Protocol I5B-JE-JGDK (b)

A Phase 1 Study of Olaratumab in Japanese Patients with Advanced Soft Tissue Sarcoma or Advanced Solid Tumors

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Approval Date: 28-Sep-2018

1. Protocol I5B-JE-JGDK (b)

A Phase 1 Study of Olaratumab in Japanese Patients with Advanced Soft Tissue Sarcoma or Advanced Solid Tumors

Olaratumab (LY3012207)

This Phase 1 study is a multicenter, nonrandomized, open–label study to evaluate intravenous olaratumab in combination with doxorubicin in Japanese patients with advanced soft tissue sarcoma or advanced solid tumors (Part A), and intravenous olaratumab alone in Japanese patients with advanced solid tumors (Part B).

Eli Lilly Japan KK
Kobe, Hyogo, Japan

Protocol Approved by Lilly: 09 Dec 2014
Amendment (a) Protocol Electronically Signed and Approved by Lilly on 26 Jun 2015
Amendment (b) Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 28-Sep-2018 GMT

2. Synopsis

Name of Investigational Product: Olaratumab	
Title of Study: A Phase 1 Study of Olaratumab in Japanese Patients with Advanced Soft Tissue Sarcoma or Advanced Solid Tumors	
Number of Planned Patients/Subjects: Enrolled: 24	**Phase of Development:** 1
Length of Study: First patient enrolled (assigned to therapy): March 2015 Estimated last patient visit: March 2019	

Objectives:

The primary objective of Part A is to evaluate the safety and tolerability of olaratumab in combination with doxorubicin in Japanese patients with advanced solid tumors, especially advanced soft tissue sarcoma.

The primary objective of Part B is to evaluate the pharmacokinetics (PK) profile of olaratumab in Japanese patients with advanced solid tumors.

The secondary objectives of Part A are:

- To evaluate the PK of olaratumab and doxorubicin
- To evaluate the immunogenicity of olaratumab
- To document any antitumor activity of olaratumab in combination with doxorubicin

The secondary objectives of Part B are:

- To evaluate the safety and tolerability of olaratumab
- To evaluate the immunogenicity of olaratumab
- To document any antitumor activity of olaratumab

The exploratory objective of Part A and Part B is to evaluate potentially relevant biomarkers related to the mechanism of olaratumab, the platelet-derived growth factor (PDGF) signaling pathway, and the pathobiology of cancer.

othersomeIStudy Design:

This study is a multicenter, non-randomized, open-label Phase 1 study consisting of 2 parts (Part A and Part B). Part A and Part B will be conducted in parallel.

Part A is designed to evaluate the safety and tolerability of olaratumab in combination with doxorubicin in Japanese patients with advanced solid tumors, especially advanced soft tissue sarcoma. This part consists of 3 cohorts. After the first 3 patients from Cohort 1 are enrolled, Cohort 2 can be opened based on safety assessment and after discussion between the investigator, the sponsor, and the Safety Assessment Committee. Cohort 3 can be opened after confirmation of tolerability in Cohort 2.

At least 6 patients will be assigned to each cohort and will receive the combination therapy of olaratumab and doxorubicin. One cycle is defined as 21 days, and the combination therapy will continue up to 6 cycles or until the cumulative dose of doxorubicin reaches 500 mg/m^2, whichever comes later.

Patients may continue to receive treatment until progressive disease, the development of unacceptable toxicity, noncompliance or withdrawal of consent by the patient, or investigator decision. If doxorubicin is discontinued, olaratumab monotherapy can be continued in the absence of progressive disease or other discontinuation criteria. For patients who discontinue olaratumab therapy during the first 6 cycles, doxorubicin may be continued (for up to 6 cycles or until the cumulative dose of doxorubicin reaches 500 mg/m^2, whichever comes later), provided no discontinuation criteria are met.

Part B is designed to evaluate the PK profile of olaratumab monotherapy in Japanese patients with advanced solid tumors. This part consists of 1 dose level. At least 6 patients will be assigned and receive the treatment of olaratumab. One cycle is defined as 21 days, and the treatment will continue until progressive disease or meeting other discontinuation criteria.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Part A

Japanese patients with advanced solid tumors, especially advanced soft tissue sarcoma which are not amenable to surgery and radiotherapy, and who are appropriate candidates for combination therapy of olaratumab and doxorubicin.

Part B

Japanese patients with advanced solid tumors who are appropriate candidates for olaratumab monotherapy after available standard therapies have failed to provide clinical benefit for their disease.

Investigational Product, Dosage, and Mode of Administration or Intervention:

Part A

- Cohort 1: 15 mg/kg of olaratumab on Day 1 and Day 8, and 25 mg/m^2 of doxorubicin on Day 1, Day 2, and Day 3 of every 21-day cycle.
- Cohort 2: 15 mg/kg of olaratumab on Day 1 and Day 8, and 75 mg/m^2 of doxorubicin on Day 1 of every 21-day cycle.
- Cohort 3: 20 mg/kg loading dose of olaratumab on Day 1 and Day 8 in Cycle 1, followed by 15 mg/kg on Day 1 and Day 8 in subsequent cycles, and 75 mg/m^2 of doxorubicin on Day 1 of every 21day-cycle.

Part B

This part consists of 1 dose level: 15 mg/kg of olaratumab on Day 1 and Day 8 of every 21-day cycle.

Planned Duration of Treatment:

Patients will be on treatment until one of the discontinuation criteria is met.
Treatment period: 21 days/cycle
Follow-up Period: 28 days

Criteria for Evaluation:

Safety: Dose-limiting toxicities, treatment-emergent adverse events (TEAEs) using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and the Medical Dictionary for Regulatory Activities (MedDRA), laboratory evaluations, vital signs, electrocardiograms and cardiac function as measured by echocardiogram.

Bioanalytical: Serum concentrations of olaratumab (Part A and B) and plasma concentrations of doxorubicin (Part A).

Pharmacokinetics: The primary parameters for analysis will be maximum observed concentration (C_{max}) and area under the concentration-time curve (AUC) from time 0 to the last time point with a measurable concentration, and AUC from time 0 to infinity of olaratumab and doxorubicin. Other noncompartmental parameters, such as half-life, clearance, and volume of distribution, may be reported.

Efficacy: Antitumor activity according to Response Evaluation Criteria in Solid Tumors version 1.1.

Biomarkers: Biomarkers related to the mechanism of olaratumab, the PDGF signaling pathway, and the pathobiology of cancer.

Statistical Methods:

Safety: Dose-limiting toxicities will be listed and summarized by frequency. Adverse events (AEs), including TEAEs, will be listed and summarized in frequency tables using MedDRA. Severity of AEs will be classified using CTCAE version 4.03. Other safety data, such as laboratory tests, echocardiography, and vital signs, will be listed and summarized, if appropriate.

Efficacy: Efficacy data will be listed. Also, efficacy data will be summarized using frequency table or summary statistics, depending on the characteristics of the data.

Pharmacokinetics: The PK parameters of olaratumab and doxorubicin will be computed by standard noncompartmental methods of analysis using Phoenix WinNonlin.

Biomarkers: Descriptive statistics for biomarkers will be provided.

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibodies
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 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.
Akt	protein kinase B
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
$AUC_{[0\text{-}96hr]}$	area under the concentration-time curve from time zero to hour 96
$AUC_{[0\text{-}168hr]}$	area under the concentration-time curve from time zero to hour 168
$AUC_{(0\text{-}tlast)}$	area under the concentration-time curve from time zero to the last time point with a measurable concentration
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).
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum observed concentration at steady state
C_{min}	minimum observed concentration
$C_{min,ss}$	minimum observed concentration at steady state
CL	clearance
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
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
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	Patients who are enrolled in the trial are those who were confirmed to be eligible and have been assigned to a 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 factors
HBV	hepatitis B virus

HCV	hepatitis C virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG1	immunoglobulin G subclass 1
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for data lock.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.
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.
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.
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
monitor	A person responsible for ensuring the investigator site complies with the monitoring plan, applicable local SOPs (if any), and global Medical SOPs. Monitors are trained on the investigational product(s), the protocol, informed consent document, any other written information provided to subjects, relevant SOPs, International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP), and all applicable laws (for example, privacy and data protection) and regulations.
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NOAEL	no-observable-adverse-effects levels

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.
patient	A subject with a defined disease.
PDGF	platelet-derived growth factor
PDGFRα	platelet-derived growth factor receptor α
PDGFRβ	platelet-derived growth factor receptor β
PK	pharmacokinetic(s)
PR	partial response
PS	performance status
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
SAC	Safety Assessment Committee
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.
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
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TK	toxicokinetic(s)
TPO	third-party organization
ULN	upper limit of normal
V	volume of distribution
VEGF	vascular endothelial growth factor

VEGFR	vascular endothelial growth factor receptor

A Phase 1 Study of Olaratumab in Japanese Patients with Advanced Soft Tissue Sarcoma or Advanced Solid Tumors

5. Introduction

5.1. Rationale and Justification for the Study

The term soft tissue sarcoma (STS) refers to a group of histologically distinct subtypes of cancer originating in the connective tissue. Soft tissue sarcoma is part of a rare and heterogeneous group of tumors that accounts for less than 1% of all adult cancers, and encompasses over 50 different subtypes. In Japan, the annual incidence rate is approximately 3 per 100,000 (Nakamura 2011). The most common types of STS in adults in Japan are malignant fibrous histiocytoma (26%), liposarcoma (23%), synovial sarcoma (9.7%), rhabdomyosarcoma (6.9%), and malignant peripheral nerve sheath tumor (6.8%) (JOA 2002). These tumors exhibit a wide range of differing behaviors and underlying molecular pathologies, and can arise anywhere in the body. The most common sites are lower limbs (26%), retroperitoneal and intraperitoneal (25%), internal organs including gastrointestinal stromal tumor (25%), upper limbs (11%), thorax (8%), and head and neck (5%) (JOA 2012).

Surgical resection, sometimes in combination with adjuvant radiotherapy is critical to the management of locoregional disease. In the locally advanced or metastatic disease settings, chemotherapy in this setting is essentially palliative in intent; doxorubicin is the standard of care for the majority of such patients, with an associated response rate of 10%-30% (D'adamo et al. 2005). Some trials have investigated a variety of combination chemotherapeutic regimens (variously employing ifosfamide, doxorubicin, vincristine, cisplatin, and dacarbazine, among others), which in some cases have yielded improvements in response rate, but have had little impact on survival. In Japan, doxorubicin monotherapy is preferred over combination use for unresectable or metastatic disease based on the result of meta-analysis (Bramwell et al. 2000), and the addition of ifosfamide to doxorubicin is used as neo-adjuvant/adjuvant settings (Iwamoto and Tanaka 2012). However, these treatments have reached a therapeutic plateau and new therapies able to improve treatment outcome are required.

Platelet-derived growth factor receptor α (PDGFRα) is a receptor tyrosine kinase that can be activated by platelet-derived growth factor (PDGF)-AA, -AB, -BB, and -CC (Heldin et al. 1998; Li et al. 2000). These growth factors are dimeric molecules composed of disulfide-linked polypeptide chains that bind to 2 receptors simultaneously and induce receptor dimerization, autophosphorylation, and intracellular signaling. A number of observations suggest that the PDGFRα plays an important role in tumorigenesis and tumor progression. Many cancer types have been shown to consistently express PDGFRα on tumor tissues, including osteosarcoma, chondrosarcoma, prostate cancer, breast cancer, ovarian cancer, glioma, melanoma, bone cancers and others. In malignant disease, the PDGF/PDGFRα axis is effective in promoting tumor growth and proliferation through both autocrine and paracrine mechanisms. PDGFRα is expressed on stromal cells, as well as on the cancer cells themselves, within certain tumors. Furthermore, studies have shown that PDGF/PDGFRα signaling affects tumor vasculature

through paracrine mediation of vascular endothelial growth factor (VEGF) production (de Jong et al. 1998; Ostman et al. 2001; Zhang et al. 2003; Shah et al. 2010). In addition to being present, PDGFRα has been shown to be highly phosphorylated in a subset of lung cancer cell lines and tumors of patients (Rikova et al. 2007). Due to its potential broad role in transformation, metastasis, and progression, PDGFRα could be an important therapeutic target for cancer treatment. Neutralizing antibodies to PDGFRα which have been already reported (LaRochelle et al. 1993; Lokker et al. 1997) inhibited the growth in vitro of PDGFRα-positive cells induced to overexpress PDGF (LaRochelle et al. 1993).

Olaratumab (LY3012207) is a recombinant human monoclonal antibody of the immunoglobulin G subclass 1 (IgG1), which specifically targets the human PDGFRα. The antibody possesses high-affinity binding for PDGFRα and blocks PDGF-AA, -BB, and -CC ligands from binding to the receptor. As a result, olaratumab inhibits ligand-induced receptor autophosphorylation and phosphorylation of the downstream signaling molecules protein kinase B (Akt) and mitogen-activated protein kinase (MAPK). Olaratumab monotherapy inhibits tumor cell growth response to PDGF signaling and survival in multiple tumor types both in vivo and in vitro. Furthermore, in human tumor xenograft models including soft tissue sarcoma (leiomyosarcoma), olaratumab demonstrates antitumor activity as a single agent and in combination with doxorubicin (Loizos et al. 2005; data on file). Based on this antitumor cell activity in tumor cell models, olaratumab has been advanced into human clinical studies.

A multicenter, open-label, dose escalation Phase 1 study (Study CP15-0601; I5B-IE-JGDC [JGDC]) of olaratumab, which has been conducted in patients with advanced solid tumors and lymphomas who no longer respond to standard therapy or for whom no standard therapy is available, has shown a favorable short- and long-term toxicity profile. No dose-limiting toxicities (DLTs) were observed in 4, 8, or 16 mg/kg weekly or in 15 or 20 mg/kg every other week. The most common adverse events (AEs), regardless of severity, experienced by ≥20% of patients were fatigue (42.1%), constipation (36.8%), diarrhea (26.3%), nausea (26.3%), and pyrexia (26.3%) (Chiorean et al. 2014). Grade 3 AEs were few and no Grade 4 or 5 events were reported.

A Phase 1 study for solid tumors in Japanese patients (Study CP15-0907; I5B-IE-JGDF [JGDF]) also demonstrated a well-tolerated safety profile in olaratumab monotherapy administered every 2 weeks (20 mg/kg) or on Days 1 and 8 every 3 weeks (10 or 15 mg/kg) without any DLTs (Doi et al. 2014).

A Phase 1b/2 randomized study evaluating the efficacy of doxorubicin with or without olaratumab in the treatment of advanced STS (Study CP15-0806; I5B-IE-JGDG [JGDG]) is currently ongoing. A preplanned efficacy interim analysis has demonstrated prolonged progression-free survival and overall survival when olaratumab (15 mg/kg on Days 1 and 8 of each 21-day cycle) was given with doxorubicin (75 mg/m^2 on Day 1 of each cycle). The toxicity profile of olaratumab combined with doxorubicin was acceptable.

In the olaratumab plus doxorubicin treatment arm, there was a slight increase in known doxorubicin-related toxicities events such as nausea, vomiting, and neutropenia. No difference

in febrile neutropenia or major gastrointestinal toxicities was observed and the overall incidence of life-threatening toxicities was similar between the treatment and control arms. Also, increased cardiotoxicity (14.1% in the olaratumab plus doxorubicin arm vs. 9.2% in the doxorubicin arm) was observed. However, this was in line with what could be expected given the higher median number of cycles of doxorubicin received by patients in the treatment arm.

Finally, the scientific justification of investigating olaratumab combined with doxorubicin in advanced STS is compelling based on the role of PDGFRα in tumor cell survival and proliferation and the evidence of antitumor effects in tumor xenograft models. The recent (Studies JGDC and JGDF) and ongoing (Study JGDG) clinical trials have shown a well-tolerated safety profile in olaratumab monotherapy and in combination with doxorubicin. Furthermore, the preliminarily observed prolongation of progression-free survival and overall survival in Study JGDG provides additional justification to conduct this study (Study I5B-JE-JGDK [JGDK]). Part A of Study JGDK is designed to evaluate the safety and tolerability of olaratumab when administered in combination with doxorubicin to Japanese patients with advanced solid tumors, especially advanced STS. This safety information will allow Japanese patients to participate in the following global Phase 3 study.

