. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the drug development or when the drug is commercially available for a shorter period if local regulations and/or ERBs impose shorter time limits.

8.2.3.2. Tumor Tissue

Collection of the following tumor tissue samples is mandatory for all patients:

- newly obtained biopsy specimens taken from the primary tumor lesion pre- and post-olaratumab monotherapy treatment will be collected. The pretreatment tissue biopsy is to be performed within the screening period. The posttreatment tissue biopsy is to be performed after completion of the lead-in cycle of olaratumab monotherapy and prior to

the initiation of combination therapy (Cycle 2). Refer to Attachment 1 for additional details. If clinically feasible, the biopsies should be taken from the same primary tumor lesion.

Collection of the following tumor tissue samples is optional for all patients:

- biopsy specimen collected at the end of the patient's study treatment. Refer to Attachment 1 for additional details. If clinically feasible, this biopsy should be taken from the same primary tumor lesion.
- tumor tissue from any post-therapy surgical resection may also be collected and provided. While this specimen is optional, it is expected this sample will be sent for analysis.

Sites should examine samples to determine adequacy of tumor tissue using their local laboratory procedures prior to the first dose of olaratumab monotherapy and again prior to the first dose of combination therapy. If additional tumor biopsies are collected as part of clinical care, they should be submitted, along with local pathology reports, for further analysis.

Details for the handling and shipping of the tumor tissue will be provided by Lilly in a separate document. The tissue samples will be obtained using appropriate method. Tumor tissue should be submitted as a newly acquired excisional or core needle (minimum 18 gauge) biopsy in formalin (10% neutral buffered). Cytological or fine-needle aspiration specimens are not acceptable. Due diligence should be used to make sure that tumor sample (not a normal adjacent or a tumor margin sample) is provided. Pathology reports accompanying tissue may also be requested. The reports must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology notes prior to submission.

Collected tumor samples will be used for research on the drug targets, disease process, pathways associated with STS and/or cancer-related conditions, immune cells/immune and tumor microenvironment functioning within the disease state and/or cancer-related conditions, MOA of olaratumab or doxorubicin, and/or research methods or in validating diagnostic tools or assay(s) related to cancer. The primary analysis of these tumor tissue samples will be focused on the assessment of expression level change of PDGFRα, PDGFRβ, and canonical ligands (*PDGF A, B, C,* and *D*) pre- and post-olaratumab monotherapy treatment. The relationship of baseline expression and expression level changes from baseline of these markers will also be evaluated. In addition, as a part of exploratory analysis mutation profiling, gene expression, sequencing and/or IHC may be performed on these tissue samples to evaluate changes in immune cell infiltration, activation, modulation, microenvironment and changes in stromal and tumor biology in response to study treatment. This may include evaluation of biomarkers related to, but not limited to, PD1 ligand and tumor infiltrating lymphocytes on tumor and stroma cells.

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

Samples will be destroyed according to a process consistent with local regulation.

8.2.3.3. Imaging Studies

A pre- and post-olaratumab monotherapy positron emission tomography (PET) scan will be collected for exploratory analyses at times specified in Attachment 1. Positron emission tomography scan analyses measure tumor metabolic activity. Associations between PET scan findings, tissue biomarkers, and CTCs will be investigated in this study.

8.2.4. Samples for Pharmacogenetics

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis (Attachment 1).

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to olaratumab and/or doxorubicin. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

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

Samples will be destroyed according to a process consistent with local regulation.

8.2.5. Samples for Immunogenicity Research

Blood samples for IG testing will be collected to determine antibody production against olaratumab. Refer to Attachment 4 for details. Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of olaratumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of olaratumab.

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.

8.3. Efficacy Evaluations

A secondary objective of the study is to document any antitumor activity. Refer to Attachment 1 for details regarding the timing of specific efficacy measures.

Tumor assessments will be performed for each patient at the times shown in Attachment 1 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. Imaging requirements include computed tomography (CT) scan or magnetic resonance imaging (MRI) of chest, abdomen, and pelvis and other areas, as clinically indicated.

Computed tomography scans, including spiral CT, are the preferred methods of measurement.

The exploratory PET Scan performed pre and post Cycle 1 will not be used to determine efficacy.

The CT portion of a PET-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with IV 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 tumor assessment used at baseline must be used consistently throughout the study. Patients will be evaluated for response according to RECIST v1.1 guidelines (Eisenhauer et al. 2009), as outlined in Attachment 8.

8.4. Procedure/Sampling Compliance

Every attempt will be made to enroll patients who have the ability to understand and comply with instructions. Noncompliant patients may be discontinued from the study.

The collection times of safety assessments, PK samples, and efficacy measurements are given as targets to be achieved within reasonable limits. The scheduled time points may be subject to minor alterations; however, the actual collection time must be correctly recorded on the eCRF.

The scheduled collection times may be modified by the sponsor based on analysis of the safety and PK information obtained during the study. Any major modifications that might affect the conduct of the study, patient safety, and/or data integrity will be detailed in a protocol amendment.

9. Data Management Methods

9.1. 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/or 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 the sponsor, applicable regulatory agencies, and applicable ERBs/ institutional review boards (IRBs) with direct access to the original source documents.

9.2. Data Capture Systems

9.2.1. Case Report Form

An electronic data capture system will be used in this study. 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.

For data handled by a data management third-party organization (TPO), CRF data and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to the Lilly data warehouse, using standard Lilly file transfer processes.

For data handled by the sponsor internally, CRF data and some or all data that are related will be managed by the sponsor and stored electronically in the sponsor's system.

9.2.2. Ancillary Data

Data managed by a central vendor will be stored electronically in the central laboratory's database system. Data will subsequently be transferred from the central vendor to the Lilly clinical laboratory results modernization (CLRM) system.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to the Lilly CLRM system.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) and will then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

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

10. Data Analyses

10.1. General Considerations

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

The analyses for this study will mostly be descriptive. For continuous variables, summary statistics will include the number of patients, mean, median, standard deviation, minimum and maximum. Categorical endpoints will be summarized using the number of patients, frequency, and percentages. For time-to-event endpoints, the Kaplan-Meier curves (Kaplan and Meier 1958) will be estimated, and quartiles and rates at various time points together with the 95% CI will be provided. Missing data will not be imputed.

The interpretation of the study results will be the responsibility of the investigator with the Lilly CRP, pharmacokineticist, and statistician. The CRP and statistician will also be responsible for the appropriate conduct of an internal review for both the final study report and any study-related material to be authorized by Lilly for publication.

This study will have 2 database locks. The first database lock will occur when the pre- and post-olaratumab monotherapy tissue biopsies and the predose C1D1 and predose C2D1 whole blood samples have been collected for all 35 evaluable patients. The main purpose of this database lock is to assess biomarker expression level changes pre- and post-olaratumab monotherapy. The safety of olaratumab will also be evaluated at this database lock. The second database lock will occur at the end of the study when all patients have either completed or discontinued from the study and the 30-day short-term follow-up period has been completed. In the second database lock, all of the study objectives will be evaluated. There will be an interim analysis to look at the biomarker data once approximately half of the evaluable patients complete the second biopsy and the predose C2D1 whole blood draw.

10.1.1. Determination of Sample Size

To investigate the primary objective, approximately 35 evaluable patients have to have completed the pre-treatment tissue biopsy, the predose C1D1 whole blood draw, 1 cycle of olaratumab monotherapy, the post-olaratumab monotherapy biopsy, and the predose C2D1 whole blood draw.

If the patient is noncompliant during olaratumab monotherapy (Cycle 1) and does not undergo the pre-treatment tissue biopsy, the post-olaratumab monotherapy biopsy, or the predose C1D1 and predose C2D1 whole blood draw, he or she will be considered nonevaluable and may be replaced.

