I5B-MC-JGDN(b) Phase 1 Oncology Protocol

A Phase 1, Open-Label, Dose-Escalation Study of Olaratumab as a Single Agent and in Combination with Doxorubicin, Vincristine/Irinotecan, or High-Dose Ifosfamide in Pediatric Patients with Relapsed or Refractory Solid Tumors

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1. Protocol I5B-MC-JGDN(b)

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Olaratumab (LY3012207)

This Phase 1 study is a multicenter, open-label, dose-escalation study of olaratumab (LY3012207) as a single agent and in combination with either doxorubicin, vincristine/irinotecan, or high-dose ifosfamide in pediatric patients with relapsed or refractory solid tumors.

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2. Synopsis

This Phase 1 study is a multicenter, open-label, dose-escalation study of olaratumab (LY3012207) as a single agent and in combination with either doxorubicin, vincristine/irinotecan, or high-dose ifosfamide in pediatric patients with relapsed or refractory solid tumors.

Clinical Protocol Synopsis: Study I5B-MC-JGDN

Name of Investigational Product: Olaratumab (LY3012207)

Title of Study: A Phase 1, Open-Label, Dose-Escalation Study of Olaratumab as a Single Agent and in Combination with Doxorubicin, Vincristine/Irinotecan, or High-Dose Ifosfamide in Pediatric Patients with Relapsed or Refractory Solid Tumors

Number of Planned Patients:	**Phase of Development:** 1
Entered/Screened: Approximately 110 Enrolled: Minimum 24 Maximum 79	

Length of Study:
Planned first patient visit: 11 February 2016
Planned last patient visit: 05 June 2019

Objectives:
The primary objective of this study is to determine a recommended dose of olaratumab in combination with at least one of the studied chemotherapy regimens in pediatric patients based on any dose-limiting toxicities (DLTs) as well as olaratumab serum exposure-matching between the adult and pediatric populations.

The secondary objectives of this study are:

- to investigate the pharmacokinetics (PK) of olaratumab as monotherapy and in combination with either doxorubicin, vincristine/irinotecan, or high-dose ifosfamide in pediatric patients;
- to assess the possible development of antibodies against olaratumab (immunogenicity) in pediatric patients; and
- to document any antitumor activity (including progression-free survival and objective response rate [ORR]) observed with olaratumab in combination with either doxorubicin, vincristine/irinotecan, or high-dose ifosfamide in pediatric patients.

The exploratory objective of this study is:

- to identify exploratory biomarkers associated with tumor response and/or safety.

Study Design: Study JGDN is a multicenter, dose-escalation, open-label Phase 1 pediatric safety clinical trial with 3 distinct components, Part A, Part B, and Part C.

Part A will consist of at least 12 evaluable pediatric patients. These patients will be treated for 1 cycle (21 days) of olaratumab monotherapy at 15 mg/kg on Day 1 and Day 8 (adult dose for which efficacy was observed in Study I5B-IE-JGDG). If the patient does not experience a DLT in the first cycle of monotherapy, or meet any other criteria for discontinuation, the patient will then receive olaratumab (15 mg/kg) plus one of 3 standard chemotherapy regimens (doxorubicin or vincristine/irinotecan or high-dose ifosfamide per investigator discretion). Treatment will continue until disease progression or other discontinuation criteria are met.

Part B will be initiated after the following criteria have been met:

- Acceptable safety results, which must include a minimum of 6 evaluable patients, and the PK profile from Part A monotherapy.
- At least one of the 15 mg/kg combination arms has met the following DLT criteria: less than one-third (that is, approximately 33.3% [minimum of 3 patients]) DLT rate. Only the combination arms in Part A that have met these criteria may be studied in Parts B and C.