The sponsor, 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. Rationale for Amendments

5.2.1. Rationale for Amendment (a)

The study was amended to add Cohort 3 in Part A to confirm the safety and tolerability of 20 mg/kg of olaratumab as the loading dose (Cycle 1), followed by 15 mg/kg in subsequent cycles, and 75 mg/m^2 of doxorubicin in every cycle.

5.2.2. Rationale for Amendment (b)

The study was amended to reduce unnecessary interventions and physical or non-physical burden for the patients after enough data was obtained to assess the primary objective and the secondary objectives.

5.3. Objectives

5.3.1. Primary Objective

The study is divided into 2 parts:

The primary objective of Part A is to evaluate the safety and tolerability of olaratumab in combination with doxorubicin in Japanese patients with advanced solid tumors, especially STS.

The primary objective of Part B is to evaluate the pharmacokinetics (PK) profile of olaratumab in Japanese patients with advanced solid tumors.

5.3.2. Secondary Objectives

The secondary objectives of Part A are:

- To evaluate the PK of olaratumab and doxorubicin
- To evaluate the immunogenicity of olaratumab
- To document any antitumor activity of olaratumab in combination with doxorubicin

The secondary objectives of Part B are:

- To evaluate the safety and tolerability of olaratumab
- To evaluate the immunogenicity of olaratumab
- To document any antitumor activity of olaratumab

5.3.3. Exploratory Objective

The exploratory objective of Part A and Part B is to evaluate potentially relevant biomarkers related to the mechanism of olaratumab, the PDGF signaling pathway, and the pathobiology of cancer.

5.4. General Introduction to Olaratumab

Olaratumab is a fully humanized monoclonal IgG1 antibody and inhibits PDGF ligands binding to the extracellular domain of PDGFR, resulting in inhibition of phosphorylation of the downstream signaling molecules such as Akt and MAPK, and has demonstrated activity in vitro and in vivo systems on cancer models known to be driven by a PDGF-PDGFRα autocrine loop (Gerber et al. 2012).

As of 31 March 2014, olaratumab has been administered to 461 patients in 8 clinical studies: 4 studies in monotherapy setting and 4 studies in combination with other anticancer agents. The primary tumor types in the clinical studies include solid tumors (2), ovarian cancer (1), non-small-cell-lung cancer (1), castration refractory prostate cancer (1), STS (1), glioblastoma multiforme (1), and gastrointestinal stromal tumors (1). As of 31 March 2014, a total of 129 patients with advanced STS have been treated in Study JGDG and interim safety data is available. The 129 patients in Study JGDG are comprised of 64 patients in Arm A (olaratumab plus doxorubicin) and 65 patients in Arm B (doxorubicin monotherapy). Overall, the frequency of any AEs was similar across the 2 arms (Arm A: 98.4%; Arm B: 98.5%). The cardiotoxicity increased, but was in line with what could be expected with the higher cumulative dose of doxorubicin in Arm A.

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

5.4.1. Mechanism of Action and In Vitro/In Vivo Activity

Unlike some tyrosine-kinase inhibitors which are anticancer agents that target PDGF/PDGFR signaling simultaneously with other targets such as c-kit, vascular endothelial growth factor (VEGF), and VEGF receptor (VEGFR), olaratumab is specific to PDGFRα and binds with high affinity (K_d: 0.04nM). Preclinical studies conducted with olaratumab as a single agent or in combination with cytotoxic chemotherapeutic agents have demonstrated antimitogenic activity in cell lines and antitumor growth activity in human xenografts models. Olaratumab blockade of PDGFRα function also inhibited skeletal metastases by human prostate cancer cells in a mouse model. Olaratumab does not cross-react with PDGFRβ or with murine PDGFRα. Therefore, in vivo experiments in mice bearing human tumor xenografts treated with olaratumab may underestimate the potential anticancer activity of olaratumab, because olaratumab cannot react with mouse stroma or regulate cancer-associated vasculature. In humans, olaratumab is expected to target and inhibit PDGFRα expressed in both tumor and stroma, thereby potentially inhibiting tumor, stroma, and vasculature (Shah et al. 2010).

5.4.2. Nonclinical Pharmacokinetics

The PK profile of olaratumab was characterized in mice, and the PK and toxicokinetics (TK) were determined as part of the monkey toxicology studies. The PK and TK of olaratumab in mice and monkeys were generally consistent with that expected for a monoclonal antibody, characterized by a moderate elimination half-life ($t_{1/2}$) and clearance (CL), and a volume of distribution (V) approximately equal to the vascular space. Increases in exposure were generally proportional to or greater than proportional to the increase in dose. Accumulation of olaratumab was evident after repeated dosing in monkeys.

The formation of antidrug antibodies (ADA) was assessed in all monkey studies. Attempts to evaluate the formation of ADA were often confounded by high circulating concentrations of olaratumab; however, ADA were measurable in several individual animals following repeated dosing in the toxicology studies, particularly in the low- and mid-dose groups. The predictive value of this nonclinical finding relative to the potential occurrence of immunogenicity in humans is unclear.

The nonclinical distribution of olaratumab has not been assessed because monoclonal antibodies are largely confined to the extracellular space. Similarly, metabolism studies of olaratumab have not been conducted since the catabolism of antibodies by mammalian systems is well understood.

5.4.3. Nonclinical Toxicology

A standard nonclinical toxicology program was conducted to assess the safety of olaratumab. The key studies using cynomolgus monkeys assessed the toxicity, TK, and development of antibodies to olaratumab and their potential impact on TK after administration by intravenous infusion over 5 weeks (4 doses), or 13 and 39 weeks with weekly dosing, followed by recovery periods of 7 or 8 weeks. Cardiovascular safety parameters (blood pressure, heart rate, and

electrocardiogram [ECG]) and neurological effects based on clinical observations were evaluated in the toxicity studies.

No clear olaratumab treatment-related adverse effects were noted in the toxicity studies. A single female treated for 39 weeks with 75 mg/kg was noted with mildly to moderately increased alanine aminotransferase (ALT), minimal individual cell necrosis, and moderate infiltrates in the liver, but this effect was not considered adverse or clearly attributable to treatment. Therefore, the no-observable-adverse-effects levels (NOAEL) were established as the highest test doses, 50 mg/kg in the 5-week study and 75 mg/kg in the 13- and 39-week studies. Antidrug antibodies were measurable in several animals following repeated dosing in the studies, mainly at the low- and mid-dose levels.

Development and reproductive toxicity studies of olaratumab in animals have not yet been conducted. For a monoclonal antibody, genotoxicity studies are not relevant, and were therefore not conducted for olaratumab.

In summary, weekly administration of olaratumab by intravenous infusion for up to 39 weeks was well tolerated and not associated with the development of any adverse effects. The monkey serum minimum observed concentration (C_{min}) (1164 μg/mL) at the NOAEL (75 mg/kg) in the 39-week study was approximately 4.5-fold greater than the threshold C_{min} (260 μg/mL) believed to be needed for antitumor activity based on tumor xenograft models. The area under the concentration-time curve from time zero to hour 168 ($AUC_{[0\text{-}168hr]}$) (284976 hr•μg/mL) following the last infusion of 75 mg/kg in the 39-week study was approximately 16.5-fold greater than exposures of olaratumab that are anticipated to be needed for antitumor activity in humans based on animal tumor models (area under the concentration-time curve from time zero to hour 96; $AUC_{[0\text{-}96hr]}$ = 17184 hr•μg/mL). Therefore, the cynomolgus monkey study adequately evaluated the safety of olaratumab at exposures that appreciably exceed those anticipated to be evaluated and effective in humans with advanced cancer.

5.4.4. Olaratumab Pharmacokinetics

Olaratumab serum concentration data are currently available from 2 Phase 1 studies, JGDC and JGDF, as well as from 5 Phase 2 studies, I5B-IE JGDA (JGDA), I5B-IE-JGDB (JGDB), I5B-IE-JGDE (JGDE), JGDG and I5B-IE-JGDH (JGDH). The serum concentration data available for Studies JGDA, JGDC, and JGDF were, however, generated using an enzyme-linked immunosorbent assay that was not fully validated. The quantitative PK results derived from the aforementioned 3 studies can therefore only be used as supporting evidence and will only be discussed briefly in the interest of completeness. The human serum assay has been subsequently optimized and validated and is being used to support all ongoing and future studies, including Study JGDK. Pharmacokinetic data were obtained using this validated serum assay from 4 Phase 2 studies, including Study JGDG.

In Study JGDG, olaratumab was tested at the dose of 15 mg/kg administered as a 60-minute infusion on Day 1 and 8 of a 21-day cycle and was tested in combination with doxorubicin in patients with STS. Steady state seemed to be reached during Cycle 3, and maximum observed concentration at steady state ($C_{max,ss}$) and minimum observed concentration at steady state

($C_{min,ss}$) ranged from 341 to 411 µg/mL and from 113 to 121 µg/mL, respectively, across Cycle 3 to 6. A mean $t_{1/2}$ estimate of 6.7 days was obtained from 7 subjects after the second dose of Cycle 1. Individual $t_{1/2}$ estimates of 14.4 and 6.7 days were obtained after the second dose of Cycle 3. It should be pointed out that the $t_{1/2}$ estimates reported here are likely to be dependent on the duration of the sampling time, which never exceeds 168 and 336 hours after the first and second dose of each cycle, respectively.

Pharmacokinetic data in other Phase 2 studies may be found in Section 6 of the IB.

The PK of olaratumab in serum had been previously studied in patients with advanced solid tumors in the Phase 1 studies: JGDC (US patients) and JGDF (Japanese patients). Olaratumab was tested at various doses ranging from 4 to 20 mg/kg administered as 1-hour intravenous infusions once a week, once every 2 weeks, or on Day 1 and Day 8 of a 21-day cycle. The concentration-time profile of olaratumab in serum following a single infusion and multiple infusions administered either once a week or once every 2 weeks in Studies JGDC and JGDF suggest that the PK of olaratumab is similar between US and Japanese patients. As discussed previously, PK data in Studies JGDC and JGDF were obtained with an assay that was not fully validated and should be interpreted with caution.

5.5. Rationale for Selection of Dose

Olaratumab 15 mg/kg administered intravenously on Days 1 and 8 of a 21-day cycle was selected as the dosage for this study (except for Cohort 3 in Part A) based on interim efficacy and safety data from Study JGDG, an open-label Phase 2 study, where a combination of 15 mg/kg olaratumab administered intravenously on Days 1 and 8 and 75 mg/m^2 doxorubicin administered intravenously on Day 1 of a 21-day cycle was tested versus doxorubicin alone at a dose of 75 mg/m^2 in patients with metastatic or locally advanced STS that was not amenable to treatment with surgery or curative radiotherapy.

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

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

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

The dosing strategy adopted for Cohort 3 of Part A of this study therefore consists of a loading cycle wherein a dose of 20 mg/kg will be administered on Day 1 and Day 8, followed by 15 mg/kg administered on Day 1 and Day 8 of every subsequent cycle.

Doxorubicin 25 mg/m^2 administered on Day 1, Day 2, and Day 3 of a 21-day cycle (3 intravenous administrations/cycle) was selected for Cohort 1 in Part A based on the approved dose in Japan. In addition, doxorubicin 75 mg/m^2 administered on Day 1 (single intravenous administration/cycle) of a 21 day-cycle was selected for Cohort 2 and 3 in Part A based on the interim efficacy data of Study JGDG and will be used in the upcoming Phase 3 study.

In Japan, doxorubicin monotherapy is most commonly used as first-line treatment for unresectable or metastatic STS patients. Doxorubicin treatment for STS was approved by Public Knowledge-Based Submission in Japan in February 2005. The label dosage of doxorubicin is 20-30 mg/m^2 for 3 consecutive days with a maximum cumulative dose of 500 mg/m^2 due to risk of myocardial damage. The globally approved dose, except in Japan, of doxorubicin is 75 mg/m^2 (single intravenous administration/cycle); however, the single intravenous administration/cycle of doxorubicin is used for patients in Japan clinical practices.

Interim data from Study JGDG, where olaratumab at the dose of 15 mg/kg administered on Days 1 and 8 of a 21-day cycle was evaluated in combination with doxorubicin at a dose of 75 mg/m^2 on Day 1 (single intravenous administration/cycle), indicated efficacy in patients with metastatic or locally advanced STS that is not amenable to treatment with surgery or curative radiotherapy.

Given the favorable safety and clinical activity data observed so far in Study JGDG and simulations performed with the current PK model, the doses of 15 or 20 mg/kg olaratumab and 25 mg/m^2 on Day 1, 2, and 3 or 75 mg/m^2 on Day 1 of a 21-day cycle doxorubicin were selected for Study JGDK.

6. Investigational Plan

6.1. Study Population

All patients meeting the eligibility requirements will be considered for enrollment. The investigators or the sponsor will not grant exceptions to eligibility criteria. Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened; however, in case that the sponsor and the investigators judge it appropriate (ie, borderline screen failure), retest may be allowed. 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] Part A

Have histological or cytological evidence of a diagnosis of advanced or metastatic solid tumor, especially STS (other than Kaposi's sarcoma and gastrointestinal stromal tumors), which is not amenable to treatment with surgery or radiotherapy. The patient must be, in the judgment of the investigator, an appropriate candidate for olaratumab and doxorubicin therapy. Patients other than STS patients must be an appropriate candidate for olaratumab therapy in combination with doxorubicin after available standard therapies have failed to provide clinical benefit for their disease.

Part B

Have histological or cytological evidence of a diagnosis of solid tumor that is advanced or metastatic. The patient must be, in the judgment of the investigator, an appropriate candidate for olaratumab monotherapy after available standard therapies have failed to provide clinical benefit for their disease.

[2] Have the presence of measurable or nonmeasurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al. 2009).

[3] Are ≥20 years of age.

[4] Have given written informed consent prior to any study-specific procedures.

[5] Have adequate organ and coagulation function, including:

a. Hematologic: Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and hemoglobin ≥9 g/dL.
b. Hepatic: Bilirubin ≤1.5 times the upper limit of normal (ULN) and ALT and aspartate aminotransferase (AST) ≤3.0 ×ULN.
c. Renal: Serum creatinine ≤1.5 ×ULN. If creatinine is above the ULN, creatinine clearance is ≥45 mL/min (Attachment 7).
d. Coagulation: international normalized ratio (INR) ≤1.5 and prothrombin time ≤1.5 ×ULN, if not receiving anticoagulation therapy. Patients on full dose anticoagulation must be on a stable dose of oral anticoagulant or low molecular

weight heparin, and if on warfarin must have therapeutic INR and have no active bleeding (defined as within 14 days prior to first dose of study medication) or pathological condition that carries a high risk of bleeding (eg, tumor involving major vessels or known varices)

[6] Have an ECOG PS of ≤1.

[7] Have discontinued previous treatments for cancer and recovered from the acute effects of therapy.

[8] (Part A only)
Have a prestudy echocardiogram with an actual left ventricular ejection fraction (LVEF) ≥50%, within 21 days prior to first dose of study medication.

[9] All patients agree to use a reliable method of birth control and to not donate sperm during the study and for at least 3 months following last dose of study drug. Acceptable methods of birth control include vasectomy (pipe cut), tubal ligation, barrier method (eg, condoms or pessary) with spermicide, an intrauterine device which has been in place for at least 3 months before first dose of study drug, or the oral contraceptive pill taken for at least 3 months before first dose of study drug.

[10] Female patients must either be women not of child-bearing potential due to surgical sterilization (at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history, or menopause.
or

women of child-bearing potential who test negative for pregnancy within 7 days before the first dose of study drug based on serum or urine pregnancy test and agree not to breast feed during the study and for 3 months following the last dose of the study drug(s)

Menopausal women include women with either

a. 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 (eg, oral contraceptives, hormones, gonadotropin releasing hormone, antiestrogens, selective estrogen receptor modulators, or chemotherapy).
or

b. spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone level greater than 40 mIU/mL.