It is hypothesized that 49% (17 out of 35) or more patients will have a reduction of at least 30% in PDGFRα level change in tissue from baseline to post-olaratumab monotherapy. The sample size of 35 patients provides a 95% CI that the hit rate (proportion of patients with at least 30% reduction in PDGFRα level change from baseline) will be between 31% and 66%, which excludes a 30% or lower hit rate.

10.1.2. Analysis Populations

Efficacy analysis: the efficacy analysis will be performed on the intent-to-treat (ITT) population, which includes all enrolled patients. The ITT population will be included in overall patient listings, in summary tables of patient demographics and disease characteristics, in the list of treatment discontinuation after enrollment, and in the analysis of efficacy.

Safety analysis: all enrolled patients who receive any quantity of IP, regardless of their eligibility for the study, will be included in the safety analysis. Safety evaluation will be performed based on the actual therapy a patient has received.

Biomarker analysis: the biomarker evaluable 1 (BE1) population will include all ITT patients with evaluable samples at both baseline and post-olaratumab monotherapy. The BE1 population will be used in the biomarker analyses for the primary objective and exploratory objectives. The biomarker evaluable 2 (BE2) population will include all ITT population with evaluable samples at both baseline and post-combination (olaratumab plus doxorubicin) therapy, and will be used in the biomarker analyses for the exploratory objectives.

10.2. Patient Disposition

All patient discontinuations will be documented, and the extent of each patient's participation in the study will be reported. If known, a reason for their discontinuation will be given.

10.3. Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics including age, sex, screening height and weight, and screening body mass index will be reported
- Baseline disease characteristics
- Historical diagnoses
- Pre-existing conditions
- Prior disease-related therapies
- Concomitant medications
- Tissue histology grouped as leiomyosarcoma (LMS) or non-LMS.

Other patient characteristics will be summarized as deemed appropriate.

10.4. Safety Analyses

All patients who receive at least 1 dose of study drug will be evaluated for safety and toxicity.

The safety and tolerability of study drug is determined by reported AEs, physical examinations, laboratory tests, ECGs, dose adjustments, and results from ECHO/MUGA scans.

All patients will be assessed regularly for potential occurrence of AEs from the time that the patient provides informed consent until 30 days after the last dose of study therapy. Adverse events will be summarized by MedDRA System Organ Class and preferred term, classified from verbatim terms. The incidence and percentage of patients with at least 1 occurrence of a

preferred term will be included, according to the most severe NCI-CTCAE Version 4.0 grade. The number of AEs reported per MedDRA preferred term will also be summarized. Causality (relationship to study drug) will be summarized separately. Duration of AE will be determined and included in listings along with action taken and outcome.

Laboratory results will be classified according to NCI-CTCAE Version 4.0. Incidence of laboratory abnormalities will be summarized; laboratory results not corresponding to an NCI-CTCAE Version 4.0 term will not be graded. Laboratory toxicity shifts from baseline to worst grade will also be provided.

The results from physical examination and vital sign measurement will be tabulated. Descriptive statistics will be provided as appropriate. Electrocardiogram and ECHO/MUGA evaluation will be listed.

10.5. Biomarker Analyses

Primary analysis:

All patients in the BE1 population will be evaluated for:

- CTC enumeration in whole blood
- PDGFRα, PDGFRβ, and canonical ligand (*PDGF-A, B, C,* and *D*) expression in tumor tissue.

The percent change from baseline for post-olaratumab monotherapy in biomarker expressions will be provided for each patient and summarized for all qualified patients. Summary of number and frequency of patients with at least 30% reduction in change from baseline PDGFRα expression will also be provided. For patients with an observed value of 0 for baseline expression or both baseline and post-olaratumab monotherapy expressions, a value of 0.1 will be used.

10.6. Efficacy

The following secondary efficacy endpoints will be measured:

Progression-free survival (PFS): is defined as the time from enrollment until the first radiographic documentation of objective progression as defined by RECIST (v1.1) (Attachment 8), or death from any cause. Patients who die without a reported prior progression will be considered to have progressed on the day of their death. Patients who did not progress or who are lost to follow-up will be censored at the day of their last radiographic tumor assessment. If no baseline or postbaseline radiologic assessment is available, the patient will be censored at the date of enrollment. If death or PD occurs after 2 or more consecutive missing radiographic visits, censoring will occur at the date of the last radiographic visit prior to the missed visits. The use of a new anticancer therapy or the performance of a surgical resection prior to the occurrence of PD will result in censoring at the date of last radiographic assessment prior to initiation of new therapy or surgical resection.

3-month PFS: estimated as the total number of patients who did not progress 3 months after enrollment divided by the total number of patients.

Overall response rate (ORR): estimated as the total number of CRs, complete responses unconfirmed (CRus), and PRs divided by the total number of patients.

Disease control rate (DCR): is computed as the total number of patients with the best overall response of CR, CRu, PR, or SD divided by the total number of patients.

Rate of Resectability: is defined as the total number of patients who are resectable (see definition of resectability in Section 4) divided by the total number of patients.

10.7. Pharmacokinetic Analyses

Pharmacokinetic parameter estimates for olaratumab will be calculated by standard noncompartmental methods of analysis in patients who have received at least 1 dose of olaratumab and have had samples collected. The primary parameters for analysis will be maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), area under the plasma concentration-time curve from time zero to the last measurable plasma concentration (AUC[0-t_{last}]), and area under the plasma concentration-time curve from time zero to infinity (AUC[0-∞]) of olaratumab, where appropriate. Other noncompartmental parameters, such as half-life ($t_{1/2}$), clearance (CL), and volume of distribution (V_d), may be reported.

Additional exploratory analyses may be performed if warranted by data and other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Lilly global PK management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

10.8. Interim Analyses

An interim analysis will be done to look at the biomarker data once approximately half of the evaluable patients complete the second tumor tissue biopsy and C2D1 whole blood draw. The purpose of this interim analysis is to review the biomarker and safety data. If this interim look at the biomarker data warrants any changes in the study conduct, it will be implemented in an appropriate manner (that is, protocol amendment). Section 10.1 describes the 2 database locks and the interim analysis that will occur in this study.

11. Informed Consent, Ethical Review, and Regulatory Considerations

11.1. 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 study in a timely manner.

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 potential risks and benefits of participating in the study and desires to participate in the study.

The investigator is ultimately responsible for ensuring that informed consent is given by each patient or legal representative before the study is started. 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 drug.

In this protocol, the term "informed consent" includes all consent given by patients or their legal representatives.

11.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites(s). 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 site(s). The ERB(s) will review the protocol as required.

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

1. the current IB and updates during the course of the study
2. ICF
3. relevant curricula vitae

11.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

2) the ICH GCP Guideline [E6]

3) applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERB(s).

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

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

11.3.1. Investigator Information

Site-specific contact information may be provided in a separate document.

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

11.3.2. Protocol Signatures

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

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

11.3.3. Final Report Signature

The final report coordinating investigator or designee will sign the 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 sponsor's responsible medical officer and statistician will 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 JGDM Study Schedule

Perform procedures as indicated in the following tables for the baseline, treatment, and posttreatment periods, respectively.

All screening/baseline evaluations are performed within 14 days prior to enrollment, unless otherwise specified. Patients who meet all criteria for enrollment will be assigned to receive treatment. After the patient signs the informed consent form, the site will register the patient in the Interactive Web Response System, which is web-based and accessible 24 hours a day.