Part B patients will be treated for 1 cycle (21 days) of olaratumab monotherapy at 20 mg/kg on Day 1 and Day 8 then receive olaratumab (20 mg/kg) plus one of 3 standard chemotherapy regimens described in Part A. Part B will be complete when at least 10 patients (regardless of assigned chemotherapy arm) are evaluable for safety of olaratumab 20 mg/kg monotherapy. Part C will be initiated when at least 10 patients (regardless of chemotherapy arm) are evaluable for safety of olaratumab 20 mg/kg from Part B. Part C patients will receive olaratumab (20 mg/kg) in combination with any of the 3 chemotherapy regimens (per investigator discretion) from Cycle 1 onward (i.e no olaratumab monotherapy in Cycle 1 of Part C). Parts B and C together will enroll up to 45 patients (15 per chemotherapy arm). Treatment will continue until disease progression or other discontinuation criteria are met.

Diagnosis and Main Criteria for Inclusion and Exclusions: Eligible patients will be <18 years of age with a diagnosis of relapsed or refractory solid tumors not amenable to curative treatment, for whom chemotherapy with doxorubicin, vincristine/irinotecan, or high-dose ifosfamide is deemed appropriate by the investigator. In addition, the patient must have adequate performance status by Lansky or Karnofsky and adequate hematologic, organ, and coagulation function. The patient must not have a hematologic malignancy, uncontrolled intercurrent illness, or active infection.

Test Product, Dosage, and Mode of Administration:

Olaratumab: for intravenous (IV) use, supplied in single-use 500 mg/50 mL vials containing 10 mg/mL of product in histidine buffer, administered to patients as an IV infusion at 15 or 20 mg/kg on Day 1 and Day 8 of each cycle. Cycles are 21 days in length.

Doxorubicin: will be administered intravenously. Doxorubicin (37.5 mg/m^2) is to be administered on Day 1 and Day 2 of each 21-day cycle, for up to 6 cycles or a cumulative dose of 450 mg/m^2.

Dexrazoxane: may be administered at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion via IV injection, beginning 30 minutes prior to each doxorubicin infusion for the prevention of cardiotoxicity. It is recommended that all patients receiving doxorubicin also receive dexrazoxane. Dexrazoxane should be administered after completion of the olaratumab infusion, prior to administration of doxorubicin.

Vincristine: will be administered intravenously. Vincristine (patients ≥ 10 kg: 1.5 mg/m^2, patients <10 kg: 0.05mg/kg. Dose is capped at 2 mg) is to be administered on Day 1 and Day 8 of each 21-day cycle.

Irinotecan: will be administered intravenously. Irinotecan (50 mg/m^2) is to be administered on Days 1, 2, 3, 4, and 5 of each 21-day cycle.

Ifosfamide: will be administered intravenously. Ifosfamide (2.8 g/m^2) is to be administered on Days 1, 2, 3, 4, and 5 of each 21-day cycle, for up to 6 cycles or a cumulative dose of 84 g/m^2.

Mesna: commercial formulations will be used and administered intravenously. Mesna should be administered at a minimum dose equal to 60% of the ifosfamide dose according to institutional guidelines.

Planned Duration of Treatment:

The planned duration of treatment is not fixed; patients will remain on study until they fulfill one of the criteria for study discontinuation.

Follow-up in post-treatment discontinuation: 30 days (±7 days) for patients with disease progression. For patients who have discontinued study treatment due to toxicity or reasons other than progressive disease, follow-up will continue every 6 weeks (±7 days) until progression.

Criteria for Evaluation:

Efficacy:

Radiographic assessments will be performed at baseline and then every 2 cycles (±7 days) until radiographic documentation of progressive disease. Response Evaluation Criteria In Solid Tumors, Version 1.1 criteria should be used for all solid tumors with the exception of central nervous system tumors. Response Assessment in Neuro-Oncology Criteria or Macdonald Criteria should be used for central nervous system tumors.

Safety: The safety and tolerability of the study treatment is determined by reported adverse events (AEs), physical exam including vital signs, clinical laboratory tests, electrocardiograms, and results of echocardiogram / multigated acquisition scans. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 and summarized by System Organ Class and preferred term.

Pharmacokinetic/Pharmacodynamic:
Blood samples will be collected at various time points for PK assessment for olaratumab levels and the levels of the combination chemotherapies. Blood samples will be collected at various time points for immunogenicity analysis.