[11] Have an estimated life expectancy of ≥3 months in the judgment of the investigator.

6.1.2. Exclusion Criteria

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

[12] Have received treatment within 21 days of the initial dose of study drug with an investigational product or non-approved use of a drug or device (other than the study drug/device used in this study) for non-cancer indications or are concurrently enrolled

in any other type of medical research judged not to be scientifically or medically compatible with this study.

[13] (Part A only)
Have received prior treatment with doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthracenediones (ie, mitoxantrone).

[14] (Part A only)
Have received prior radiation therapy to the mediastinal/pericardial area.

[15] Have symptomatic central nervous system (CNS) malignancy or metastasis (screening not required). Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids and/or anticonvulsants, and their disease is asymptomatic and radiographically stable for at least 60 days.

[16] Have an elective or a planned major surgery to be performed during the course of the study.

[17] Have an uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure > class II of the New York Heart Association guideline, severe myocardial insufficiency, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

[18] Have unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction 6 months prior to study entry.

[19] Have a known allergy to any of the treatment components.

[20] Have a history of allergic reactions attributed to compounds of chemical or biologic composition similar to that of olaratumab.

[21] Have a known active fungal, bacterial, and/or known viral infection, including:

a. human immunodeficiency virus (screening is not required);
b. hepatitis A virus (screening is not required);
c. hepatitis B virus (HBV) or hepatitis C virus (HCV) (screening is required – a documentation of a negative test result within 6 months prior to enrollment must be available for HBV [see the details below*] and HCV [antibodies or ribonucleic acid according to local standard]).

   * have evidence of, or test positive for, HBV. A positive test for HBV is defined as:
   positive for hepatitis B surface antigen
   or
   positive for anti-hepatitis B core antibody and positive for HBV deoxyribonucleic acid (DNA)
   or
   positive for anti-hepatitis B surface antibody and positive HBV DNA.

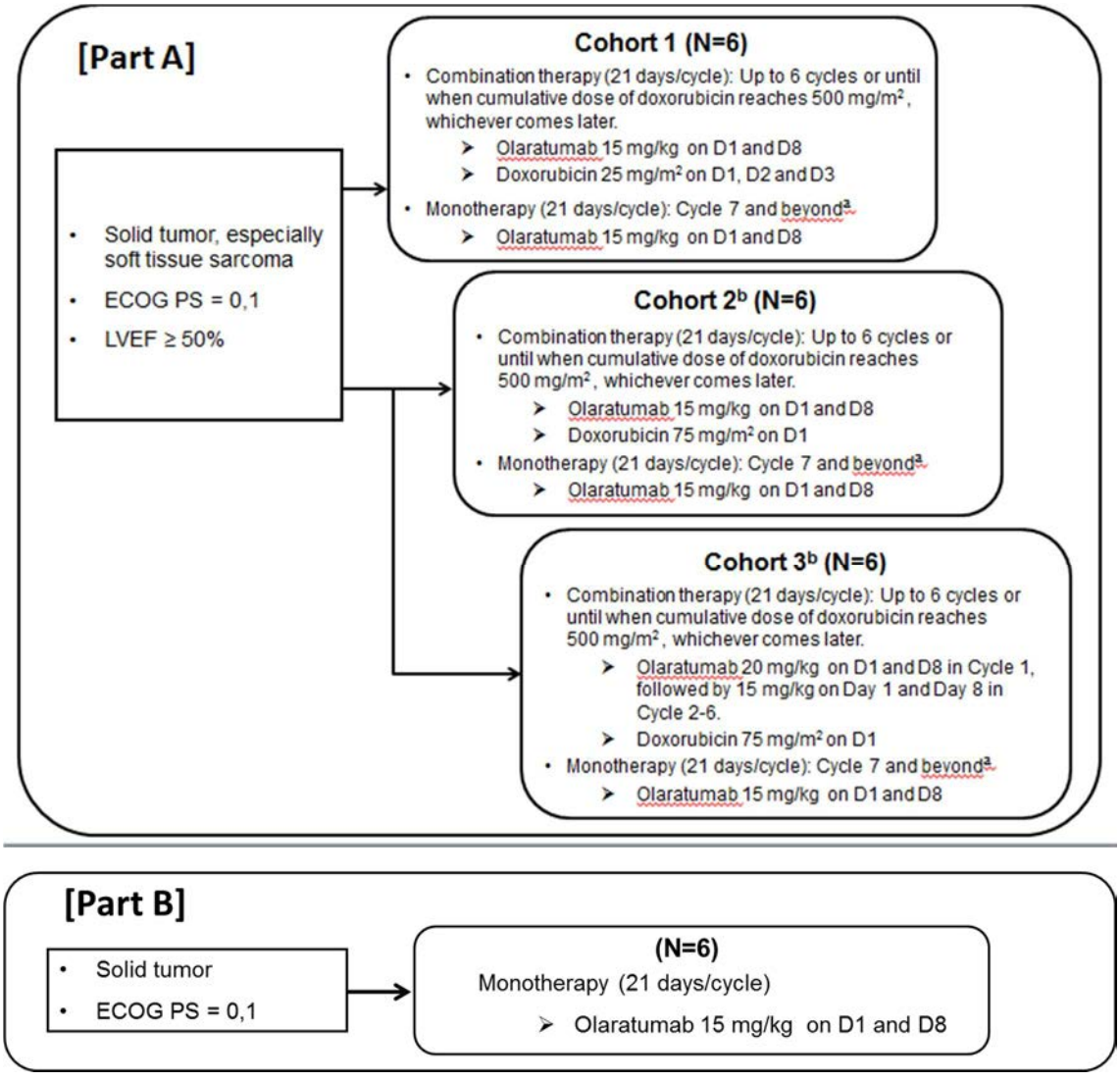
[22] Have a corrected QT interval of >470 msec on screening ECG

[23] Have a second primary malignancy that, in the judgment of the investigator and sponsor, may affect the interpretation of results.

6.2. Summary of Study Design

This is a multicenter, nonrandomized, open-label, Phase 1 study. The study is divided into 2 parts, Part A and Part B. Part A and Part B will be conducted in parallel. The DLT evaluation of Cohort 1, 2 and 3 in Part A will be performed independently. The study design is summarized in Figure JGDK.6.1.

Refer to Attachment 1 for the Study Schedule.



Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance score; D= day; N = number of patients; LVEF = left ventricular ejection fraction

[a] For patients whose cumulative dose of doxorubicin does not reach 500 mg/m2 during the first 6 cycles due to dose reductions or omissions, doxorubicin can be administrated up to 500 mg/m2 on Cycle 7 and beyond, at the discretion of the investigator.

[b] Refer to Section 7.2.1.4 for the timing to open Cohort 2 and 3.

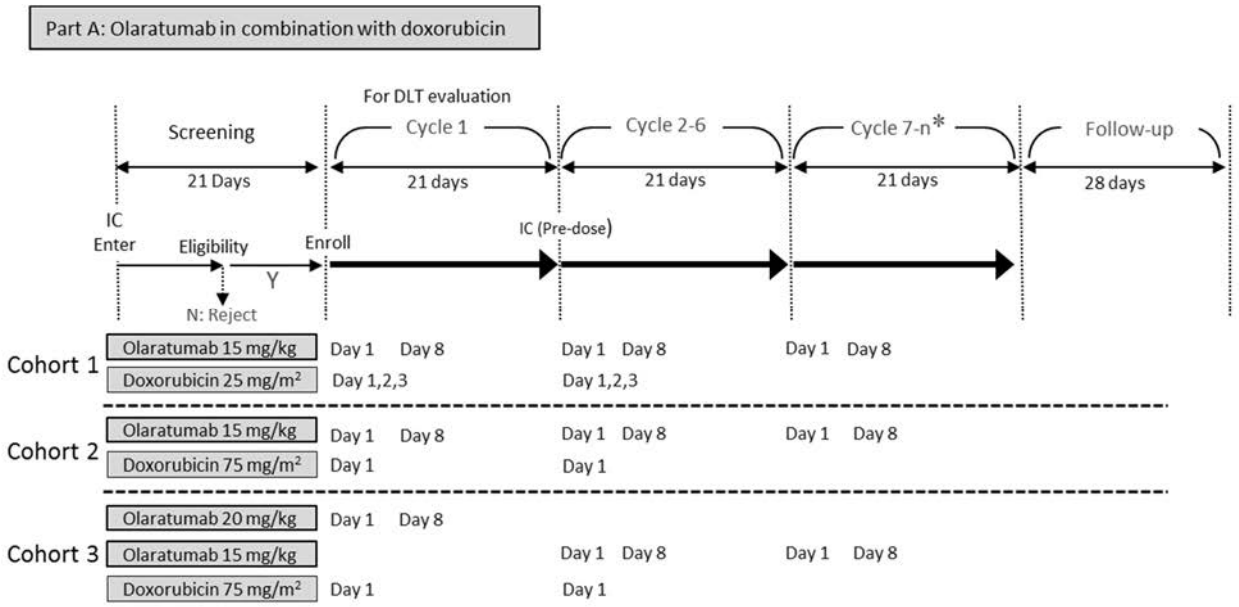
Figure JGDK.6.1. Illustration of study design for Protocol I5B-JE-JGDK.

Part A is designed to evaluate the safety and tolerability of olaratumab in combination with doxorubicin in Japanese patients with advanced solid tumors, especially advanced STS.

Part A consists of 3 cohorts (Figure JGDK.6.1). At least 6 patients will be assigned to Cohort 1. Similarly, at least 6 patients will be assigned to Cohort 2 and 3:

- Cohort 1: 15 mg/kg of olaratumab on Day 1 and Day 8, and 25 mg/m^2 of doxorubicin on Day 1, Day 2, and Day 3 up to 6 cycles or until when cumulative dose of doxorubicin reaches 500 mg/m^2, whichever comes later, every 21 day-cycle.
- Cohort 2: 15 mg/kg of olaratumab on Day 1 and Day 8, and 75 mg/m^2 of doxorubicin on Day 1 up to 6 cycles or a cumulative dose of doxorubicin reaches 500 mg/m^2, whichever comes later, every 21 day-cycle.
- Cohort 3: 20 mg/kg loading dose of olaratumab on Day 1 and Day 8 in Cycle 1, followed by 15 mg/kg on Day 1 and Day 8 in subsequent cycles, and 75 mg/m^2 of doxorubicin on Day 1 up to 6 cycles or a cumulative dose of doxorubicin reaches 500 mg/m^2, whichever comes later, every 21 day-cycle.

An overview of the study design for Part A is shown in Figure JGDK.6.2.

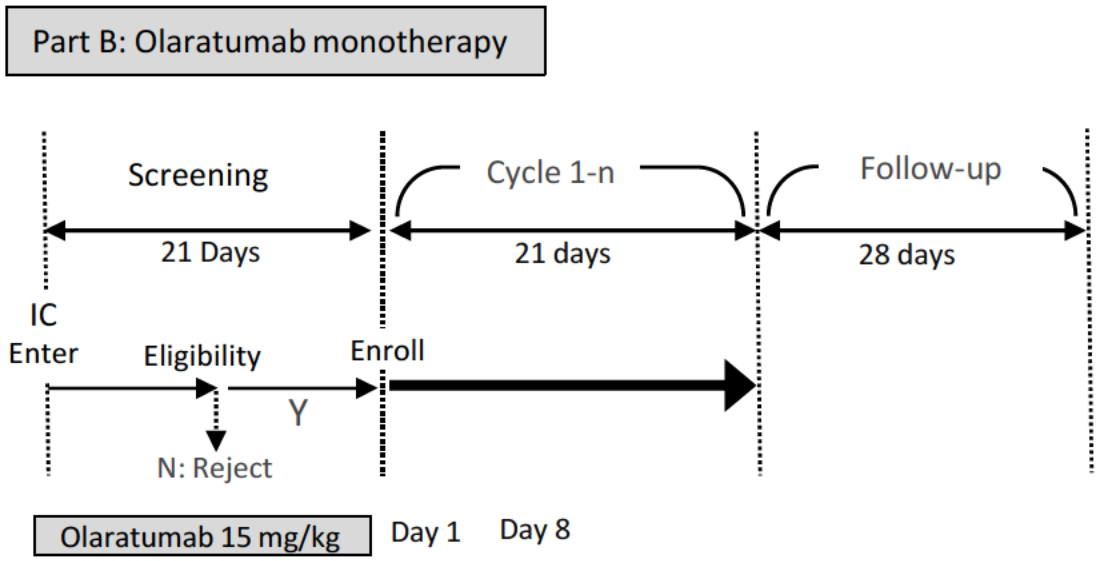


Abbreviations: DLT = dose-limiting toxicity; IC = informed consent; n = number; N = no; Y = yes.

Figure JGDK.6.2. Illustration of study schedule in Part A.

Part B is designed to evaluate the PK profile of olaratumab monotherapy in Japanese patients with advanced solid tumors. This part consists of 1 dose regimen (Figure JGDK.6.1). At least 6 patients will be assigned to receive olaratumab monotherapy treatment: 15 mg/kg of olaratumab on Day 1 and Day 8 every 21 day-cycle.

An overview of the study design for Part B is shown in Figure JGDK.6.3.



Abbreviations: IC = informed consent; n = number; N= no; Y = yes.

Figure JGDK.6.3. Illustration of study schedule in Part B.

6.3. Discontinuations

6.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor clinical research physician (CRP) and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product 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 investigational product 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 investigational product.

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

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator/Physician Decision
  - the investigator/physician decides that the patient should be discontinued from the study or study drug(s)
  - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug(s) occurs prior to introduction of the other agent
- Patient Decision
  - the patient requests to be discontinued from the study or study drug
- Sponsor Decision
  - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- The patient has evidence of objective progressive disease by radiological assessments (RECIST version 1.1) or deteriorating clinical symptoms of progressive disease. (Patients with objective progressive disease can be treated continuously based on the clinical symptoms at the discretion of the investigator.)
- The patient experiences unacceptable toxicity.
- The patient is significant noncompliant with study procedures and/or treatment (Section 7.6).
- The patient becomes pregnant.
- Both doxorubicin and olaratumab in Part A or olaratumab in Part B are discontinued (Section 7.2.2.1).

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

6.3.2. Discontinuation of Study Sites

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

6.3.3. Discontinuation of the Study

The study will be discontinued if Lilly, while considering the rights, safety, and well-being of the patient(s), judges it 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

Olaratumab will be supplied as a sterile preservative-free solution for intravenous 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 pharmacopeia grade. Each single-use vial of olaratumab is packaged in a 50-mL nominal volume United States Pharmacopeia type I glass vial, stoppered with a FluroTec® coated latex-free stopper, and sealed with an aluminum seal and a flip-off cap.

Olaratumab must be stored under refrigeration at 2°C to 8°C with protection from light. The detailed information is described in a separate procedural manual.

For doxorubicin, investigators should consult the separate procedural manual that will be provided by sponsor or its representative/delegate for complete packaging and labeling information. Doxorubicin hydrochloride will be supplied as one of clinical study materials by Lilly.

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

7.2. Study Drug Administration

The investigator or designee is responsible for:

- explaining the correct use of the investigational agent(s) and planned duration of each individual's treatment to the site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of study drug dispensation and collection, and
- returning 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(s) so that the situation can be assessed.

7.2.1. Dosing Schedule

The dosing schedule and mode of administration are summarized in Table JGDK.7.1.

Table JGDK.7.1. Dosing Regimens (21-day cycles)

		Drug	Treatment	Day	Infusion duration
Part A	Cohort 1	Olaratumab[a]	15 mg/kg I.V. infusion	Days 1 and 8	Approximately 60 minutes
		Doxorubicin[a,b]	25 mg/m^2 I.V. infusion	Days 1, 2, 3	Approximately 30 minutes
	Cohort 2	Olaratumab[a]	15 mg/kg I.V. infusion	Days 1 and 8	Approximately 60 minutes
		Doxorubicin[a,b]	75 mg/m^2 I.V. infusion	Days 1	Approximately 30 minutes
	Cohort 3	Olaratumab[a]	20 mg/kg I.V. infusion	Days 1 and 8 in Cycle 1	Approximately 60 minutes
			15 mg/kg I.V. infusion	Days 1 and 8 in Cycle 2 and beyond	Approximately 60 minutes
		Doxorubicin[a,b]	75 mg/m^2 I.V. infusion	Days 1	Approximately 30 minutes
Part B		Olaratumab	15 mg/kg I.V. infusion	Days 1 and 8	Approximately 60 minutes

Abbreviation: I.V. = intravenous.