Baseline Schedule of Activities

Procedure Category	Protocol Sections	Procedure	Study Period: Baseline		Comments
			Cycle: BL		
			Visit: 0		
			Duration: Up to 14 days (except where noted)		
			Relative Day from Enrollment: ≤14	≤7	
Study Entry/ Enrollment	11.1	Informed Consent	X (within 28 days of enrollment)		Written informed consent must be obtained prior to any study-specific screening evaluations. For screening purposes, required assessments performed prior to the date of consent may be used provided they are noted exceptions.
	6.1 7.2.3.1.2.4	Inclusion/Exclusion Evaluation and IWRS		X	Patients who meet all criteria for enrollment will be assigned to receive treatment. After the patient signs the ICF, the site will register the patient in the IWRS. After enrollment, patients should receive their first dose of treatment within 72 hours (3 days) whenever possible.
Medical History	8.1.2	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.
	6.1	Demography	X		Year of birth, sex, and race/ethnicity will be collected at baseline.
	6.1	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.
Physical Examination	6.1	Physical Examination		X	Physical examination at baseline includes height, weight, and BSA measurement.
	6.1 Attachment 6	ECOG Performance Status		X	Refer to Attachment 6 for details.
	6.1	Vital Signs		X	Vital signs include blood pressure, pulse, and temperature.
Concomitant Medications	7.5	Concomitant Medications	X		Concomitant medications will be recorded, including any taken within 30 days prior to start of study treatment (C1D1).
Lab/ Diagnostic Tests	6.1.1 Attachment 2	Hematology	X		Screening evaluations done within 7 days prior to enrollment do not have to be repeated. Testing will be performed locally for patient management and centrally for analysis purposes.
	6.1.1 Attachment 2	Serum Chemistry	X		Screening evaluations done within 7 days prior to enrollment do not have to be repeated. Testing will be performed locally for patient management and centrally for analysis purposes.
	6.1.1 Attachment 2	Coagulation Profile	X		Screening evaluations done within 7 days prior to enrollment do not have to be repeated. Testing will be performed locally only.
	Attachment 2	Urinalysis	X		Screening evaluations done within 7 days prior to enrollment do not have to be repeated. Includes a routine UA, and if clinically indicated a microscopic analysis. If routine analysis indicates > 2+ proteinuria, then a 24-hour urine must be collected and must demonstrate ≤ 1000 mg of protein in 24 hours. Testing will be performed locally only.

		Study Period	Baseline		
		Cycle	BL		
		Visit	0		
		Duration	Up to 14 days (except where noted)		
		Relative Day from Enrollment	≤14	≤7	
Procedure Category	**Protocol Sections**	**Procedure**			**Comments**
Lab/ Diagnostic Tests	6.1.1 Attachment 2	Pregnancy Test		X	Serum β-HCG or urine pregnancy test (women of child-bearing potential only) within 7 days prior to enrollment. If the pregnancy test performed for inclusion purposes is positive, confirm by repeating a serum or urine pregnancy test. The results of this test will not be collected on the eCRF. Testing will be performed locally only.
	6.1.1 Attachment 2	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. Testing will be performed locally only.
	8.2.3	Tumor Tissue Biopsy	X (within 28 days of enrollment)		When submitting a tissue biopsy, sites should examine samples to determine adequacy of tumor tissue using their local laboratory procedures prior to first dose of olaratumab monotherapy. If additional tumor biopsies are collected as part of clinical care, they should be submitted, along with local pathology reports for further analysis (refer to Section 8.2.3 for details).
	8.1.3.1 9.2.2	ECG	X (within 28 days of enrollment)		A single 12-lead ECG is to be obtained within 28 days prior to enrollment (refer to Section 8.1.3.1 and Section 9.2.2 for details). ECGs will be read locally and measurements will be electronically submitted to a central vendor.
	8.1.3.2	Echocardiogram or MUGA Scan	X (within 28 days of enrollment)		Within 28 days prior to enrollment (refer to Section 8.1.3.2 for details).
	8.2.3.3	PET Scan	X (within 28 days of enrollment)		Within 28 days prior to enrollment. PET scans will be read locally by the investigator and sent to a central vendor where the images will be stored.
Efficacy Assessment	Attachment 8	Imaging Studies (CT/MRI) Tumor Assessments (according to RECIST v1.1)	X (within 28 days of enrollment)		Within 28 days prior to enrollment (refer to Attachment 8 for details). CT/MRI scans will be read locally and a scan will also be sent for storage at a central vendor.
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; C = cycle; CT= computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FSH = follicle-stimulating hormone; ICF = informed consent form; IWRS = Interactive Web Response System; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; PET = positron emission tomography; RECIST = Response Evaluation Criteria in Solid Tumors; UA = urinalysis.

On-Study-Treatment Schedule of Activities

		Study Period	Treatment Period				
			Olaratumab Monotherapy		Combination Therapy Olaratumab + Doxorubicin		
		Cycle (21-day cycle ±3 days)	1		2-7		
		Relative Day within Cycle (±3 days)	1[a,b]	8[a]	1[a,b]	8[a]	
Procedure Category	**Protocol Section**	**Procedure**					**Comments**
Physical Examination	6.1	Physical Examination	X	X	X	X	Physical examination during treatment period includes weight and BSA measurement. Patients should be weighed on D1 and D8 of each cycle and BSA calculated.
	6.1 Attachment 6	ECOG Performance Status	X		X		Complete prior to treatment infusion. Refer to Attachment 6 for details.
	6.1	Vital Signs	X	X	X	X	Vital signs include blood pressure, pulse, and temperature. During the Observation Period (initial 2 cycles of olaratumab therapy), collect vital signs 3 times: • within 15 minutes (+5 minutes) prior to olaratumab infusion • within 1 hour (+5 minutes) after completion of the olaratumab infusion • within 1 hour (+5 minutes) after completion of the doxorubicin infusion. Thereafter (Cycles 3+), obtain vital signs 2 times: within 15 minutes (+5 minutes) prior to olaratumab infusion within 1 hour (+5 minutes) after completion of the doxorubicin infusion.
Lab/ Diagnostic Tests	Attachment 2	Hematology	X	X	X	X	Laboratory assessments may be done within 7 days prior to D1 and D8 of each cycle. See Attachment 2 for details. Testing will be performed locally for patient management and centrally for analysis purposes.
	Attachment 2	Serum Chemistry	X		X		Laboratory assessments may be done within 7 days prior to D1 of each cycle. See Attachment 2 for details. Testing will be performed locally for patient management and centrally for analysis purposes.
	Attachment 2	Coagulation Profile	X		X		Perform on D1 every other cycle or as clinically indicated. See Attachment 2 for details. Testing will be performed locally only.
	Attachment 2	Urinalysis	X		X		Laboratory assessments may be done within 7 days prior to D1 of every other cycle or as clinically indicated. Includes a routine UA, and, if clinically indicated, a microscopic analysis. If routine analysis indicates >2+ proteinuria, then a 24-hour urine must be collected and must demonstrate ≤1000 mg of protein in 24 hours. Testing will be performed locally only.
	Attachment 2	Pregnancy Test	X		X		Serum β-HCG or urine pregnancy test on D1 of every cycle or per local practice (whichever is of shorter duration). If a pregnancy test performed on D1 of the cycle is positive, confirm with a serum or urine pregnancy test (pregnancy test results are not recorded on the eCRF). If results are positive, the investigator is to consult with the Lilly CRP. Testing will be performed locally only.
	8.2.2 Attachment 4	PK Samples	See Attachment 4 for specific time points				Whole blood samples collected for olaratumab serum PK measurements.