[a] Doxorubicin will be administered approximately 1 hour after the completion of the olaratumab infusion on the days when both olaratumab and doxorubicin are administered.

[b] Doxorubicin administration in each 21-day cycle up to 6 cycles or until when a cumulative dose reaches 500 mg/m^2, whichever comes later.

7.2.1.1. Olaratumab

With the exception of the 20 mg/kg loading dose of olaratumab on Days 1 and 8 in Cycle 1 of Cohort 3, all patients will receive 15 mg/kg of olaratumab on Days 1 and 8 of each 21 day treatment cycle, administered as an intravenous infusion over approximately 60 minutes, until progressive disease or meeting the other discontinuation criteria. Patients enrolled in Part A can be hospitalized for the first 8 days in Cycle 1, according to routine institutional practice.

The dose of olaratumab is dependent upon the patient's weight in kilograms. A change of weight ≥10% (increase or decrease) from baseline will result in re-calculation of olaratumab dose to be administered.

7.2.1.2. Doxorubicin

In Part A only, all patients will receive 25 mg/m^2 of doxorubicin on Day 1/2/3 (Cohort 1) or 75 mg/m^2 of doxorubicin on Day 1 (Cohort 2 and 3) of each 21-day cycle, administered as an intravenous infusion over approximately 30 minutes. Doxorubicin will be administered for up to 6 cycles until progressive disease or meeting the other discontinuation criteria. For patients whose cumulative dose of doxorubicin does not reach 500 mg/m^2 during the first 6 cycles (because of dose reductions or omissions), doxorubicin can be administrated up to 500 mg/m^2 at the following cycles at the discretion of the investigator. On the days when both olaratumab and

doxorubicin are administered, doxorubicin will be administered approximately 1 hour after the completion of the olaratumab infusion.

If a patient completes 6 cycles, olaratumab monotherapy can be continued in the absence of disease progression or other discontinuation criteria.

If doxorubicin is discontinued (eg, for reasons of toxicity), olaratumab monotherapy can be continued. For patients who discontinue olaratumab during the first 6 cycles of treatment, doxorubicin may be continued (for up to 6 cycles or up to 500 mg/m^2 at the discretion of the investigator).

The dose of doxorubicin will be calculated using body surface area and is dependent upon the patient's baseline height in centimeters. A change of weight ≥10% from baseline will result in re-calculation of doxorubicin dose to be administered based on body surface area.

7.2.1.3. Dose-Limiting Toxicity Determination (Part A)

Dose-limiting toxicity is defined as an AE during Cycle 1 (first 21 days from Day 1 in Cycle 1) that is possibly related to the study drug(s) (olaratumab and/or doxorubicin) and fulfills any one of the following criteria using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (v4.03):

- CTCAE Grade 3 or above nonhematologic toxicity. Exceptions will be made for:
  - Nausea, vomiting, diarrhea, constipation, or electrolyte abnormality that can be controlled with treatment.
  - Fatigue and anorexia.
  - Transient (ie, ≤1 week) Grade 3 elevations of ALT and/or AST without evidence of other hepatic injury.
- Febrile neutropenia.
- Grade 4 anemia.
- Grade 4 neutropenia lasting >1 week.
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia requiring platelet transfusion.
- Toxicities which require dose reduction or omission of study drug(s) (olaratumab and/or doxorubicin) during Cycle 1.
- Any other significant toxicity deemed by the primary investigator and Lilly CRP/clinical research scientist (CRS) to be dose limiting (eg, any toxicity that is possibly related to the study medication that requires the discontinuation of the patient from the study during Cycle 1).

In the event of a Grade 3 or 4 infusion-related reaction, the patient will be replaced; however, the event will not be considered a DLT. An evaluable patient for DLT is defined as a patient who takes 100% of planned dose in Cycle 1 or a patient who experiences DLT in Cycle 1. If a patient is judged to be non-evaluable for DLT, the patient will be replaced by a new patient.

7.2.1.4. Initiation of Cohort 2 and 3 in Part A

After first 3 patients from Cohort 1 are enrolled, Cohort 2 can be opened based on safety assessment and after discussion between the investigator and the sponsor. In addition, the

sponsor should consult with Safety Assessment Committee (SAC) about the appropriateness for the timing. Cohort 3 can be opened after confirmation of tolerability in Cohort 2.

7.2.1.5. Tolerability Confirmation (Part A)

Tolerability confirmation will be judged if frequency of DLT is confirmed less than 33% each of cohort. At least 6 patients will be enrolled in each cohort and evaluated for DLT during Cycle 1 (first 21 days from Day 1 in Cycle 1).

- If 0 or 1 out of 6 evaluable patients experience DLTs, it will be judged that the dose is tolerable for Japanese patients.
- If 2 patients experience DLTs at any given dose, the sponsor will examine the safety data and consult with the SAC as needed. The sponsor and the investigators will decide if the dose is intolerable or if additional patients will be enrolled to the same dose level for further investigation.
- If ≥3 patients experience DLTs at any given dose, it will be judged that the dose is not tolerable for Japanese patients.

7.2.2. Dose Adjustments and Delays

7.2.2.1. Delays and Omission

In the case that olaratumab or doxorubicin cannot be administered due to any reason including toxicity, the administration can be delayed beyond the time window within the cycle. If the planned administration cannot be conducted within the cycle, the dose is defined as an omission. For olaratumab-related toxicity ≥Grade 3 not adequately controlled with appropriate supportive care, olaratumab should not be administered until the toxicity becomes ≤Grade 2 or returns to pretreatment baseline.

Part A

Illustrative examples of dose adjustments are shown in Attachment 5.

In general, discontinuation of 1 study drug (olaratumab or doxorubicin) will not necessitate discontinuation of the other study drug. Dose omission, delays, or discontinuation of olaratumab due to an olaratumab-related toxicity will not alter those of doxorubicin. Similarly, olaratumab therapy should not be altered for doxorubicin-related toxicity.

Day 1 of Cycles 2 through 7 (the first cycle of olaratumab monotherapy for the patients who receive doxorubicin on Cycle 7 or later, by reason that cumulative dose of doxorubicin does not reach 500 mg/m^2 during the first 6 cycles) is defined as the 21st day after the first doxorubicin administration in the previous cycle. Day 1 of Cycle 8 (the second cycle of olaratumab monotherapy for the patients who receive doxorubicin on Cycle 7 or later, by reason that cumulative dose of doxorubicin does not reach 500 mg/m^2 during the first 6 cycles) or any of the following cycles is defined as the 21st day after the first olaratumab administration in the previous cycle. In the case that olaratumab is delayed or omitted for any reason (including AEs), administration of doxorubicin will continue according to the original schedule. Dose delay of olaratumab on Day 8 is allowed until 7 days before Day 1 of the following cycle. Upon

resolution of the event(s) causing the delay and omission in olaratumab administration, olaratumab treatment will resume according to a Day 1/Day 8 schedule. In this study, every effort will be made to synchronize administration of olaratumab and doxorubicin according to the original dosing schedule; therefore, olaratumab may be administered for up to 4 weeks in a row.

If olaratumab is not administered for more than 21 days from Day 1 of the following scheduled cycle due to an olaratumab related-toxicity that does not resolve, or if more than 2 toxicity-related olaratumab dose reductions are required, treatment with olaratumab will be permanently discontinued.

In the case that doxorubicin is delayed or omitted for any reason (including AEs), administration of olaratumab will continue according to the original schedule. If doxorubicin is not administered for more than 21 days from Day 1 of the following scheduled cycle due to a doxorubicin-related toxicity that does not resolve, treatment with doxorubicin will be permanently discontinued.

If both doxorubicin and olaratumab are discontinued, the patient will be discontinued from the study.

Part B

Day 1 of each cycle (Cycle 2 and beyond) is defined as the 21st day after the first olaratumab administration in the previous cycle.

When olaratumab is not administered on the scheduled day, study therapy will resume provided resolution of the event(s) causing the delay. Dose delay of olaratumab on Day 8 is allowed until 7 days before Day 1 of the following cycle. If olaratumab is discontinued, the patient will be discontinued from the study.

7.2.2.2. Dose Reductions

Olaratumab

Olaratumab dose can be reduced to a lower dose to either 12 or 10 mg/kg (15 mg/kg if the toxicity occurs during Cycle 1 of Cohort 3 in Part A), in accordance with the general guidelines shown in Section 7.2.2.3. Once the dose of olaratumab is reduced, re-escalation to the prior dose level is not permitted.

Doxorubicin (Part A)

Dose reduction between cycles in Cohort 1, 2 and 3

Doxorubicin dose can be reduced to a lower dose in accordance with the general guidelines shown in Section 7.2.2.4. Once the dose of doxorubicin is reduced, re-escalation to the prior dose level is not permitted.

Dose reduction within a cycle in Cohort 1

In principle, doxorubicin must be administered on Day 1/2/3 consecutively. No breaks between these administration days are allowed; that is, dose reduction within a cycle is not permitted. The dose must remain constant over these 3 days. In the case that doxorubicin on Day 2/3 or Day 3 cannot be administered due to doxorubicin-related toxicity (or any other reasons), those administrations should be omitted. If a patient recovers from the toxicity sufficiently, and then doxorubicin administration can be resumed, a lower dose than the prior dose level must be selected in accordance with the general guidelines shown in Section 7.2.2.4. However, if the investigators judge that the dose reduction is unnecessary, the dose does not to be reduced in the case that the investigators and the sponsor agree.

7.2.2.3. Guidelines for Olaratumab Dose Reduction

7.2.2.3.1. Hematologic Toxicity

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

7.2.2.3.2. Nonhematologic Toxicity

Specific guidelines for dose reduction in patients who experience infusion-related reactions while receiving treatment with olaratumab are found in Section 8.1.3.4.

General guidelines for dose modification for other nonhematologic toxicities related to olaratumab are shown in Table JGDK.7.2.

Table JGDK.7.2. General Guidelines for Dose Modification Due to Nonhematologic Toxicities Related to Olaratumab

Reaction Grade	Required Dose Modification
Grade 1	No dose modification is required.
Grade 2	At the investigator's discretion, the patient may continue to receive olaratumab per protocol, provided that the event does not pose a serious health risk or is easily treated. If necessary, the patient may be dose reduced up to 2 dose reductions (to 12 mg/kg and subsequently to 10 mg/kg) during the study.
Grade 3	For a Grade 3 toxicity not adequately controlled with appropriate supportive care, the dosing must not be administered until toxicity is ≤Grade 1 or has returned to pretreatment baseline; treatment may then resume at a reduced dose of 12 mg/kg (15 mg/kg if the toxicity occurs during Cycle 1 of Cohort 3 in Part A). If toxicity recurs after therapy resumes, a second dose reduction (to 10 mg/kg) is permitted. If more than 2 toxicity-related olaratumab dose reductions are required, treatment with this agent will be permanently discontinued.
Grade 4	The dose must not be administered until dose toxicity is ≤Grade 1 or has returned to baseline. Treatment may then resume with the dose reduced to 10 mg/kg (15 mg/kg if the toxicity occurs during Cycle 1 of Cohort 3 in Part A). If toxicity recurs after therapy resumes, olaratumab treatment will be discontinued.

7.2.2.4. Guidelines for Doxorubicin Dose Reduction (Part A)

7.2.2.4.1. Hematologic Toxicity

Doxorubicin will not be administered if the patient's ANC is <1000 cells/mm^3 or if the platelet count is <100,000 cells/mm^3. When necessary, the next treatment cycle should be delayed until the ANC is ≥1000 cells/mm^3 and the platelet count is ≥100,000 cells/mm^3. See Table JGDK.7.3 for doxorubicin dose reduction for neutropenia.

Table JGDK.7.3. General Guidelines for Doxorubicin Dose Reduction Due to Neutropenia

	Required Dose Modification	
Toxicity	**Cohort 1 (25 mg/m^2 on Day1/2/3)**	**Cohort 2 and 3 (75 mg/m^2 on Day1)**
≥Grade 3 neutropenic fever/infection	Approximately 60 mg/m^2 (20 mg/m^2 on Day 1/2/3)	Approximately 60 mg/m^2
Grade 4 neutropenia lasting longer than 7 days	Approximately 60 mg/m^2 (20 mg/m^2 on Day 1/2/3)	Approximately 60 mg/m^2
Second incidence of either: 1) ≥Grade 3 neutropenic fever/infection 2) Grade 4 neutropenia lasting longer than 7 days	Second level of dose reduction to 45 mg/m^2 (15 mg/m^2 on Day 1/2/3)	Second level of dose reduction to 45 mg/m^2

7.2.2.4.2. Nonhematologic Toxicity

In the case of hyperbilirubinemia and elevated AST, dose reduction of doxorubicin should be considered. See Table JGDK.7.4 for doxorubicin dose reduction for hyperbilirubinemia and elevated AST.

Table JGDK.7.4. General Guidelines for Doxorubicin Dose Reduction Due to Hyperbilirubinemia and Elevated AST

Serum bilirubin concentration (mg/dL)	AST (IU/L)	Required Dose Reduction (Cohort 1, 2 and 3)
1.5 to 3.0	or, 60 to 180	50%
3.1 to 5.0	or, >180	75%
>5.0	-	Discontinuation

Abbreviation: AST = aspartate aminotransferase.

7.2.2.4.3. Cardiovascular

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

Patients will undergo baseline LVEF determination by echocardiogram. This evaluation may be repeated at any time during the study if clinically indicated. If an echocardiogram conducted on study indicates a resting LVEF is <50%, then the echocardiogram should be repeated for monitoring. If there is an absolute decrease in LVEF of >20% from the previous evaluation, or if the actual LVEF decreases to ≤40%, then doxorubicin should be discontinued. Doxorubicin should also be discontinued if the patient develops Grade 3 or 4 left ventricular systolic dysfunction (symptomatic congestive heart failure).

7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive olaratumab in combination with doxorubicin (Cohort 1, 2 or 3 in Part A) or olaratumab monotherapy (Part B), at the investigator's discretion. Before each patient's enrollment into the study, an eligibility check must be conducted at the investigational site to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor or designee will confirm the dose and identification number assignment for each patient. For initiation of Cohort 2 and 3, refer to Section 7.2.1.4.

7.4. Blinding

This is an open-label study.

7.5. Concomitant Therapy

No other chemotherapy, immunotherapy, radiation therapy, hormonal cancer therapy, surgery for cancer, or experimental medications will be permitted while patients are participating in this study.

Patients must receive full supportive care therapies concomitantly during the study, including antiemetic treatment as per institutional guidelines. Granulocyte colony stimulating factors (G-CSF) may be used in accordance with American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2006), and if they adhere to the dosage and administration described in the Japan Package Insert. Granulocyte colony stimulating factor treatment as the primary prophylaxis is not permitted and pegfilgrastim are not permitted. Granulocyte colony

stimulating factors must be discontinued at least 24 hours before beginning the next cycle of treatment.

Appropriate documentation for all forms of premedications, supportive care, and concomitant medications (eg, medications such as sedatives, antibiotics, analgesics, antihistamines, corticosteroids, erythropoietin; procedures such as paracentesis, thoracentesis; blood products such as blood cells, platelets, fresh frozen plasma transfusions) must be captured on the electronic case report form (eCRF). Erythropoietin/blood product use and platelet transfusions may be used in accordance with ASCO guidelines (Schiffer et al. 2001; Rizzo et al. 2010).

7.6. Treatment Compliance

Olaratumab and doxorubicin (Part A) or olaratumab (Part B) will be administered at the investigational sites, under the direction of the investigator. As a result, a patient's compliance with study drug administration is ensured. Patients should attend scheduled clinic visits and must comply with study criteria under their control. Deviation(s) from the prescribed dosage regimen should be recorded on the CRF.

8. Safety, Pharmacokinetic, and Efficacy Data Collection

8.1. Safety Evaluations

The safety and tolerability of olaratumab have been assessed in nonclinical toxicology studies and the results from these studies are detailed in the IB. This Phase 1 study contains detailed safety monitoring that will permit initial characterization of the safety profile of olaratumab in combination with doxorubicin in patients. Study procedures and their timing, including collection of blood and urine samples, are described in the Study Schedule (Attachment 1).

Standard laboratory tests, including chemistry, hematology, coagulation and urinalysis panels, will be performed. A pregnancy test will be administered if applicable. Other clinical laboratory tests will also be collected. Attachment 2 lists the specific tests that will be performed for this study.

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). Table JGDK.8.1 presents a summary of AE and SAE reporting guidelines. Table JGDK.8.1 also shows which database or system is 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. All AEs observed will be graded using CTCAE (v4.03).

The NCI-CTCAE (v4.03) 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 (v4.03). Any minor version of CTCAE (v4.03) may be used for this study. Minor CTCAE (v4.03) updates from the NCI will not necessitate a protocol amendment. For AEs without matching terminology within the NCI-CTCAE (v4.03) 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 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 drug 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 drug(s) 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 are 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 or study drug via eCRF.

The investigator decides whether he or she interprets the observed AEs as either related to disease, to the 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 treatment.

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.

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

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 (ie, 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.

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 the Lilly Safety System.

8.1.2.2.1. Prior to Administration of Study Drug(s)

During screening, all AEs and SAEs (regardless of relatedness to protocol procedures) are collected after the patient has signed the informed consent form (ICF). For patients who do not enroll in the trial (ie, have not received at least 1 dose of olaratumab), only AEs and SAEs related to protocol procedures are required to be collected.

8.1.2.2.2. On Therapy

All AEs and SAEs, regardless of relatedness to study drug(s) 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 drug(s) or protocol procedures, occurring during the follow-up visit must be reported to Lilly or its designee. The follow-up visit starts on the day after the patient and the investigator agree to discontinue the study treatment and extends 28 days (±5 days) from the last dose of study drug (olaratumab or doxorubicin). For patients who discontinue from the study treatment after a treatment delay, the follow-up visit can be performed after the allowed time window if it is difficult to perform the follow-up procedures within this time period. In such a situation, the follow-up visit should be performed as early as possible. At the end of the follow-up visit, the patient will be required to have specific safety assessments (Attachment 1).

Following the safety assessments, which mark the end of the follow-up visit, the patient will be discontinued from the study, unless there is an ongoing AE or SAE that is possibly related to study drug. In this instance, the patient should be monitored in subsequent follow-up visits 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.

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, 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 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 Development Core Safety Information in the IB and that the investigator identifies as related to study drug or procedure. 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

The AE and SAE reporting guidelines are summarized in Table JGDK.8.1 and in Attachment 6.

Table JGDK.8.1. Adverse Event and Serious Adverse Reporting Guidelines for Study JGDK

Timing	Types of AEs/SAEs Reported	Collection Database	Lilly Safety System
Pretreatment (baseline assessments) (Starts at the signing of informed consent and ends just before the first dose of study drug)	Preexisting conditions All AEs regardless of relatedness All SAEs regardless of relatedness	X X X	 X
On therapy (Starts at first dose of study drug[s] and ends at last dose of study drug[s])	All AEs regardless of relatedness All SAEs regardless of relatedness	X X	 X
Follow-up (Starts on the day after the patient and the investigator agree to discontinue the study treatment and extends 28 days [±5 days] from the last dose of study drug [olaratumab or doxorubicin]).	All AEs regardless of relatedness All SAEs regardless of relatedness	X X	 X
Subsequent follow-up visits (prior to patient discontinuation from the study), if necessary	Ongoing AEs possibly related to study drug(s), or protocol procedures Ongoing SAEs possibly related to protocol procedures or study drug	X X	 X
Patient no longer on study	All SAEs possibly related to protocol procedures or study drug 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. Vital Signs

Pulse rate, respiration rate, temperature, and supine blood pressure will be measured as specified in the Study Schedule and as clinically indicated (Attachment 1). Vital signs will be collected before any blood samples are collected at the specified time.

8.1.3.2. Electrocardiograms

Serial 12-lead digital ECGs will be collected during the study. Electrocardiograms should be collected prior to any blood draws scheduled at the same time point

For each patient, ECGs will be collected according to the Study Schedule (Attachment 1) and the Pharmacokinetic Sampling, ECG, and Immunogenicity Sampling Schedule (Attachment 4). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Single local ECGs will be obtained at screening (within 21 days prior to the first administration of study drug). Consecutive triplicate ECGs will be obtained at approximately 1-minute intervals.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed 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 at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient for symptoms (eg, palpitations, near syncope, syncope) to determine whether 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 from at least 1 of the replicate ECGs from each time point.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will then conduct a full overread on 1 of the replicate ECGs (including all intervals). A report based on data from this overread will be issued to the investigative sites. For each set of replicates, the RR and QT intervals and heart rate will be determined on the ECGs that were not fully overread. These data are not routinely reported back to the investigative site.

All data from the overreads will be placed in the Lilly database for analytical and study report purposes. Any clinically significant finding that was not present on the fully overread ECG but was present on the partially overread ECG (where only RR, QT, and heart rate is assessed) will be reported to the investigator and to Lilly.

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

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

When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, 12-lead digital ECGs will be performed annually (±2 weeks) except for the ECG scheduled to be performed at the follow-up visit; each assessment will be conducted locally according to the procedure at the respective site. Investigators will still be responsible for patient safety management, however centralized review will no longer be mandatory. If clinically indicated, 12-lead digital ECGs can be performed more frequently.

8.1.3.3. Echocardiograms

Echocardiogram scans will be performed locally at the time points according to the Study Schedule (Attachment 1). The scans must be performed within 3 days prior to any treatment administration in these respective cycles.

8.1.3.4. Infusion-Related Reactions

The NCI-CTCAE definition of infusion-related reactions is provided in Attachment 8.

Symptoms occurring during or following infusion of olaratumab may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome. In the setting of symptoms occurring during or following infusion of olaratumab, investigators are encouraged to use the AE term "infusion-related reaction" and any additional terms (including those not listed here) that best describe the event.

Consistent with usual medical practice, selected parenteral medications may be utilized for Grade 2 allergic/hypersensitivity reaction as detailed below. The Lilly CRP or CRS should be contacted immediately if questions arise concerning the grade of the reaction.

The following are treatment guidelines for olaratumab infusion-related reactions:

In general, if a patient experiences a Grade 1 or 2 infusion-related reaction, the infusion should stop and the patient should be treated with an antihistamine (for example diphenhydramine hydrochloride), steroids (for example dexamethasone), acetaminophen, and oxygen (as appropriate), according to standard medical practices. After recovery, the infusion rate should be decreased 50% for the duration of the infusion. After a Grade 1 or 2 infusion reaction, patients should be premedicated with antihistamines, steroids, acetaminophen, etc., as appropriate for subsequent infusions.

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

A patient has to be carefully observed for potential infusion-related reactions for approximately 60 minutes after olaratumab administration, especially after the first 2 administrations. If a

patient should have an infusion-related reaction to olaratumab, all attempts should be made to obtain an anti-olaratumab antibody blood sample as close to the onset of the event as possible, at the resolution of the event, and 28 days following the event. In addition, these samples may be assessed for levels of olaratumab (PK assay).

8.1.4. Safety Monitoring

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

Representatives from Lilly Global Patient Safety will specifically monitor SAEs. Lilly will review SAEs within time frames mandated by company standard operating procedures. The Lilly CRP/CRS will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist, and periodically review:

- Trends in safety data.
- Laboratory analyses.
- Adverse events.
- If a study patient experiences elevated ALT $\geq$5 × ULN and elevated total bilirubin $\geq$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 (Attachment 3).

For interstitial lung disease and suspected interstitial lung disease cases diagnosed after starting the study drug (Day 1 in Cycle 1), external specialists may evaluate its related examination results such as image data. The investigator should provide the test results, including imaging examination and pathological examination, upon request by Lilly.

8.1.5. Complaint Handling

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

Complaints related to 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 complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed 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 lists the schedule for PK and immunogenicity sample collections and ECG schedule for this study.

8.2.1. Samples for Study Qualification and Health Monitoring

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

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.

8.2.2. Samples for Drug Concentration Measurements Pharmacokinetics

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

8.2.2.1. Pharmacokinetic Samples

At the visits and times specified in the Pharmacokinetic Sampling, ECG and Immunogenicity Sampling Schedule (Attachment 4), blood samples of approximately 3 mL each will be collected to determine the serum concentrations of olaratumab. In Part A, blood samples of approximately 3 mL each will also be collected to determine the plasma concentrations of doxorubicin. A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and Lilly. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

These samples will be analyzed at a laboratory designated by the sponsor. Serum concentrations of olaratumab will be assayed using a validated enzyme-linked immunosorbent assay method. Plasma concentrations of doxorubicin will be assayed using a validated liquid chromatography with tandem mass spectrometry method.

The PK samples will be stored at a facility designated by the sponsor.

The remaining plasma/serum from the samples collected for PK may be pooled and used for exploratory metabolism work as deemed appropriate.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 years following last patient visit for the study.

When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, PK samples will no longer be collected except for sampling required for the follow-up visit (Attachment 4).

8.2.3. Samples for Immunogenicity Research

Blood samples of approximately 4 mL for immunogenicity testing will be collected to determine antibody production against olaratumab. A schedule for immunogenicity sample collection is provided in Attachment 4. 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 28 days following the event. An immunogenicity sample should also be collected approximately 28 days after the discontinuation of treatment (ie, 28-day follow-up visit).

Immunogenicity will be assessed by a validated assay designed to detect ADA in the presence of olaratumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of olaratumab.

Detailed instructions for collecting, processing, storing, and shipping the samples will be provided by the sponsor in a separate procedural manual.

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.

When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, immunogenicity samples will no longer be collected except for sampling required for the follow-up visit or in the event of an infusion-related reaction (Attachment 4).

8.2.4. Samples for Translational Research

Exploratory analyses will assess the potentially relevant biomarkers obtained from blood samples. Tumor tissue submission is optional and tumor specimens might be used if available.

- Blood samples and tumor tissues (if available) will be used for the analysis of potential biomarkers related to the mechanism of olaratumab, the PDGF signaling pathway, and the pathobiology of cancer.

Gene expression profiling and/or genetic analyses will not be conducted in any samples collected in this study.

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

- plasma samples from whole blood (see Section 8.2.4.1)

Optional samples for biomarker research that should be collected from patients in the study where possible are the following:

- archived tumor tissue (see Section 8.2.4.2)

Samples will be collected at the times specified in Attachment 1.

The translational research 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 or designee. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study treatment.

Patients will not receive results of these investigations except where required by local law. Samples will be destroyed according to a process consistent with local regulation.

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

8.2.4.1. Blood Sample for Plasma Collection

Circulating markers may include, but are not limited to, markers relevant to the mechanism of olaratumab, the PDGF signaling pathway, and the pathobiology of cancer.

8.2.4.2. Optional Tumor Tissue Samples

Collection of tumor tissue samples (blocks or slides) is optional for participation in this study. If provided, due diligence should be used to make sure that tumor specimen (not a normal adjacent or a tumor margin sample) is provided. Pathology notes accompanying archival tissue may also be requested. If paraffin-embedded whole blocks will be submitted, the whole blocks will be sectioned. After testing has been completed, the paraffin-embedded whole blocks will be returned to the site. Whole blocks can be returned sooner, if requested by the sites. Partial blocks and slides will not be returned.

Immunohistochemistry may be performed on these tissue samples to assess potential associations with biomarkers relevant to pathways associated with the mechanism of olaratumab, the PDGF signaling pathway, and the pathobiology of cancer and cancer-related conditions, and may also be used for related research methods and clinical outcomes. Additional exploratory markers studied may include, but are not limited to, markers relevant to the PDGF pathway.

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.

Each patient will be assessed by one or more of the following radiologic tests for tumor measurement:

- Computed tomography scan
- Magnetic resonance imaging

Each patient's full extent of disease will also be assessed with:

- Tumor measurement by RECIST version 1.1 (Eisenhauer et al. 2009)
- Evaluation of PS

To confirm objective responses, all lesions should be radiologically assessed, and the same radiologic method used for the initial response determination should be repeated at least 4 weeks following the initial observation of an objective response. If a patient is discontinued from the study, repeat radiology assessments may be omitted if clear clinical signs of progressive disease are present.

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 CRF or lab requisition form.

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/IRB 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.

For data handled by a data management third-party organization (TPO), eCRF 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 sponsor.

For data handled by the sponsor internally, eCRF 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 generic labs system and/or the TPO 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 generic labs system and/or the TPO system.

Electrocardiogram data will be stored electronically in the central database system of Lilly's central review organization. Data will subsequently be transferred from the central review organization system to the Lilly generic labs system and/or the TPO system.

When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, electrocardiogram data will no longer be stored electronically in the central vendor's system.

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

The study design requires 6 patients at each cohort in Part A for assessing the DLTs observed. This sample size was not based on a statistical power calculation.

In Part B, 6 patients are needed to evaluate PK and safety profile of olaratumab monotherapy. This sample size was estimated empirically based on other Phase 1 oncology studies. The estimation precision of PK parameters in this study is expected to be similar to that in previous studies (Study JGDC and Study JGDF), although there are no inter-subject variability data on a new assay.

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

The interpretation of the study results will be the responsibility of the investigator with the sponsor's 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.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Detailed information regarding the planned statistical analyses will be described in the Statistical Analysis Plan.

10.2. Patient Disposition

The analysis populations are defined as follows:

- Enrolled Population: Anyone who signed the informed consent and who was confirmed to be eligible and have been assigned to a treatment will be included in this population.
- FAS Population: All enrolled patients who received any amount of study drugs (either olaratumab or doxorubicin) will be included in the FAS Population. The FAS Population is based on the intent-to-treat principle and will be used for the analysis of baseline characteristics, efficacy data, safety data, and biomarkers.
- DLT Population: All enrolled patients who will complete Cycle 1 (initial 21-day treatment period), or who will discontinue due to DLT during Cycle 1, will be included in the DLT Population. Patients who will discontinue during Cycle 1 due to other reasons than DLT will be excluded from the DLT Population. The DLT Population will be used for summarizing a proportion of patients with DLT.

Number (percent) of patients in the Enrolled Population, the FAS Population, or the DLT Population (Part A only) will be summarized by part and cohort.

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 patient discontinuation will be given.

Number (percent) of patients who discontinued will also be summarized by part and reason for discontinuation and by part and cohort.

10.3. Patient Characteristics

Demographic and baseline characteristics (ie, age [years], age categories [<65 years vs. ≥65 years], gender, height [cm], weight [kg], and ECOG PS), pre-treatment disease characteristics (ie, cancer type, TNM staging at the time of diagnosis, sites of metastatic disease, and duration of disease [months from first confirmation of cancer to first dose]), prior anticancer treatments or surgery (ie, type of therapy, regimen, and prior surgery), and medical history will be summarized by part and cohort for the FAS Population.

10.4. Safety Analyses

All safety evaluations will be based on the FAS Population (except a DLT summary). Safety variables listed below will be summarized by part and cohort (and by study visit/time point, if applicable).