Procedure Category	Protocol Section	Procedure	Study Period: Treatment Period — Olaratumab Monotherapy: Cycle 1 (21-day cycle ±3 days): Relative Day within Cycle (±3 days): 1[a,b]	8[a]	Combination Therapy Olaratumab + Doxorubicin: Cycle 2-7: 1[a,b]	8[a]	Comments
	8.2.5 Attachment 4	Immunogenicity Samples	See Attachment 4 for specific time points				Whole blood samples collected. 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.
Lab/ Diagnostic Tests	8.2.4	Pharmacogenetic Whole Blood Sample for DNA storage	X				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.
	8.2.3 Attachment 4	Plasma sample for exploratory biomarkers	X	See Attachment 4 for specific time points			Plasma sample collected. C1D1 at predose, C2D1 (combination therapy pre-dose) and at the end of the patient's study treatment. See Section 8.2.3.1 and Attachment 4 for details and specific time points.
	8.2.3 Attachment 4	Serum sample for exploratory biomarkers	X	See Attachment 4 for specific time points			Serum sample collected. C1D1 at predose, C2D1 (combination therapy pre-dose) and at the end of the patient's study treatment. See Section 8.2.3.1 and Attachment 4 for details and specific time points.
	8.2.3 Attachment 4	Mandatory Whole Blood Collection for Circulating Tumor Cells	X	See Attachment 4 for specific time points			Collect mandatory peripheral whole blood samples predose at C1D1, C1D8, C2D1, C2D8, and C3D1, and at end of the patient's study treatment or at the time of surgical resection. See Section 8.2.3.1 and Attachment 4 for details.
	8.2.3	Mandatory Tumor Tissue			X		Mandatory tumor tissue must be collected up to 3 days prior to the first dose of C2D1. When submitting a specimen from a tumor resection after or during combination therapy, sites should examine samples to determine adequacy of tumor tissue using their local laboratory procedures. If additional tumor biopsies are collected as part of clinical care, they should be submitted, along with pathology reports, for further analysis. See Section 8.2.3.2 for details.
	8.1.3.1	ECG	X		X		Twelve-lead ECGs are to be collected on Day 1 of monotherapy Cycle 1 and on Day 1 of combination therapy Cycles 2-7. Patients who stop doxorubicin prior to Cycle 7 will undergo the same cardiac monitoring assessment. ECGs will be read locally and measurements will be electronically submitted to a central vendor.
	8.1.3.2	Echocardiogram or MUGA				X	Echocardiograms or MUGA scans must be performed at the end of combination therapy Cycles 5 and 7 and when clinically indicated. After Cycle 7, (resting LVEF ≥50%), perform echocardiograms or MUGA at the 30-day follow-up visit. Patients who stop doxorubicin prior to Cycle 7 will undergo the same cardiac monitoring assessment. For patients with LVEF <50% or other cardiac dysfunction, perform more frequently, if clinically indicated.
	8.2.3.3	PET Scan			X		Mandatory PET scan must be collected up to 3 days prior to the first dose of C2D1. PET scans will be read locally by the investigator and sent to a central vendor where the images will be stored.

		Study Period	Treatment Period				
			Olaratumab Monotherapy		Combination Therapy Olaratumab + Doxorubicin		
		Cycle (21-day cycle ±3 days)	1		2-7		
		Relative Day within Cycle (± 3 days)	1[ab]	8[a]	1[a]	8[ab]	
Procedure Category	**Protocol Section**	**Procedure**					**Comments**
Efficacy Assessment	Attachment 8	Imaging Studies (CT/MRI) Tumor Assessments (according to RECIST v1.1)			X		Imaging studies and tumor assessments are to be obtained every 6 weeks (up to 7 days before), irrespective of treatment cycles as calculated from enrollment, 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 Attachment 8 for details. CT/MRI scans will be read locally and a scan will also be sent for storage at a central vendor.
Adverse Events Collection/ CTCAE Grading	8.1.2	Toxicity Assessment	X	X	X	X	All AEs considered at least possibly related to study treatment will be followed until resolution, stabilization, or return to baseline, or until deemed irreversible.
Concomitant Therapy	7.5	Concomitant Medications	X	X	X	X	Concomitant medications will be recorded throughout the treatment period, including those taken during the 30 days after the last dose of all study treatment.
Premedication	7.2.2	Administer premedication prior to olaratumab treatment	X	X	X	X	Premedicate all patients with the following medications (or equivalent): a histamine H1 antagonist (eg, diphenhydramine) and dexamethasone intravenously 30–60 minutes prior to the olaratumab doses on Days 1 and 8 of Cycle 1. For subsequent cycles, premedicate all patients with a histamine H1 antagonist (eg, diphenhydramine) intravenously 30-60 minutes prior to each dose of olaratumab.
	7.2.2	Administer dexrazoxane prior to doxorubicin			X		Dexrazoxane is recommended for all patients receiving 5 or more cycles of doxorubicin.
Study Treatment	7.1.2	Administer olaratumab	X	X	X	X	Administer through completion of Cycle 7 or until PD, surgical resection, unacceptable toxicity, death, or other withdrawal criteria are met.
	7.1.3	Administer doxorubicin			X		Administered to all patients during combination therapy for up to a maximum of 6 cycles (Cycles 2-7) (unless previous unacceptable toxicity).
Patient Disposition			X		X		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.

Abbreviations: β-HCG = beta human chorionic gonadotropin; AE = adverse event; BSA = body surface area; C = cycle; CR = complete response; CRP = clinical research physician; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; PD = progressive disease; PET = positron emission tomography; PK = pharmacokinetic; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; UA = urinalysis.

[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).

[b] Relative day within each cycle (≤3 days). Procedure allowed up to 3 days before D1.

Posttreatment Discontinuation Follow-Up Schedule of Activities

		Study Period	Posttreatment 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	6.1	Physical examination	X		Physical examination will include weight.
	6.1 Attachment 6	ECOG performance status	X		Refer to Attachment 6 for details.
	6.1	Vital signs	X		Includes blood pressure, pulse, and temperature.
Lab/ Diagnostic Tests	Attachment 2	Hematology	X		See Attachment 2 for details. Testing will be performed locally for patient management and centrally for analysis purposes.
	Attachment 2	Serum chemistry	X		See Attachment 2 for details. Testing will be performed locally for patient management and centrally for analysis purposes.
	Attachment 2	Coagulation profile	X		See Attachment 2 for details. Testing will be performed locally only.
	Attachment 2	Urinalysis	X		Includes a routine UA and, if clinically indicated, a microscopic analysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine collection (to assess protein) must be obtained. Testing will be performed locally only.
	Attachment 2	Pregnancy test	X		Serum or urine pregnancy test. If the pregnancy test is positive, confirm with a serum or urine 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. If results are positive, the investigator is to consult with the Lilly CRP. Testing will be performed locally only.
	8.1.3.1	ECG	X		Twelve-lead ECGs are to be collected for all patients at the short-term follow-up visit. ECGs will be read locally and measurements will be electronically submitted to a central vendor.
	8.1.3.2	Echocardiogram or MUGA	X		Echocardiogram or MUGA scans are to be collected for all patients at the short-term follow-up visit.
	Attachment 4	PK sample	X		See Attachment 4.
	Attachment 4	Immunogenicity sample	X		See Attachment 4. In addition, if a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the short-term follow-up after the IRR.
	8.2.3 Attachment 4	Plasma sample for exploratory biomarkers	X		Plasma sample collected at 30-day follow-up visit. See Section 8.2.3.1 for details.
	8.2.3 Attachment 4	Serum sample for exploratory biomarkers	X		Serum sample collected at 30-day follow-up visit. See Section 8.2.3.1 for details.
Efficacy Assessments	Attachment 8	Imaging Studies (CT/MRI) Tumor Assessments (according to RECIST v1.1)	X (if applicable)	X	For patients who discontinue study treatment, or complete 6 cycles of combination therapy, and have not progressed, imaging studies and tumor assessments are to be obtained every 6 weeks (±7 days) until PD, irrespective of treatment cycles, until documented progression as calculated from baseline scan. Patients who have had surgical resection will not be followed for subsequent progression by imaging studies. CT/MRI scans will be read locally and a scan will also be sent for storage at a central vendor.

		Study Period	Posttreatment 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**
Adverse Events Collection/ CTCAE Grading	8.1.2	Toxicity assessment	X	X[a]	All AEs considered at least possibly related to study treatment will be followed until resolution, stabilization, or 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	7.5	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; eCRF = electronic case report form; IRR = infusion-related reaction; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; PD = progressive disease; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; UA = urinalysis.

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).

[a] Follow up for safety: Patients who undergo surgical resection will be followed for safety for approximately 30 days (±7 days) after surgery.

Long-term follow-up begins the day after short-term follow up is completed.

Attachment 2. Protocol JGDM Clinical Laboratory Tests

All laboratory screening evaluations are to be performed within 14 days prior to enrollment, unless otherwise specified. Eligibility for inclusion in this clinical trial will be based on local clinical laboratory results (not transcribed onto electronic case report forms); duplicate samples will be submitted to the central laboratory. Treatment decisions may be based upon results of tests performed locally. 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	
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Glucose, random
Coagulation Test[a]	Albumin
Prothrombin time (PT)	Total protein
Partial Thromboplastin Time (PTT)	Chloride
International normalized ratio (INR)	Thyroid-stimulating hormone
	Direct bilirubin
Urinalysis[a,c]	
Specific gravity	
pH	**Pregnancy test[a,e]**
Protein	
Glucose	**Follicle-stimulating hormone (FSH)[a,f]**
Ketones	
Blood	
Urine leukocyte esterase	
Other[d]	
Immunogenicity samples	
PK samples	
Biomarker samples	

Abbreviations: CRP = clinical research physician; D = Day; PK = pharmacokinetics; RBC = red blood cells; WBC = white blood cells

a Assayed by local or investigator-designated laboratory.

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

c If urinary protein is ≥2+ at evaluations, a 24-hour urine collection (to assess protein) must be collected and must be ≤1000 mg of protein in 24 hours (up to 3 business days is allowed if the weekend).

d Assayed by a sponsor-designated (central) laboratory.

e Serum pregnancy test will be performed at screening in females of child-bearing potential only. If the baseline serum test is positive, a repeat serum or urine pregnancy test will be done. While on-study, a serum or urine pregnancy test will be performed in females of child-bearing potential only on D1 of every cycle or per local practice (whichever is of shorter duration) and at the short-term follow-up visit. If the pregnancy test performed on D1 of each cycle is positive, confirm with a serum or urine pregnancy test. If results are positive, the investigator is to consult with the Lilly CRP.

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

Attachment 3. Protocol JGDM 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 (HGB)	
Hematocrit (HCT)	**Hepatic Coagulation[a]**
Erythrocytes (RBC)	Prothrombin time (PT)
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils[b]	
Lymphocytes	**Hepatic Serologies[a,c]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets (PLT)	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	
Alanine aminotransferase (ALT)	**Recommended Autoimmune Serology:**
Aspartate aminotransferase (AST)	Anti-nuclear antibody[a]
Gamma-glutamyl transferase (GGT)	Anti-smooth muscle antibody[a]
Creatine phosphokinase (CPK)	

Abbreviations: CRF = case report form; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated laboratory.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

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

Attachment 4. Protocol JGDM Biomarker, Pharmacokinetic, and Immunogenicity Blood Sampling Schedule

Cycle	Day	Dosing		Sampling Time (hour)[a]	Olara PK[b]	IG[c,d]	Whole Blood for CTC Analyses	Plasma	Serum
		Doxorubicin	Olaratumab						
1	1			Prior to olaratumab infusion[f]	X	X	X	X	X
			X						
				Within 5 min post olaratumab infusion	X				
	8			Prior to olaratumab infusion[f]	X	X	X		
			X						
				Within 5 min post olaratumab infusion	X				
2	1			Prior to infusion[f]	X	X	X	X	X
			X						
		X							
				Within 5 min post doxorubicin injection	X				
	2			24 hours ± 3 hours	X				
	5			96 hours ± 3 hours	X				
	8			Prior to olaratumab infusion[f]	X		X		
			X						
				Within 5 min post olaratumab infusion	X				
	9			24 hours ± 3 hours	X				
	10			48 hours ± 3 hours	X				
	12			96 hours ± 3 hours	X				
	18			240 hours ± 3 hours	X				
3	1			Prior to olaratumab infusion[f]	X	X	X		
			X						
		X							
				Within 5 min post doxorubicin infusion	X				
	8			Prior to olaratumab infusion[f]	X				
			X						
				Within 5 min post olaratumab infusion	X				
5, 7	1			Prior to olaratumab infusion[f]	X	X			
30-day follow-up				Anytime	X	X	X[e]	X	X

Abbreviations: CTC = circulating tumor cells; IG = immunogenicity; min = minutes; olara = olaratumab; PK = pharmacokinetic.

a Time 0 is defined as end of infusion.

b Samples of approximately 3 mL of whole blood will be drawn into tubes. For the olaratumab samples, olaratumab serum PK measurements will be performed.

c Samples of approximately 4 mL will be collected.

d In addition to the scheduled immunogenicity sampling, in the event of an infusion-related reaction, samples are to be collected as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event.

e At end of the patient's study treatment.

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

Attachment 5. Protocol JGDM Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events (SAEs)

When contacting Lilly to report a SAE, please have the following information available:

Patient Demographics

- patient identification (number), sex, date of birth, origin, height, and weight

Study Identification

- full trial protocol number, investigator's name, investigator's number

Study Drug

- drug code or drug name, unit dose, total daily dose, frequency, route, start dose, cycle details, start date and last dose date (if applicable)

Adverse Event

- description, date of onset, severity, treatment (including hospitalization), action taken with respect to study drug, clinical significance, test and procedure results (if applicable)

Relationship to Study Drug & Protocol Procedures

Concomitant Drug Therapy

- indication, total daily dose, duration of treatment, start date, action taken

In Case of Death

- cause, autopsy finding (if available), date, relationship to study drug and protocol procedures.

Attachment 6. Protocol JGDM ECOG Performance Status

Eastern Cooperative Oncology Group (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 performance of a light or sedentary nature, for example, light housework, 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 7. Protocol JGDM 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:

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

For serum creatinine concentration in μmol/L:

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

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

Reference: Cockcroft and Gault 1976.

Attachment 8. Protocol JGDM RECIST Criteria

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

Measurability of Tumor at Baseline

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

Measurable

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

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

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

Nonmeasurable

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

Special Considerations for Lesion Measurability

Bone lesions:

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

Cystic lesions:

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

Lesions with Prior Local Treatment:

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

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

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

Nontarget Lesions

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

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

Specifications by Methods of Measurement

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

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

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

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

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

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

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

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

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

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

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

Response Criteria

Evaluation of Target Lesions

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

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

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

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

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

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

Evaluation of Nontarget Lesions

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

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

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

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

Evaluation of Best Overall Response

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

Time Point Response

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

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

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

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

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

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

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

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

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

Frequency of Tumor Re-Evaluation

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

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from first dose.

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

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

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

Independent Review of Response and Progression

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

Attachment 9. Protocol JGDM CYP3A4, CYP2D6, and P-gp Inhibitors and Inducers of Doxorubicin

CYP3A4 Inducers	Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors
Aminoglutethimide	Clarithromycin	Amiodarone
Bosentan	Chloramphenicol	Amprenavir
Carbamazepine	Cobicistat	Aprepitant[a]
Efavirenz (in liver only)	Conivaptan	Atazanavir
Fosphenytoin	Cremophor EL	Cimetidine
Nafcillin	Cyclosporine	Ciprofloxacin
Nevirapine	Delavirdine	Clotrimazole
Oxcarbazepine	Diclofenac	Darunavir
Pentobarbital	Diltiazem	Darunavir and ritonavir
Phenobarbital	Elvitegravir and ritonavir	Desipramine
Phenytoin	Enoxacin	Doxycycline
Primidone	Fosamprenavir	Dronedarone
Rifabutin	Grapefruit juice, starfruit, and Seville oranges	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	

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

Abbreviation: CYP = cytochrome P450.