- Study drug exposure of olaratumab or doxorubicin: number of cycles, number of infusions, duration of treatment (weeks), cumulative dose (mg/kg or mg/m^2), dose intensity (mg/kg/week or mg/m^2/week), relative dose intensity (%), treatment delays, treatment omissions, treatment reductions, and treatment interruptions.
- TEAEs: MedDRA will be used for categorizing to System Organ Class and Preferred Term. National Cancer Institute-Common Terminology Criteria for Adverse Events will be used for identifying grade and/or relevant event term. In addition to TEAEs, all AEs, SAEs, study drug-related AEs and SAEs, AEs leading to treatment discontinuation (olaratumab or doxorubicin in Part A and olaratumab in Part B), and AEs leading to treatment delay/omission/reduction/interruption (olaratumab or doxorubicin in Part A and olaratumab in Part B) will be summarized.
- DLT: In Part A, the number of patients who experienced any DLTs during Cycle 1 will be summarized by cohort using the DLT Population.
- Deaths, SAEs, other significant AEs: these findings will be listed by patients.
- PS, physical exams, vital signs, laboratory tests and ECG: actual measurements, as well as categorized values of laboratory tests, vital signs, and ECG parameters, will be summarized by part, cohort, and study visit/time point.

10.5. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of the study drug and have had samples collected.

Pharmacokinetic parameter estimates for olaratumab and doxorubicin will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be maximum observed concentration (C_{max}) and AUC from time 0 to the last time point with a measurable concentration ($AUC[0\text{-}t_{last}]$), and AUC from time 0 to infinity ($AUC_{0\text{-}\infty}$) of olaratumab and doxorubicin. Other noncompartmental parameters such as $t_{1/2}$, CL, and V may be reported. Additional exploratory analyses may be performed if warranted by data and other validated PK software programs (eg, NONMEM) may be used if appropriate and approved by 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.

10.6. Efficacy

Efficacy data will be summarized by part and cohort using the FAS population. Efficacy data includes the objective response rate with confirmed partial response (PR) or complete response (CR), and the disease control rate with confirmed PR, CR, or stable disease (SD) as best overall response according to RECIST version 1.1. Progression-free survival and duration of response will also be included in efficacy data.

10.7. Biomarker Analyses

Descriptive statistics and visual plots of time course (if applicable) for biomarkers will be provided.

10.8. Interim Analyses

Safety data evaluation for Part A will be performed after 3 patients in Cohort 1 are enrolled.

The SAC is authorized to review available safety data. The SAC may consist of members external to Lilly.

Safety and/or PK data will be reviewed during the study, if needed, for doxorubicin dosing schedule change, modifications to the doxorubicin dosing schedule strategy or to the amount of olaratumab dosage, or other design elements.

If it is deemed that enough data are obtained to assess the primary objective and the secondary objectives, a clinical study report might be created before the last patient visit. In this case, all data until the data cutoff date will be used for the analysis of safety, efficacy, biomarker, and PK. All data defined in the protocol will continue to be collected from patients on treatment after the data cutoff date unless otherwise specified. These data may be reported separately and the analyses on all patients, including these data, may not be performed.

In addition, the sponsor may consider interim analyses for regulatory communication purposes and/or scientific disclosures. In this case, collected data may be summarized.

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.

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/IRB 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)/IRB(s) will review the protocol as required.

The study site's ERB(s)/IRB(s) should be provided with the following:

- the current IB or Patient Information Leaflet, Package Insert, Protocol or Summary of Product Characteristics and updates during the course of the study
- ICF
- 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).

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.

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 investigator chosen by the sponsor or designee will serve as the clinical study report coordinating investigator.

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 I5B-JE-JGDK Study Schedule

Study Schedule for Protocol I5B-JE-JGDK – Part A: Screening and Cycle 1

	Screening			Cycle 1				
Relative day within a cycle	**≤21**	**≤14**	**≤7**	**1**	**2**	**3**	**8**	**Comments**
Informed consent	X							Informed consent form signed (prior to performance of any protocol-specific tests/procedures and patients must be ≥20 years of age).
Medical history		X						Includes past and current medical conditions, treatments, and alcohol/tobacco use.
Pregnancy test			X					Serum or urine: Pregnancy test is only required for females of child-bearing potential.
Physical examination		X		X[a]			X[a]	Includes medical interview, height (at screening only), weight, and body surface area.
Vital signs		X		X[b]			X[c]	Pulse rate, respiration rate, temperature, and supine blood pressure will be measured.
ECOG performance status		X		X[a]				
NYHA classification		X						
ECG	X			**See Attachment 4**				Screening ECGs will be performed locally. Obtain ECGs before any associated blood draws.
Echocardiogram	X							Echocardiogram will be performed locally. Data obtained before patient's consent may be used as the screening data if the relevant tests are conducted within the allowed time window.
Hematology		X		X[a]			X[a]	
Serum chemistry		X		X[a]			X[a]	
Coagulation		X		X[a]				
Urinalysis		X		X[a]				
Hepatitis B and C virus	X							Includes tests for Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody and Hepatitis C antibody. Test for Hepatitis B DNA will be performed as necessary.
CTCAE v4.03 grading	X			X	X[d]	X[d]	X	Throughout study as needed.
Concomitant medications	X			X	X[d]	X[d]	X	
Radiological tumor assessment	X							Data obtained before patient's consent can be used as screening data if the relevant tests are conducted within the allowed time window.
PK sampling				**See Attachment 4**				
Immunogenicity sampling				**See Attachment 4**				
Blood sampling for translational research				X[a]				Plasma samples will be collected from whole blood.
Tumor tissue submission				X				If available.
Olaratumab administration				X[e]			X[e]	
Doxorubicin administration				X	X[d]	X[d]		

Study Schedule for Protocol I5B-JE-JGDK – Part A: Screening and Cycle 1

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; NYHA = New York Heart Association; PK = pharmacokinetic.

[a] Predose only.

[b] Vital sign measurements will be obtained prior to and at the completion of each olaratumab administration, and prior to each doxorubicin administration.

[c] Vital sign measurements will be obtained prior to and at the completion of olaratumab administration, and approximately one hour following the completion of olaratumab administration.

[d] Cohort 1 only.

[e] 15 mg/kg in Cohort1 and 2, and 20 mg/kg as loading dose in Cohort 3.

Study Schedule for Protocol I5B-JE-JGDK – Part A: Cycle 2 and beyond

	Cycle 2-6				Cycle 7-n		Follow-Up[c]	
Relative day within a cycle	1[a]	2	3	8	1[b]	8		
Allowance (days)	+3			±3[d]	+3	±3	±5	**Comments**
Informed consent	X							Informed consent form signed (prior to beginning of Cycle 2).
Pregnancy test	X[e]				X[e]		X	Should be performed approximately every 6 weeks (i.e., at the beginning of Cycle 3 and every other cycle thereafter) during the study.
Physical examination	X[e]				X[e]		X	Includes medical interview, weight, and body surface area.
Vital signs	X[f]			X[f]	X[f]	X[f]	X	Pulse rate, respiration rate, temperature, and supine blood pressure will be measured.
ECOG performance status	X[e]				X[e]		X	
ECG	**See Attachment 4**							Obtain ECGs before any associated blood draws.
Echocardiogram	X[e]				X[e]		X	Should be performed locally at Cycles 5 and 7 (within 3 days prior to the treatment on Day 1, but re-measurement is not necessary in case of dose delay of Day 1) and follow-up visit.
Hematology	X[e]			X[e]	X[e]	X[e]	X	
Serum chemistry	X[e]			X[e]	X[e]	X[e]	X	
Coagulation	X[e]				X[e,h]		X	Should be performed approximately every 6 weeks (ie, at the beginning of Cycle 3 and every other cycle thereafter).
Urinalysis	X[e]				X[e,h]		X	
CTCAE v4.03 grading	X	X[g]	X[g]	X	X	X	X	Throughout study as needed.
Concomitant medications	X	X[g]	X[g]	X	X	X	X	
Radiological tumor assessment	X				X		X	Prior to Cycles 3 and 5 (no more than 14 days prior to Day 1 Cycle 3 and 5), then every 2-4 cycles as clinically indicated.
PK sampling	**See Attachment 4**							
Immunogenicity plasma sampling	**See Attachment 4**							
Olaratumab administration	X			X	X	X		
Doxorubicin administration	X	X[g]	X[g]					

Study Schedule for Protocol I5B-JE-JGDK – Part A: Cycle 2 and beyond

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PK = pharmacokinetic.

[a] If neither olaratumab nor doxorubicin are administered on this date, Day 1 will be the next following day when either olaratumab or doxorubicin is actually administered.

[b] If olaratumab is not administered on this date, Day 1 will be the next following day when olaratumab is actually administered.

[c] The follow-up period starts on the day after the patient and the investigator agree to discontinue study treatment and extends 28 days (±5 days) from the last dose of study drug (olaratumab or doxorubicin). Note (exception): For patients who discontinue from study treatment after a treatment delay, the follow-up visit can be performed after the allowed time window, if it is difficult to perform the follow-up procedures within this time period. In such a situation, the follow-up visit should be performed as early as possible.

[d] No time window is allowed for Day 8 in Cycle 3.

[e] Predose only.

[f] Vital sign measurements will be obtained prior to each olaratumab administration.

[g] Cohort 1 only.

[h] When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, coagulation test and urinalysis will no longer be mandatory.

Study Schedule for Protocol I5B-JE-JGDK – Part B: Screening and Cycle 1

	Screening			Cycle 1		
Relative day within a cycle	**≤21**	**≤14**	**≤7**	**1**	**8**	**Comments**
Informed consent	X					Informed consent form signed (prior to performance of any protocol-specific tests/procedures and patients must be ≥20 years of age).
Medical history		X				Includes past and current medical conditions, treatments, and alcohol/tobacco use.
Pregnancy test			X			
Physical examination		X		X[a]	X[a]	Includes medical interview height (at screening only) and weight.
Vital Signs		X		X[b]	X[b]	Pulse rate, respiration rate, temperature, and supine blood pressure will be measured.
ECOG performance status		X		X[a]		
NYHA classification		X				
ECG	X			**See Attachment 4**		Screening ECGs will be performed locally. Obtain ECGs before any associated blood draws.
Hematology		X		X[a]	X[a]	
Serum chemistry		X		X[a]	X[a]	
Coagulation		X		X[a]		
Urinalysis		X		X[a]		
Hepatitis B and C virus	X					Includes tests for Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody and Hepatitis C antibody. Test for Hepatitis B DNA will be performed as necessary.
CTCAE v4.03 grading	X			X	X	Throughout study as needed.
Concomitant medications	X			X	X	
Radiological tumor assessment	X					Data obtained before patient's consent can be used as screening data if the relevant tests are conducted within the allowed time window.
PK Sampling				**See Attachment 4**		
Immunogenicity sampling				**See Attachment 4**		
Blood sampling for translational research				X[a]		Plasma samples will be collected from whole blood.
Tumor tissue submission				X		If available.
Olaratumab administration				X	X	

Study Schedule for Protocol I5B-JE-JGDK – Part B: Screening and Cycle 1

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; NYHA = New York Heart Association; PK = pharmacokinetic.

[a] Predose only.

[b] Vital sign measurements will be obtained prior to and at the completion of olaratumab administration, and approximately one hour following the completion of olaratumab administration.

Study Schedule for Protocol I5B-JE-JGDK – Part B: Cycle 2 and beyond

Relative Day Within a Cycle	Cycle 2-n		Follow-Up[b]	Comments
	1[a]	8		
Allowance (days)	**+3**	**±3[c]**	±5	
Pregnancy test	X[d]		X	Should be performed approximately every 6 weeks (ie, at the beginning of Cycle 3 and every other cycle thereafter) during the study.
Physical examinations	X[d]		X	Includes medical interview and weight.
Vital signs	X[e]	X[e]	X	Pulse rate, respiration rate, temperature, and supine blood pressure will be measured
ECOG performance status	X[d]		X	
ECG	**See Attachment 4**			Obtain ECGs before any associated blood draws.
Hematology	X[d]	X[d]	X	
Serum chemistry	X[d]	X[d]	X	
Coagulation	X[d,f]		X	Should be performed approximately every 6 weeks (ie, at the beginning of Cycle 3 and every other cycle thereafter).
Urinalysis	X[d,f]		X	
CTCAE v4.03 grading	X	X	X	Throughout study as needed.
Concomitant medications	X	X	X	
Radiological tumor assessment	X		X	Prior to Cycles 3 and 5 (no more than 14 days prior to Day 1 Cycle 3 and 5), then every 2-4 cycles as clinically indicated.
PK sampling	**See Attachment 4**			
Immunogenicity sampling	**See Attachment 4**			
Olaratumab administration	X	X		

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PK = pharmacokinetic.

[a] If olaratumab is not administered on this date, Day 1 will be the next following day when olaratumab is actually administered.

[b] The follow-up period starts on the day after the patient and the investigator agree to discontinue the study treatment and extends 28 days (±5 days) from the last dose of olaratumab. Note (exception): For patients who discontinue from the study treatment after a treatment delay, the follow-up visit can be performed after the allowed time window, if it is difficult to perform the follow-up procedures within this time period. In such a situation, the follow-up visit should be performed as early as possible.

[c] No time window is allowed for Day 8 in Cycle 3.

[d] Predose only.

[e] Vital sign measurements will be obtained prior to each olaratumab administration.

[f] When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, coagulation test and urinalysis will no longer be mandatory.

Attachment 2. Protocol I5B-JE-JGDK Clinical Laboratory Tests

Clinical Laboratory Tests[a]

Hematology:	**Clinical Chemistry:**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Chloride
Mean cell hemoglobin concentration	Calcium
Leukocytes (WBC)	Albumin
Neutrophils	Total protein
Lymphocytes	Blood urea nitrogen
Monocytes	Creatinine
Eosinophils	Alkaline phosphatase
Basophils	Alanine aminotransferase
Platelets	Aspartate aminotransferase
	Total bilirubin
Urinalysis[f]	Lactate dehydrogenase
Specific gravity	Magnesium
pH	Phosphorus
Protein	Glucose
Glucose	
Ketones	**Pregnancy test (serum or urine)**
Blood	Human chorionic gonadotropin[c]
	Follicle-stimulating hormone[b,d]
	Viral serology[b, e]
Coagulation[f]	Hepatitis B surface antigen
Prothrombin time	Hepatitis B surface antibody
International normalized ratio	Hepatitis B core antibody
Activated partial thromboplastin time	Hepatitis B DNA
	Hepatitis C antibody

Abbreviations: DNA = deoxyribonucleic acid; RBC = red blood cells; WBC = white blood cells.

[a] Local- or investigator-designated laboratory.

[b] Performed only at screening.

[c] To be done for women of child-bearing potential

[d] To be done for women only when needed to confirm postmenopausal status.

[e] Each of these tests will be completed unless results have been obtained from the patients within the last 6 months.

[f] When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, coagulation test and urinalysis will no longer be mandatory.

Attachment 3. Protocol I5B-JE-JGDK Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
Erythrocyte count (RBC)	Prothrombin time
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
Alanine aminotransferase	**Anti-nuclear antibody[a]**
Aspartate aminotransferase	
Gamma glutamyl transferase	**Anti-smooth muscle antibody[a]**
Creatine phosphokinase	

Abbreviations: Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory.