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

Attachment 10. Protocol JGDM Protocol Amendment I5B-MC-JGDM(c) Summary: A Phase 1b Trial to Assess the Modulation of Biological Markers in Patients with Potentially Resectable Soft Tissue Sarcoma Treated with Olaratumab Monotherapy Followed by Olaratumab plus Doxorubicin Combination Therapy

Overview

Protocol I5B-MC-JGDM, A Phase 1b Trial to Assess the Modulation of Biological Markers in Patients with Potentially Resectable Soft Tissue Sarcoma Treated with Olaratumab Monotherapy Followed by Olaratumab plus Doxorubicin Combination Therapy, 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 term QTcF was defined in the abbreviations and definition section.
- Fridericia's QT correction formula was added for patients with bundle branch block.
- Exclusion criteria 22 was updated by removing language related to the patient's ability to adhere to the protocol and to indicate the exclusion criteria refers to a concomitant systemic disorder the patient is currently experiencing.
- Exclusion criteria 23 was corrected.
- Section 7.1.2. was updated to reference the Pharmacy Manual rather than text from the manual.
- A clarification was made in Section 7.2.3.1 for dose delays that collection of PK samples should be derived from time the actual olaratumab dose was given vs when dose was originally expected.
- Section 8.2.3.2. was corrected for tumor tissue from any posttherapy surgical resection to be optional rather than required.
- Section 10.1. and 10.1.1. was clarified to add the C1D1 predose blood draw to the definition of an evaluable patient.
- A clarification was made in the schedule of events to both treatment and baseline PET scan to move them to the appropriate place in the schedule.
- A change was made in the timing of pre-Dose PK sample in order to allow for samples to be collected before pre-medications are administered.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore. Where existing language is underlined, additions have been identified by the use of double underscore.

4. Abbreviations and Definitions

QTcF Fridericia's QT corrected interval

6.1.2. Exclusion Criteria

[9] Have adequate hematologic, organ, coagulation, and cardiac function within 2 weeks (14 days) prior to enrollment:

- 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.
- Platelet count ≥100 x 10^9/L.
- Hemoglobin ≥9.0 g/dL. No transfusions are allowed within 2 weeks (14 days) prior to enrollment.
- Creatinine clearance ≥45 mL/min (refer to Attachment 7 for the Cockcroft-Gault formula).
- Proteinuria ≤1000 mg in 24 hours (if routine urinalysis indicates ≥2+ proteinuria).
- Total bilirubin below upper limit of normal (ULN) (except for patients with Gilbert's Syndrome, who must have a total bilirubin <3 mg/dL).
- Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤3.0 × ULN; if the liver has tumor involvement, AST and ALT ≤5.0 × ULN are acceptable.
- An adequate coagulation function as defined by International Normalized Ratio ≤1.5 x ULN or prothrombin time ≤1.5 x ULN, and partial thromboplastin time or activated partial thromboplastin time ≤1.5 x ULN if not receiving anticoagulation therapy. For patients receiving anticoagulants, exceptions to these coagulation parameters are allowed if they are within the intended or expected range for their therapeutic use. Patients must have no history of active bleeding (defined as within 14 days of first dose of study drug) or pathological condition that carries a high risk of bleeding (for example, tumor involving major vessels or known esophageal varices).

[19] Have a Bazett's corrected QT interval of >450 msec for males and >470 msec for females on screening ECG utilizing Bazett's correction. For bundle branch block patients, have a QTcF interval of >450 msec for males and >470 msec for females on screening electrocardiogram (ECG) utilizing Fridericia's correction.

[22] Have ~~a~~ serious pre-existing medical conditions that in the opinion of the investigator would exclude the patient as a candidate for this study~~.concomitant systemic disorder (for example, active infection including human immunodeficiency virus, or cardiac disease) that , in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol~~.[23]Have a known allergy to any of the treatment components including a history of allergic reactions attributed to compounds of chemical or biological composition similar to olaratumab ~~intravenous (IV) injection on Day 1~~.

6.2 Summary of Study Design

- **Long-term follow-up:** begins the day after short-term follow-up is completed.
  - Follow-up for progression - Patients who discontinue study treatment, or have completed 6 cycles of combination therapy, and have not progressed and have not initiated a new systemic treatment for their disease will be assessed for progression by imaging studies every 6 weeks (~~=~~≤7 days) until PD. Patients who have had surgical resection will not be followed for subsequent progression by imaging studies.

7.1.2. Olaratumab

Please refer to the Pharmacy Manual for information on preparing the olaratumab dosing solution for infusion.

~~Prepared Olaratumab Dosing Solution for Infusion: Chemical and physical in-use stability for the prepared olaratumab dosing solution has been demonstrated for up to 24 hours below 25ºC (77ºF) in the concentration range of 1.2 mg/mL to 6.4 mg/mL. It is recommended that the prepared dosing solution be used immediately to minimize the risk of microbial contamination. If not used immediately, the prepared olaratumab dosing solution must be stored under refrigeration at 2ºC-8ºC (36ºF-46ºF) for a duration not to exceed 24 hours. If the prepared solution is held at room temperature (below 25ºC [77ºF]), it must be used within 4 hours. Do not freeze and/or shake prepared olaratumab dosing solution for infusion.~~

~~Aseptic technique is to be used when preparing and handling olaratumab. Patients are to receive a loading dose of 20 mg/kg on Days 1 and 8 in the monotherapy lead-in cycle, and again on Days 1 and 8 in the first cycle of combination therapy (Cycle 2), followed by 15 mg/kg of olaratumab on Days 1 and 8 of each subsequent 21-day treatment cycle (Cycle 3-Cycle 7), administered as an IV infusion. On the days that both olaratumab and doxorubicin are administered, olaratumab~~

~~will be administered prior to doxorubicin. The dose of olaratumab is dependent upon the patient's body weight (Section 7.3.1). Actual body weight will be used for dose calculation. Subsequent doses of olaratumab must be recalculated if there is a ≥10% change (increase or decrease) in body weight; subsequent doses may be recalculated if there is a <10% change in body weight from prior dose and considered clinically relevant by the treating investigator.~~

~~Olaratumab is compatible with commonly used infusion containers. Refer to the IB or pharmacy manual for detailed information. Olaratumab concentration of below 1.2 mg/ml in prepared dose should be avoided due to dilution of excipients, which are important in maintaining stability.~~

~~The dose of olaratumab will be aseptically withdrawn from the vial and transferred to a sterile infusion bag or an evacuated glass container. To prepare the dose, a sufficient quantity of sterile normal saline (0.9% weight/volume) solution should be added (or removed in the case of a prefilled container such as AVIVA) to make the total volume 250 mL. The container should be gently inverted to ensure adequate mixing. In some cases, the volume of infusion solution required may exceed the 250-mL scenario described here to keep the infusion solution concentration within the desired range stated above. This situation may be more likely with the required loading dose of 20 mg/kg given in Cycle 1, but may also apply to any subsequent cycle depending on the patient's body weight. In case of dose volumes >250 mL, an empty 500-mL container of acceptable material of construction can be used without addition of any normal saline. A pre-filled container (filled with 0.9% normal saline) of >250 mL size can be used as long as the material of construction is acceptable and the concentration of olaratumab in prepared dose remains within 1.2 mg/mL to 6.4 mg/mL.~~

~~The dose should be infused over approximately 60 minutes. The infusion rate should not exceed 25 mg/min. Infusion durations longer than 60 minutes are permitted in specific circumstances (that is, for patients with higher body weight for whom the upper limit of infusion rate is limited or in the setting of prior olaratumab Grade 1-2 infusion-related reaction [IRR]); the infusion duration must always be accurately recorded.~~

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

7.2.1. Treatments Administered

Table JGDM 1 Treatment Regimens

Treatment	Cycle Length (Days)	Study Drug	Dose	Timing	Route
Monotherapy Cycle 1	21	Olaratumab[a]	20 mg/kg	approximately 1 hour infusion D1, D8	IV
		1-hour (±5 minutes) Observation Period[b]			