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

Attachment 4. Protocol I5B-JE-JGDK Pharmacokinetic Sampling, ECG, and Immunogenicity Sampling Schedule

Part A – Cohort 1

PK Sample Number[a]	Cycle	Day	Dosing[b]		PK Sampling Time	PK[c]		ECG[d]	Immunogenicity[e,f]
			Olaratumab	Doxorubicin		Olaratumab	Doxorubicin		
		-4 ~ -1			Planned time for pre-infusion of olaratumab on Day 1			X[g]	
1	1	1			Pre-infusion of olaratumab	X		X	X
			X						
2					Immediately postinfusion of olaratumab	X			
				X					
3					Immediately postinfusion of doxorubicin (Approx 1 5 h postinfusion of olaratumab)	X	X		
		2		X					
4					Immediately postinfusion of doxorubicin (Approx 24 h postinfusion of olaratumab)	X	X		
		3		X					
5					Immediately postinfusion of doxorubicin (Approx 48 h postinfusion of olaratumab)	X	X		
6		4			72 ± 6 h postinfusion of olaratumab	X			
7		8			Pre-infusion of olaratumab (Approx 168 h postinfusion of olaratumab on Day 1)	X[h]		X[h]	
			X						
8					Immediately postinfusion of olaratumab	X[i]			
9					1 h ± 10 min postinfusion of olaratumab	X[i]			
10		10			48 ± 6 h postinfusion of olaratumab	X[i]			
11		11			72 ± 6 h postinfusion of olaratumab	X[i]			
12		15			168 ± 8 h postinfusion of olaratumab	X[i]			
13	2	1			Pre-infusion of olaratumab (Approx 336 h [14 days] postinfusion of olaratumab on Cycle 1 Day 8)	X[j]		X[j]	X[j]
			X						
14					Immediately postinfusion of olaratumab	X[k]			
15		8			Pre-infusion of olaratumab	X[i]			
			X						
16					Immediately postinfusion of olaratumab	X[i]			
17	3	1			Pre-infusion of olaratumab	X[k]		X[k]	X[k]
			X						
18					Immediately postinfusion of olaratumab	X[k]			
				X					
19					Immediately postinfusion of doxorubicin (Approx 1 5 h postinfusion of olaratumab)	X[k]	X[l]		
		2		X					
20					Immediately postinfusion of doxorubicin (Approx 24 h postinfusion of olaratumab)	X[k]	X[l]		
		3		X					
21					Immediately postinfusion of doxorubicin (Approx 48 h postinfusion of olaratumab)	X[k]	X[l]		
22		4			72 ± 6 h postinfusion of olaratumab	X[k]			
23		8			Pre-infusion of olaratumab (Approx 168 h postinfusion of olaratumab on Day 1)	X[h,k]		X[h,k]	
			X						
24					Immediately postinfusion of olaratumab	X[i]			

PK Sample Number[a]	Cycle	Day	Dosing[b]		PK Sampling Time	PK[c]		ECG[d]	Immunogenicity[e,f]
			Olaratumab	Doxorubicin		Olaratumab	Doxorubicin		
25					1 h ± 10 min postinfusion of olaratumab	X[i]			
26		10			48 ± 6 h postinfusion of olaratumab	X[i]			
27		11			72 ± 6 h postinfusion of olaratumab	X[i]			
28		15			168 ± 8 h postinfusion of olaratumab	X[i]			
29	4	1			Pre-infusion of olaratumab (Approx 336 h [14 days] postinfusion of olaratumab on Cycle 3 Day 8)	X[j]		X[j]	
			X						
30					Immediately postinfusion of olaratumab	X[k]			
31		8			Pre-infusion of olaratumab	X[i]			
			X						
32					Immediately postinfusion of olaratumab	X[i]			
33	5	1			Pre-infusion of olaratumab	X[k]		X[k]	X[k]
			X						
34					Immediately postinfusion of olaratumab	X[k]			
35		8			Pre-infusion of olaratumab	X[i]			
			X						
36					Immediately postinfusion of olaratumab	X[i]			
37	7, then every 2 cycles	1			Pre-infusion of olaratumab	X[n]		X[o]	X[n]
			X						
38	Follow-Up[m]				28-Day follow-up visit[m]	X		X[o]	X

Abbreviations: Approx. = approximately; ECG = electrocardiogram; h = hour; min = minute; PK = pharmacokinetics.

a Pharmacokinetic Sample Number is numbered based on the case that olaratumab monotherapy is continued up to 7 or 8 cycles.

b On the days that both olaratumab and doxorubicin are administered, olaratumab will be administered prior to doxorubicin. Olaratumab 15 mg/kg and doxorubicin 25 mg/m^2 will be administered as an approximately 60-minute and 30-minute infusions, respectively.

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

d Electrocardiogram should be collected prior to any blood draws scheduled at the same time point.

e Samples of approximately 4 mL will be collected.

f 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 28 days following the event.

g Time-matched baseline ECGs (triplicates) will be taken within 4 days prior to Day 1 of Cycle 1, at the planned time for pre-infusion of olaratumab on Day 1.

h If the second olaratumab administration in the cycle is delayed, olaratumab PK sampling and ECG will still be conducted at approximately 168 h postinfusion of olaratumab on Day 1. An additional olaratumab PK sample should then also be collected prior to the second olaratumab administration in the cycle.

i If the second olaratumab administration in the cycle is delayed, the specified olaratumab PK sampling will be conducted based on the day of the second olaratumab administration in the cycle.

j If the first olaratumab administration or the initiation of Cycles 2 or 4 is delayed, olaratumab PK and immunogenicity sampling and ECG will still be conducted at approximately 336 h (14 days) postinfusion of olaratumab on Day 8 of Cycles 1 or 3. An additional olaratumab PK sample should then also be collected prior to the first olaratumab administration in Cycles 2 or 4.

k If the first olaratumab administration in the cycle is delayed, the specified olaratumab PK and immunogenicity sampling and ECG will be conducted based on the day of the first olaratumab administration in the cycle.

l If doxorubicin administration is delayed, doxorubicin PK sampling on Days 1-3 will be conducted after the first, second, and third doses of doxorubicin in the cycle, respectively.

m When only olaratumab is discontinued before Cycle 6 (doxorubicin continues for up to 6 cycles or until when a cumulative dose reaches), this PK and immunogenicity sampling and ECG will be taken at the nearest planned visit to 28 days after the last dose of olaratumab.

n When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, PK samples and immunogenicity samples will no longer be collected.

o When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, 12-lead digital ECGs will be performed annually (±2 weeks) except at the follow-up visit; each assessment will be conducted locally according to the procedure at the respective site. Investigators will still be responsible for patient safety management, but centralized review will not be mandatory. If clinically indicated, 12-lead digital ECGs can be performed more frequently.

Part A – Cohort 2 and 3

PK Sample Number[a]	Cycle	Day	Dosing[b]		PK Sampling Time	PK[c]		ECG[d]	Immuno-genicity[e,f]
			Olaratumab	Doxorubicin		Olaratumab	Doxorubicin		
		-4 ~ -1			Planned time for pre-infusion of olaratumab on Day1			X[g]	
					Approx. 2 h after the planned time for pre-infusion of olaratumab on Day 1			X[g]	
1	1	1			Pre-infusion of olaratumab	X		X	X
			X						
2					Immediately postinfusion of olaratumab	X			
				X					
3					Immediately postinfusion of doxorubicin (Approx 1 5 h postinfusion of olaratumab)	X	X		
4					0.5 h ± 5 min postinfusion of doxorubicin		X	X	
5					1 h ± 10 min postinfusion of doxorubicin		X		
6					2 h ± 10 min postinfusion of doxorubicin		X		
7					4 ± 0.5 h postinfusion of doxorubicin		X		
8					8 ± 1 h postinfusion of doxorubicin		X		
9		2			24 ± 3 h postinfusion of olaratumab (Approx 24 h postinfusion of doxorubicin)	X	X		
10		3			48 ± 6 h postinfusion of olaratumab (Approx 48 h postinfusion of doxorubicin)	X	X		
11		4			72 ± 6 h postinfusion of olaratumab (Approx 72 h postinfusion of doxorubicin)	X	X		
12		8			Pre-infusion of olaratumab (Approx 168 h postinfusion of olaratumab/doxorubicin on Day 1)	X[h]	X[h]	X[h]	
			X						
13					Immediately postinfusion of olaratumab	X[i]			
14					1 h ± 10 min Postinfusion of olaratumab	X[i]		X[i]	
15		10			48 ± 6 h Postinfusion of olaratumab	X[i]		X[i]	
16		11			72 ± 6 h Postinfusion of olaratumab	X[i]		X[i]	
17		15			168 ± 8 h Postinfusion of olaratumab	X[i]		X[i]	
18	2	1			Pre-infusion of olaratumab (Approx 336 h [14 days] postinfusion of olaratumab on Cycle 1 Day 8)	X[j]		X[j]	X[j]
			X						
19					Immediately postinfusion of olaratumab	X[k]			
20		8			Pre-infusion of olaratumab	X[i]			
			X						
21					Immediately postinfusion of olaratumab	X[i]			
22	3	1			Pre-infusion of olaratumab	X[k]		X[k]	X[k]
			X						
23					Immediately postinfusion of olaratumab	X[k]			
				X					
24					Immediately postinfusion of doxorubicin (Approx 1 5 h postinfusion of olaratumab)	X[k]	X[l]		
25					0.5 h ± 5 min postinfusion of doxorubicin		X[l]	X[l]	
26		2			24 ± 3 h postinfusion of olaratumab (Approx 24 h postinfusion of doxorubicin)	X[k]	X[l]		
27		3			48 ± 6 h postinfusion of olaratumab (Approx 48 h postinfusion of doxorubicin)	X[k]	X[l]		

PK Sample Number[a]	Cycle	Day	Dosing[b]		PK Sampling Time	PK[c]		ECG[d]	Immunogenicity[e,f]
			Olaratumab	Doxorubicin		Olaratumab	Doxorubicin		
28		4			72 ± 6 h postinfusion of olaratumab (Approx 72 h postinfusion of doxorubicin)	X[k]	X[l]		
29					Pre-infusion of olaratumab (Approx 168 h postinfusion of olaratumab/doxorubicin on Day 1)	X[h,k]	X[h,l]	X[h,k]	
		8	X						
30					Immediately postinfusion of olaratumab	X[i]			
31					1 h ± 10 min postinfusion of olaratumab	X[i]		X[i]	
32		10			48 ± 6 h postinfusion of olaratumab	X[i]		X[i]	
33		11			72 ± 6 h postinfusion of olaratumab	X[i]		X[i]	
34		15			168 ± 8 h postinfusion of olaratumab	X[i]		X[i]	
35	4	1			Pre-infusion of olaratumab (Approx 336 h [14 days] postinfusion of olaratumab on Cycle 3 Day 8)	X[j]		X[j]	
			X						
36					Immediately postinfusion of olaratumab	X[k]			
37		8			Pre-infusion of olaratumab	X[i]			
			X						
38					Immediately postinfusion of olaratumab	X[i]			
39	5	1			Pre-infusion of olaratumab	X[k]		X[k]	X[k]
			X						
40					Immediately postinfusion of olaratumab	X[k]			
41		8			Pre-infusion of olaratumab	X[i]			
			X						
42					Immediately postinfusion of olaratumab	X[i]			
43	7, then every 2 cycles	1			Pre-infusion of olaratumab	X[n]		X[o]	X[n]
			X						
44	Follow-Up[m]				28-Day follow-up visit[m]	X		X[o]	X

Abbreviations: Approx. = approximately; ECG = electrocardiogram; h = hour; min = minute; PK = pharmacokinetics.

a Pharmacokinetic Sample Number is numbered based on the case that olaratumab monotherapy is continued up to 7 or 8 cycles.

b On the days that both olaratumab and doxorubicin are administered, olaratumab will be administered prior to doxorubicin. Olaratumab 15 mg/kg and doxorubicin 75 mg/m^2 will be administered as an approximately 60-minute and 30-minute infusions, respectively.

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

d Electrocardiogram should be collected prior to any blood draws scheduled at the same time point.

e Samples of approximately 4 mL will be collected.

f 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 28 days following the event.

g Time-matched baseline ECGs (triplicates) will be taken within 4 days prior to Day 1 of Cycle 1, at the planned time for pre-infusion of olaratumab and 1 h ± 10 min postinfusion of olaratumab (approx. 2 h after pre-infusion of olaratumab) on Day 1.

h If the second olaratumab administration in the cycle is delayed, PK sampling for olaratumab and ECG will still be conducted at approximately 168 h postinfusion of olaratumab on Day 1 and PK sampling for doxorubicin will still be conducted at approximately 168 h postinfusion of doxorubicin on Day 1. An additional olaratumab PK sample should then also be collected prior to the second olaratumab administration in the cycle.

i If the second olaratumab administration in the cycle is delayed, the specified olaratumab PK sampling and ECG will be conducted based on the day of the second olaratumab administration in the cycle.

j If the first olaratumab administration or the initiation of Cycle 2 or 4 is delayed, olaratumab PK and immunogenicity sampling and ECG will be conducted at approximately 336 h (14 days) postinfusion of olaratumab on Day 8 of Cycles 1 or 3. An additional olaratumab PK sample should then also be collected prior to the first olaratumab administration in Cycles 2 or 4.

k If the first olaratumab administration in the cycle is delayed, the specified olaratumab PK and immunogenicity sampling and ECG will be conducted based on the day of the first olaratumab administration in the cycle.

l If doxorubicin administration is delayed, the specified doxorubicin PK sampling and ECG will be conducted based on the day of the doxorubicin administration.

m When only olaratumab is discontinued before Cycle 6 (doxorubicin continues for up to 6 cycles or until when a cumulative dose reaches), this PK and immunogenicity sampling and ECG will be taken at the nearest planned visit to 28 days after the last dose of olaratumab.

n When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, PK samples and immunogenicity samples will no longer be collected.

o When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, 12-lead digital ECGs will be performed annually (±2 weeks) except at the follow-up visit; each assessment will be conducted locally according to the procedure at the respective site. Investigators will still be responsible for patient safety management, but centralized review will not be mandatory. If clinically indicated, 12-lead digital ECGs can be performed more frequently.

Part B

PK Sample Number[a]	Cycle	Day	Dosing[b] Olaratumab	PK Sampling Time	PK[c] Olaratumab	ECG[d]	Immunogenicity[e,f]
		-4 ~ -1		Planned time for pre-infusion of olaratumab on Day 1		X[g]	
				Approx. 1 h after the planned time for pre-infusion of olaratumab on Day 1		X[g]	
				Approx. 2 h after the planned time for pre-infusion of olaratumab on Day 1		X[g]	
1	1	1		Pre-infusion of olaratumab	X	X	X
			X				
2				Immediately postinfusion of olaratumab	X	X	
3				1 h ± 10 min postinfusion of olaratumab	X	X	
4		2		24 ± 3 h postinfusion of olaratumab	X	X	
5		3		48 ± 6 h postinfusion of olaratumab	X	X	
6		4		72 ± 6 h postinfusion of olaratumab	X	X	
7		8		Pre-infusion of olaratumab (Approx 168 h postinfusion of olaratumab on Day 1)	X[h]	X[h]	
			X				
8				Immediately postinfusion of olaratumab	X[i]	X[i]	
9				1 h ± 10 min postinfusion of olaratumab	X[i]	X[i]	
10		10		48 ± 6 h postinfusion of olaratumab	X[i]	X[i]	
11		11		72 ± 6 h postinfusion of olaratumab	X[i]	X[i]	
12		15		168 ± 8 h postinfusion of olaratumab	X[i]	X[i]	
13	2	1		Pre-infusion of olaratumab (Approx 336 h [14 days] postinfusion of olaratumab on Cycle 1 Day 8)	X[j]	X[j]	X[j]
			X				
14				Immediately postinfusion of olaratumab	X	X	
15		8		Pre-infusion of olaratumab	X[i]	X[i]	
			X				
16				Immediately postinfusion of olaratumab	X[i]	X[i]	
17	3	1		Pre-infusion of olaratumab	X	X	X
			X				
18				Immediately postinfusion of olaratumab	X	X	
19				1 h ± 10 min postinfusion of olaratumab	X	X	
20		2		24 ± 3 h postinfusion of olaratumab	X	X	
21		3		48 ± 6 h postinfusion of olaratumab	X	X	
22		4		72 ± 6 h postinfusion of olaratumab	X	X	
23		8		Pre-infusion of olaratumab (Approx 168 h postinfusion of olaratumab on Day 1)	X[h]	X[h]	
			X				
24				Immediately postinfusion of olaratumab	X[i]	X[i]	
25				1 h ± 10 min postinfusion of olaratumab	X[i]	X[i]	
26		10		48 ± 6 h postinfusion of olaratumab	X[i]	X[i]	
27		11		72 ± 6 h postinfusion of olaratumab	X[i]	X[i]	
28		15		168 ± 8 h postinfusion of olaratumab	X[i]	X[i]	

PK Sample Number[a]	Cycle	Day	Dosing[b] Olaratumab	PK Sampling Time	PK[c] Olaratumab	ECG[d]	Immunogenicity[e,f]
29	4	1		Pre-infusion of olaratumab (Approx 336 h [14 days] postinfusion of olaratumab on Cycle 3 Day 8)	Xj	Xj	
			X				
30				Immediately postinfusion of olaratumab	X	X	
31		8		Pre-infusion of olaratumab	Xi	Xi	
			X				
32				Immediately postinfusion of olaratumab	Xi	Xi	
33	5	1		Pre-infusion of olaratumab	X	X	X
			X				
34				Immediately postinfusion of olaratumab	X	X	
35		8		Pre-infusion of olaratumab	Xi	Xi	
			X				
36				Immediately postinfusion of olaratumab	Xi	Xi	
37	7, then every 2 cycles	1		Pre-infusion of olaratumab	Xk	Xl	Xk
			X				
38	Follow-Up			28-Day follow-up visit	X	Xl	X

Abbreviations: Approx. = approximately; ECG = electrocardiogram; h = hour; min = minute; PK = pharmacokinetics.

a Pharmacokinetic Sample Number is numbered based on the case that olaratumab monotherapy is continued up to 7 or 8 cycles.

b Olaratumab 15 mg/kg will be administered as an approximately 60-minute infusion.

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

d Electrocardiogram should be collected prior to any blood draws scheduled at the same time point.

e Samples of approximately 4 mL will be collected.

f 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 28 days following the event.

g Time-matched baseline ECGs (triplicates) will be taken within 4 days prior to Day 1 of Cycle 1, at the planned time for pre-infusion of olaratumab, immediately postinfusion of olaratumab (approx. 1 h after pre-infusion of olaratumab) and 1 h ± 10 min postinfusion of olaratumab (approx. 2 h after pre-infusion of olaratumab) on Day 1.

h If the second olaratumab administration in the cycle is delayed, olaratumab PK sampling and ECG will still be conducted at approximately 168 h postinfusion of olaratumab on Day 1. An additional olaratumab PK sample should then also be collected prior to the second olaratumab administration in the cycle.

i If the second olaratumab administration in the cycle is delayed, the specified olaratumab PK sampling and ECG will be conducted based on the day of the second olaratumab administration in the cycle.

j If the initiation of Cycle 2 or 4 is delayed, olaratumab PK and immunogenicity sampling and ECG will still be conducted at approximately 336 h (14 days) postinfusion of olaratumab on Day 8 of Cycles 1 or 3. An additional olaratumab PK sample should then also be collected prior to the first olaratumab administration on Day 1 of Cycles 2 or 4.

k When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, PK samples and immunogenicity samples will no be longer collected.

l When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, 12-lead digital ECGs will be performed annually (±2 weeks) except at the follow-up visit; each assessment will be conducted locally according to the procedure at the respective site. Investigators will be still responsible for patient safety management, but any centralized review will not be mandatory. If clinically indicated, 12-lead digital ECGs can be performed more frequently.

Attachment 5. Protocol I5B-JE-JGDK Olaratumab and Doxorubicin Dosing Scenarios for Dose Delay and Omission

Olaratumab delay or omission in Cohort 1

Cycle	Day	Olaratumab	Doxorubicin
No olaratumab delay/omission			
N	1	X	X
	2		X
	3		X
	8	X	
	15		
N+1	1 (22)	X	X
	2 (23)		X
	3 (24)		X
	8 (29)	X	
Olaratumab delay			
N	1	X	X
	2		X
	3		X
	8	No administration	
	15	X	
N+1	1 (22)	X	X
	2 (23)		X
	3 (24)		X
	8 (29*)	X	
Olaratumab delay			
N	1	No administration	X
	2		X
	3		X
	8	X	
	15	X	
N+1	1 (22*)	X	X
	2 (23)		X
	3 (24)		X
	8 (29*)	X	

Cycle	Day	Olaratumab	Doxorubicin
Olaratumab delay and omission			
N	1	No administration	X
	2		X
	3		X
	8	No administration	
	15	X	
N+1	1 (22*)	X	X
	2 (23)		X
	3 (24)		X
	8 (29*)	X	
Olaratumab omission			
N	1	No administration	X
	2		X
	3		X
	8	No administration	
	15	No administration	
N+1	1 (22)	Discontinuation of olaratumab	X
	2 (23)		X
	3 (24)		X
	8 (29)		

N: 2 to 5

( ): Relative days from the Day 1 of Cycle N.

*: Upon resolution of the event(s) causing the delay and omission in olaratumab administration, olaratumab treatment will resume according to a Day 1/Day 8 schedule. In this study, every effort will be made to synchronize administration of olaratumab and doxorubicin according to the original dosing scheme; therefore, olaratumab may be administered for up to 4 weeks in a row in circumstances of a 1- or 2-week delay.

Doxorubicin delay or omission in Cohort 1

Cycle	Day	Olaratumab	Doxorubicin**
No Doxorubicin delay/omission			
N	1	X	X
	2		X
	3		X
	8	X	
	15		
N+1	1 (22)	X	X
	2 (23)		X
	3 (24)		X
	8 (29)	X	
Doxorubicin delay			
N	1	X	No administration
	2		
	3		
	8	X	X
	9		X
	10		X
	15		
N+1	1 (29*)	X	X
	2 (30)		X
	3 (31)		X
	8 (36)	X	
Doxorubicin delay			
N	1	X	No administration
	2		
	3		
	8	X	No administration
	9		
	10		
	15		X
	16		X
	17		X
N+1	1 (36*)	X	X
	2 (37)		X
	3 (38)		X
	8 (43)	X	

Cycle	Day	Olaratumab	Doxorubicin**
Doxorubicin omission			
N	1	X	No administration
	2		
	3		
	8	X	No administration
	9		
	10		
	15		No administration
	16		
	17		
N+1	1 (22)	X	Discontinuation of doxorubicin
	2 (23)		
	3 (24)		
	8 (29)	X	

N: 2 to 5

( ): Relative days from the Day 1 of Cycle N.

*: Day 1 of each cycle (Cycle 2 and beyond) is defined as the 21st day after the first doxorubicin administration in the previous cycle.

**: In principle, doxorubicin must be administered on Day 1/2/3 consecutively. In the case that doxorubicin on Day 2/3 or Day 3 cannot be administered due to doxorubicin-related toxicity (or any other reasons), those administrations should be omitted.

Olaratumab delay or omission in Cohort 2 and 3

Cycle	Day	Olaratumab	Doxorubicin
No olaratumab delay/omission			
N	1	X	X
	8	X	
	15		
N+1	1 (22)	X	X
	8 (29)	X	
Olaratumab delay			
N	1	X	X
	8	No administration	
	15	X	
N+1	1 (22)	X	X
	8 (29*)	X	
Olaratumab delay			
N	1	No administration	X
	8	X	
	15	X	
N+1	1 (22*)	X	X
	8 (29*)	X	
Olaratumab delay and omission			
N	1	No administration	X
	8	No administration	
	15	X	
N+1	1 (22*)	X	X
	8 (29*)	X	
Olaratumab omission			
N	1	No administration	X
	8	No administration	
	15	No administration	
N+1	1 (22)	Discontinuation of olaratumab	X
	8 (29)		

N: 2 to 5

( ): Relative days from the Day 1 of Cycle N.

*: Upon resolution of the event(s) causing the delay and omission in olaratumab administration, olaratumab treatment will resume according to a Day 1/Day 8 schedule. In this study, every effort will be made to synchronize administration of olaratumab and doxorubicin according to the original dosing scheme; therefore, olaratumab may be administered for up to 4 weeks in a row in circumstances of a 1- or 2-week delay.

Doxorubicin delay or omission in Cohort 2 and 3

Cycle	Day	Olaratumab	Doxorubicin
No Doxorubicin delay/omission			
N	1	X	X
	8	X	
	15		
N+1	1 (22)	X	X
	8 (29)	X	
Doxorubicin delay			
N	1	X	No administration
	8	X	X
	15		
N+1	1 (29*)	X	X
	8 (36)	X	
Doxorubicin delay			
N	1	X	No administration
	8	X	No administration
	15		X
N+1	1 (36*)	X	X
	8 (43)	X	
Doxorubicin omission			
N	1	X	No administration
	8	X	No administration
	15		No administration
N+1	1 (22)	X	Discontinuation of doxorubicin
	8 (29)	X	

N: 2 to 5

( ): Relative days from the Day 1 of Cycle N.

*: Day 1 of each cycle (Cycle 2 and beyond) is defined as the 21st day after the first doxorubicin administration in the previous cycle.

Attachment 6. Protocol I5B-JE-JGDK 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, 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 7. Protocol I5B-JE-JGDK 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 I5B-JE-JGDK NCI-CTCAE (v4.03) Infusion-Related Reactions

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

Abbreviations: hr = hour; I.V. = intravenous; NSAID = nonsteroidal anti-inflammatory drug.

Attachment 9. Protocol I5B-JE-JGDK (b) Amendment Summary
A Phase 1 Study of Olaratumab in Japanese Patients with Advanced Soft Tissue Sarcoma or Advanced Solid Tumors

Overview

Protocol I5B-JE-JGDK [A Phase 1 Study of Olaratumab in Japanese Patients with Advanced Soft Tissue Sarcoma or Advanced Solid Tumors] has been amended to reduce unnecessary interventions and physical or non-physical burden for the patients after enough data was obtained to assess the primary objective and the secondary objectives. The new protocol is indicated by Amendment (b) 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:

- **Section 8.1.3.2, Section 9.2.2 and Attachment 4:**
  The central review of ECGs will not be mandatory, and the frequency of ECGs was reduced for any patient under treatment over 3 years.
- **Section 8.2.2.1 and Section 8.2.3:**
  PK samples/immunogenicity samples will not be collected except for sampling required for the follow-up visit or the event of an infusion-related reaction for any patient under treatment over 3 years..
- **Attachment 1 and Attachment 2:**
  Coagulation test and urinalysis will not be mandatory for any patient under treatment over 3 years.
- Minor editorial changes were made for accuracy, consistency and clarity.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

2. Synopsis

Length of Study:

~~Estimated first patient visit: February 2015~~First patient enrolled (assigned to therapy): March 2015 Estimated last patient visit: ~~July 2016~~ March 2019

5.2. Rationale for Amendments

5.2.1. Rationale for Amendment (a)

The study was amended to add Cohort 3 in Part A to confirm the safety and tolerability of 20 mg/kg of olaratumab as the loading dose (Cycle 1), followed by 15 mg/kg in subsequent cycles, and 75 mg/m^2 of doxorubicin in every cycle.

5.2.2. Rationale for Amendment (b)

The study was amended to reduce unnecessary interventions and physical or non-physical burden for the patients after enough data was obtained to assess the primary objective and the secondary objectives.

8.1.3.2. Electrocardiograms

When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, 12-lead digital ECGs will be performed annually (±2 weeks) except for the ECG scheduled to be performed at the follow-up visit; each assessment will be conducted locally according to the procedure at the respective site. Investigators will still be responsible for patient safety management, however centralized review will no longer be mandatory. If clinically indicated, 12-lead digital ECGs can be performed more frequently.

8.2.2.1. Pharmacokinetic Samples

When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, PK samples will no longer be collected except for sampling required for the follow-up visit (Attachment 4).

8.2.3. Samples for Immunogenicity Research

When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, immunogenicity samples will no longer be collected except for sampling required for the follow-up visit or in the event of an infusion-related reaction (Attachment 4).

9.2.2. Ancillary Data

When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, electrocardiogram data will no longer be stored electronically in the central vendor's system.

10.8. Interim Analyses

If it is deemed that enough data are obtained to assess the primary objective and the secondary objectives, a clinical study report might be created before the last patient visit. In this case, all data until the data cutoff date will be used for the analysis of safety, efficacy, biomarker, and PK. All data defined in the protocol will continue to be collected from patients on treatment after the data cutoff date unless otherwise specified. These data may be reported separately and the analyses on all patients, including these data, may not be performed.

Attachment 1. Protocol I5B-JE-JGDK Study Schedule

Study Schedule for Protocol I5B-JE-JGDK – Part A: Screening and Cycle 1

b Vital sign measurements will be obtained prior to and at the completion of each olaratumab administration, and prior to each doxorubicin administration.

Study Schedule for Protocol I5B-JE-JGDK – Part A: Cycle 2 and beyond

	Cycle 2-6				Cycle 7-n		Follow-Up[c]	
Relative day within a cycle	1[a]	2	3	8	1[b]	8		
Allowance (days)	+3			±3[d]	+3	±3	±5	**Comments**
Coagulation	X[e]				X[e,h]		X	Should be performed approximately every 6 weeks (ie, at the beginning of Cycle 3 and every other cycle thereafter).
Urinalysis	X[e]				X[e,h]		X	

h When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, coagulation test and urinalysis will no longer be mandatory.

Study Schedule for Protocol I5B-JE-JGDK – Part B: Cycle 2 and beyond

	Cycle 2-n		Follow-Up[b]	
Relative Day Within a Cycle	**1[a]**	**8**		**Comments**
Allowance (days)	**+3**	**±3[c]**	±5	
Coagulation	X[d,f]		X	Should be performed approximately every 6 weeks (ie, at the beginning of Cycle 3 and every other cycle thereafter).
Urinalysis	X[d,f]		X	

f When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, coagulation test and urinalysis will no longer be mandatory.

Attachment 2. Protocol I5B-JE-JGDK Clinical Laboratory Tests

Urinalysis[f]
Specific gravity
pH
Protein
Glucose
Ketones
Blood

Coagulation[f]
Prothrombin time
International normalized ratio
Activated partial thromboplastin time

f When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, coagulation test and urinalysis will no longer be mandatory.

Attachment 4. Protocol I5B-JE-JGDK Pharmacokinetic Sampling, ECG, and Immunogenicity Sampling Schedule

Part A – Cohort 1

PK Sample Number[a]	Cycle	Day	Dosing[b]		PK Sampling Time	PK[c]		ECG[d]	Immunogenicity[e,f]
			Olaratumab	Doxorubicin		Olaratumab	Doxorubicin		
37	7, then every 2 cycles	1			Pre-infusion of olaratumab	X[n]		X[o]	X[n]
			X						
38	Follow-Up[m]				28-Day follow-up visit[m]	X		X[o]	X

n When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, PK samples and immunogenicity samples will no longer be collected.

o When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, 12-lead digital ECGs will be performed annually (±2 weeks) except at the follow-up visit; each assessment will be conducted locally according to the procedure at the respective site. Investigators will still be responsible for patient safety management, but centralized review will not be mandatory. If clinically indicated, 12-lead digital ECGs can be performed more frequently.

Part A – Cohort 2 and 3

PK Sample Number[a]	Cycle	Day	Dosing[b]		PK Sampling Time	PK[c]		ECG[d]	Immuno-genicity[e,f]
			Olaratumab	Doxorubicin		Olaratumab	Doxorubicin		
43	7, then every 2 cycles	1			Pre-infusion of olaratumab	X[n]		X[o]	X[n]
			X						
44	Follow-Up[m]				28-Day follow-up visit[m]	X		X[o]	X

n When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, PK samples and immunogenicity samples will no longer be collected.

o When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, 12-lead digital ECGs will be performed annually (±2 weeks) except at the follow-up visit; each assessment will be conducted locally according to the procedure at the respective site. Investigators will be still responsible for patient safety management, but any centralized review will not be mandatory. If clinically indicated, 12-lead digital ECGs can be performed more frequently.

Part B

PK Sample Number[a]	Cycle	Day	Dosing[b]	PK Sampling Time	PK[c]	ECG[d]	Immunogenicity[e,f]
			Olaratumab		Olaratumab		
37	7, then every 2 cycles	1		Pre-infusion of olaratumab	X[k]	X[l]	X[k]
			X				
38	Follow-Up			28-Day follow-up visit	X	X[l]	X

k When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, PK samples and immunogenicity samples will no longer be collected.

l When enough data for the analysis of the primary and the secondary endpoints has been collected as determined by the sponsor and the patient has continued the study treatment for more than 3 years, 12-lead digital ECGs will be performed annually (±2 weeks) except at the follow-up visit; each assessment will be conducted locally according to the procedure at the respective site. Investigators will be still responsible for patient safety management, but any centralized review will no longer be mandatory. If clinically indicated, 12-lead digital ECGs can be performed more frequently.

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