Combination Therapy Cycle 2	21	Olaratumab[a]	20 mg/kg	approximately 1 hour infusion D1, D8	IV
		1-hour (±5 minutes) Observation Period[b] followed by			
		Doxorubicin[c]	75 mg/m^2	IV injection on D1	IV
Combination Therapy Cycle 3 – Cycle 7	21	Olaratumab[a]	15 mg/kg	approximately 1 hour infusion D1, D8	IV
		Doxorubicin[c]	75 mg/m^2	IV injection on D1	IV

Abbreviations: D = day; eCRF = electronic case report form; IRR = infusion-related reaction; IV = intravenous; PO = orally.

a Premedicate all patients with the following (or equivalent) medications: a histamine H1 antagonist (for example, diphenhydramine) and dexamethasone intravenously 30–60 minutes prior to the olaratumab doses on Days 1 and 8 of Cycle 1. For subsequent cycles, premedicate all patients with a histamine H1 antagonist (for example, diphenhydramine) intravenously 30-60 minutes prior to each dose of olaratumab. Additional premedication may be provided at the investigator's discretion. Premedication **must be** provided in the setting of a prior Grade 1-2 IRR, as detailed in Section 7.2.2 and Section 7.2.3.1.1.1. All premedication administered must be adequately documented in the eCRF.

b A 1-hour (+5 minutes) Observation Period is required after the administration of the initial 2 cycles of olaratumab. During the Observation Period, collect vital signs 3 times: 1) within 15 minutes (+5 minutes) prior to olaratumab infusion, 2) within 1 hour (+5 minutes) after completion of the olaratumab infusion, and 3) within 1 hour (+5 minutes) after completion of the doxorubicin infusion. If no evidence of an IRR manifests during the initial 2 cycles of olaratumab, then no observation period is required for subsequent treatment cycles. In the event an IRR occurs thereafter, then the 1-hour Observation Period should be reinstituted; see Section 7.1.2. Thereafter (Cycles 3+), obtain vital signs 2 times: 1) within 15 minutes (+5 minutes) prior to olaratumab infusion and 2) within 1 hour (+5 minutes) after completion of the doxorubicin infusion.

c Administer doxorubicin according to institutional guidelines and/or clinical practice as an IV injection or as an infusion ~~in less than~~within 60 minutes. Decrease the rate of doxorubicin administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occurs. Infusion or injection start and end times will need to be recorded. Starting with Cycle 2, dexrazoxane may be administered at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion according to instructions provided in the pharmacy manual for this study, beginning within 30 minutes prior to the doxorubicin infusion for prevention of cardiotoxicity. It is recommended that all patients receiving 5 or more cycles of doxorubicin receive dexrazoxane.

7.2.3.1. Dose Delays, Modifications, and Discontinuations

~~To begin dosing at each cycle, the following criteria must be fulfilled:~~After treatment has been initiated, in order to start the next cycle the following criteria must be fulfilled:

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

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

- Platelets ≥100 × 10^3/μL (100,000/μL; ≥100 × 10^9/L)
- Hemoglobin ≥~~9~~8 g/dL
- Creatinine clearance ≥45 mL/min (refer to Attachment 7 for the Cockcroft-Gault formula)
- Proteinuria ≤1000 mg in 24 hours (if routine urinalysis indicates ≥2+ proteinuria) (to be performed every other cycle)
- Total bilirubin below ULN
- AST and ALT ≤3.0 x ULN, or ≤5 x ULN if the transaminase elevation is due to liver metastases
- Olaratumab-related AEs that are NCI-CTCAE Version 4.0 Grade <2 or equivalent severity to baseline

Delays:

In general, dose delays of 1 study drug (olaratumab or doxorubicin) due to toxicity guidances outlined in Sections 7.2.3.1.1 and 7.2.3.1.2 will not necessitate delays of the other study drug.

Treatment may be delayed for up to 21 days (1 equivalent cycle) to allow a patient sufficient time for recovery from study drug-related toxicity. If a patient does not recover from the toxicity within 42 days (2 equivalent cycles) from Day 1 of the previous treatment cycle, then the patient must be discontinued from study therapy.

Any procedure or sample collection whose timing is related to olaratumab dosing is to be completed according to when the olaratumab dose was actually administered, not when that dose was expected to occur. Samples whose adjusted timing would fall outside of the treatment cycle duration due to dose delay may be omitted.]

7.5 Concomitant Therapy

Bis~~o~~phosphonate 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.

7.6.1. Evaluable Patients

If the patient is noncompliant during olaratumab monotherapy (Cycle 1) and does not undergo the post-olaratumab monotherapy biopsy or the C1D1 pre-dose and C2D1 predose whole blood sample collection due to reasons other than drug-related toxicity, he or she will be considered nonevaluable for the primary objective. These patients may be replaced to ensure that 35 patients complete the pre-treatment tissue biopsy, the C1D1 pre-dose whole blood sample collection, 1 cycle of olaratumab monotherapy, and the post-olaratumab monotherapy biopsy, and the associated C2D1 predose whole blood sample collection.

8.1.2.2.3. Follow-Up Visit

All AEs and SAEs, regardless of relatedness to study drugs or protocol procedures, occurring during the follow-up visit (Visit 801) must be reported to Lilly or its designee. The follow-up visit begins the day after the patient and the investigator agree that the patient will no longer continue study treatment ~~starts following the last dose of study drug~~. At the end of the follow-up visit, the patient will be required to have specific safety assessments (Attachment 1). The timing of these safety assessments is 30 ± 7 days after the last dose of study drug.

8.1.3.1. Electrocardiograms

Table JGDM.6 provides Bazett's QT heart rate correction formula. Table JGDM.8.3 provides Fridericia's QT correction formula for patients with bundle branch block.

Table JGDM.6. Bazett's QT Heart Rate Correction Formula

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

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

Table JGDM 8.3 Fridericia's QT Correction Formula

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

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.

8.1.3.2. Echocardiograms/MUGA Scans

An ECHO or MUGA scan is required within 28 days prior to enrollment for all patients. Thereafter, ECHO or MUGA scans, whichever technique was used initially (as described in Section 7.2.3.1.2.2), must be performed at the end of Cycles 5 and 7, and when clinically indicated. For patients with LVEF <50% or other cardiac dysfunction, perform more frequently, if clinically indicated. After Cycle 7 (for patients with resting LVEF ~~>~~≥50%), an ECHO or MUGA scan should be obtained at the 30-day follow-up visit (refer to the Study Schedule [Attachment 1]).

Patients who stop doxorubicin prior to Cycle 7 ~~(with resting LVEF >~~≥50%) will undergo cardiac monitoring assessment at the 30-day follow-up visit (refer to the Study Schedule [Attachment 1]) with whichever technique (ECHO or MUGA scan) was used initially (as described in Section 7.2.3.1.2.2).

8.2.3.2. Tumor Tissue

Collection of the following tumor tissue samples is mandatory for all patients:

- newly obtained biopsy specimens taken from the primary tumor lesion pre- and post-olaratumab monotherapy treatment will be collected. The pretreatment tissue biopsy is to be performed within the screening period. The posttreatment tissue biopsy is to be performed after completion of the lead-in cycle of olaratumab monotherapy and prior to the initiation of combination therapy (Cycle 2). Refer to Attachment 1 for additional details. If clinically feasible, the biopsies should be taken from the same primary tumor lesion.
- ~~tumor tissue from any posttherapy surgical resection should also be collected and provided.~~

Collection of the following tumor tissue samples is optional for all patients:

- biopsy specimen collected at the end of the patient's study treatment. Refer to Attachment 1 for additional details. If clinically feasible, this biopsy should be taken from the same primary tumor lesion.
- tumor tissue from any posttherapy surgical resection may also be collected and provided. While this specimen is optional, it is expected this sample will be sent for analysis.

8.3 Efficacy Evaluations

Computed tomography scans, including spiral CT, are the preferred methods of measurement.

The exploratory PET Scan performed pre and post cycle 1 will not be used to determine efficacy.

10.1 General Considerations

This study will have 2 database locks. The first database lock will occur when the pre- and post-olaratumab monotherapy tissue biopsies and the pre-dose C1D1 and ~~the~~ predose C2D1 whole blood sample have been collected for all 35 evaluable patients. The main purpose of this database lock is to assess biomarker expression level changes pre- and post-olaratumab monotherapy. The safety of olaratumab will also be evaluated at this database lock. The second database lock will occur at the end of the study when all patients have either completed or discontinued from the study and the 30-day short-term follow-up period has been completed. In the second database lock, all of the study objectives will be evaluated. There will be an interim analysis to look at the biomarker data once approximately half of the evaluable patients complete the second biopsy and the predose C2D1 whole blood draw.

10.1.1. Determination of Sample Size

To investigate the primary objective, approximately 35 evaluable patients have to have completed the pre-treatment tissue biopsy, the predose C1D1 whole blood draw, 1 cycle of olaratumab monotherapy, the post-olaratumab monotherapy biopsy, and the predose C2D1 whole blood draw.

If the patient is noncompliant during olaratumab monotherapy (Cycle 1) and does not undergo the pre-treatment tissue biopsy, the post-olaratumab monotherapy biopsy, or the pre-dose C1D1 and predose C2D1 whole blood draw, he or she will be considered nonevaluable and may be replaced.

10.8. Interim Analyses

An interim analysis will be done to look at the biomarker data once approximately half of the evaluable patients complete the second tumor tissue biopsy and C2D1 whole blood draw. The purpose of this interim analysis is to review the biomarker and safety data. If this interim look at the biomarker data warrants any changes in the study conduct, it will be implemented in an appropriate manner (that is, protocol amendment). Section 10.1 describes the 2 database locks and the interim analysis that will occur in this study.

Attachment 1. Protocol JGDM Study Schedule

Baseline Schedule of Activities

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

Procedure Category	Protocol Sections	Procedure		Comments
Medical History	6.1	Prior Treatment Therapies of Underlying Disease	X	Prior treatment includes any treatment for underlying disease, including maintenance therapy. Start and stop dates should be documented as well. ~~Previous therapy must be completed ≥4 weeks (28 days) prior to enrollment.~~
Lab/ Diagnostic Tests	8.2.3.3	PET Scan	X (within 28 days of enrollment)	Within 28 days prior to enrollment. PET scans will be read locally by the investigator and sent to a central vendor where the images will be stored.
Efficacy Assessment	~~8.2.3.3~~	~~PET Scan~~	~~X (within 28 days of enrollment)~~	~~Within 28 days prior to enrollment. PET scans will be read locally by the investigator and sent to a central vendor where the images will be stored.~~

On-Study-Treatment Schedule of Activities

Study Period	Treatment Period			
	Olaratumab Monotherapy		Combination Therapy Olaratumab + Doxorubicin	
Cycle (21-day cycle ± 3 days)	1		2-7	
Relative Day within Cycle (± 3 days)	1[ab]	8[a]	1[ab]	8[a]

Procedure Category	Protocol Section	Procedure					Comments
Lab/ Diagnostic Tests	8.2.3.3	PET Scan			X		Mandatory PET scan must be collected up to 3 days prior to the first dose of C2D1. PET scans will be read locally by the investigator and sent to a central vendor where the images will be stored.
	8.1.3.2	Echocardiogram or MUGA				X	Echocardiograms or MUGA scans must be performed at the end of combination therapy Cycles 5 and 7 and when clinically indicated. After Cycle 7, (resting LVEF ≥~~>~~50%), perform echocardiograms or MUGA at the 30-day follow-up visit. Patients who stop doxorubicin prior to Cycle 7 ~~(with resting LVEF ≥>50%)~~ will undergo the same cardiac monitoring assessment. For patients with LVEF <50% or other cardiac dysfunction, perform more frequently, if clinically indicated.

		Study Period	Treatment Period				
			Olaratumab Monotherapy		Combination Therapy Olaratumab + Doxorubicin		
		Cycle (21-day cycle ± 3 days)	1		2-7		
		Relative Day within Cycle (± 3 days)	1[ab]	8[a]	1[ab]	8[a]	
Procedure Category	Protocol Section	Procedure					Comments
Efficacy Assessment	Attachment 8	Imaging Studies (CT/MRI) Tumor Assessments (according to RECIST v1.1)			X		Imaging studies and tumor assessments are to be obtained every 6 weeks (~~±~~up to 7 days before), irrespective of treatment cycles as calculated from enrollment, 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 Attachment 8 for details. CT/MRI scans will be read locally and a scan will also be sent for storage at a central vendor.
	~~8.2.3.3~~	~~PET Scan~~			~~X~~		~~Mandatory PET scan must be collected up to 3 days prior to the first dose of C2D1. PET scans will be read locally by the investigator and sent to a central vendor where the images will be stored.~~

Abbreviations: β-HCG = beta human chorionic gonadotropin; AE = adverse event; BSA = body surface area; C = cycle; CR = complete response; CRP = clinical research physician; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; PD = progressive disease; PET = positron emission tomography; PK = pharmacokinetic; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; UA = urinalysis.

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).

b Relative day within each cycle (≤3 days). Procedure allowed up to 3 days before D1.

Attachment 2. Protocol JGDM Clinical Laboratory Tests

Clinical Chemistry

Serum Concentrations of the following:

~~Gammaglutamyl transferase~~

Attachment 4. Protocol JGDM Biomarker, Pharmacokinetic, and Immunogenicity Blood Sampling Schedule

Cycle	Day	Dosing		Sampling Time (hour)[a]	Olara PK[b]	IG[c,d]	Whole Blood for CTC Analyses	Plasma	Serum
		Doxorubicin	Olaratumab						
1	1			~~Within 15 min before~~Prior to olaratumab infusion[f]	X	X	X	X	X
			X						
				Within 5 min post olaratumab infusion	X				
	8			~~Within 15 min before~~Prior to olaratumab infusion[f]	X	X	X		
			X						
				Within 5 min post olaratumab infusion	X				
2	1			~~Within 15 min before~~Prior to infusion[f]	X	X	X	X	X
			X						
		X							
				Within 5 min post doxorubicin injection	X				
	2			24 hours ± 3 hours	X				
	5			96 hours ± 3 hours	X				
	8			~~Within 15 min before~~Prior to olaratumab infusion[f]	X		X		
			X						
				Within 5 min post olaratumab infusion	X				
	9			24 hours ± 3 hours	X				
	10			48 hours ± 3 hours	X				
	12			96 hours ± 3 hours	X				
	18			240 hours ± 3 hours	X				
3	1			~~Within 15 min before~~Prior to olaratumab infusion[f]	X	X	X		
			X						
		X							
				Within 5 min post doxorubicin infusion	X				
	8			~~Within 15 min before~~Prior to olaratumab infusion[f]	X				
			X						
				Within 5 min post olaratumab infusion	X				
5, 7	1			~~Within 15 min before~~Prior to olaratumab infusion[f]	X	X			
30-day follow-up				Anytime	X	X	X[e]	X	X

Abbreviations: CTC = circulating tumor cells; IG = immunogenicity; min = minutes; olara = olaratumab; PK = pharmacokinetic.

a Time 0 is defined as end of infusion.

b Samples of approximately 3 mL of whole blood will be drawn into tubes. For the olaratumab samples, olaratumab serum PK measurements will be performed.

c Samples of approximately 4 mL will be collected.

d In addition to the scheduled immunogenicity sampling, in the event of an infusion-related reaction, samples are to be collected as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event.

e At end of the patient's study treatment.

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