Tailoring Genetics and Biomarkers:
Samples will be collected at various time points for nonpharmacogenomic biomarker research. A whole blood sample will be collected for pharmacogenomics analysis.

Tumor Tissue Biomarker:
Patients may provide a previously archived primary or metastatic tumor tissue sample (paraffin block or unstained slides). Additional voluntary pre- and post-treatment tumor tissue samples may be requested for further biomarker research.

Statistical Methods:
The primary objective of this study is to determine a safe dose of olaratumab alone or in combination with chemotherapy regimens that can be administered to pediatric patients. The study will enroll a minimum of 12 patients in Part A. Safety reviews will be performed prior to opening Parts B and C of the study.

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

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

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

Efficacy: Exploratory efficacy analysis will be performed to investigate antitumor activity within each combination arm. Progression-free survival curves and the median with 90% confidence interval (CI) will be estimated using Kaplan-Meier method. The objective response rate (ORR = complete response [CR] + partial response [PR]) and disease control rate (DCR=CR + PR + stable disease) and the 90% exact CI will be tabulated for each cohort.

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

3. Table of Contents

A Phase 1, Open-Label, Dose-Escalation Study of Olaratumab as a Single Agent and in Combination with Doxorubicin, Vincristine/Irinotecan, or High-Dose Ifosfamide in Pediatric Patients with Relapsed or Refractory Solid Tumors

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4. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibody
AE	Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
assent	Agreement from a minor or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some Institutional Review Boards [IRBs]/ethical review boards [ERBs]).
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
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).
CHF	congestive heart failure
CI	confidence interval
C_{min}	minimum plasma concentration
$C_{min,1}$	minimum serum concentration at the end of Cycle 1
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
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECHO	echocardiogram
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least one dose of study treatment.
enter	Patients who are entered in the trial are those who have signed the informed consent form directly or through their legally acceptable representatives.
ERB/IRB	ethical review board/institutional review board: /A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factors
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure

ICF	informed consent form
ICH	International Conference on Harmonisation
IgG1	immunoglobulin subclass G1
INR	international normalized ratio
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for datalock.
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.
IRR	infusion-related reaction
IV	intravenous
IWRS	Interactive Web Response System
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
LMS	leiomyosarcoma
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
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

mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NOAEL	no-observable-adverse-effects level
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participants are aware of the drug therapy received during the study.
ORR	objective response rate
OS	overall survival
patient	a subject with a defined disease
PD	pharmacodynamic
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PDX	patient-derived xenograft
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PopPK	population pharmacokinetics
PR	partial response
PT	prothrombin time
PTT or aPTT	partial thromboplastin time
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria In Solid Tumors
refractory disease	as disease progression after receiving at least one course of standard chemotherapy without prior demonstration of a radiographic response to chemotherapy

relapsed disease	disease progression following demonstration of a radiographic response of the primary tumor and or metastatic site or occurrence of new site of disease on or off oncologic therapy
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	To screen a patient who was previously declared a screen failure for the same study
RT	radiation therapy
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	A patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
sponsor	The party who takes responsibility for the initiation, management and/or financing of a clinical study.
STS	soft tissue sarcoma
study completion	This study will be considered complete after all patients have completed treatment and their safety summary visit.
SUSAR	suspected unexpected serious adverse reactions
TBI	total body irradiation
TCGA	The Cancer Genome Atlas
TE	treatment-emergent
TK	toxicokinetics
TPO	third-party organization
ULN	upper limit of normal

5. A Phase 1, Open-Label, Dose-Escalation Study of Olaratumab as a Single Agent and in Combination with Doxorubicin, Vincristine/Irinotecan, or High-Dose Ifosfamide in Pediatric Patients with Relapsed or Refractory Solid Introduction

5.1. Rationale and Justification for the Study

Platelet-derived growth factor receptor α (PDGFRα) autocrine signaling has been implicated in the pathogenesis of sarcomas (Fleming et al. 1992; McDermott et al. 2009), which are recognized to originate from PDGFR-positive mesenchymal cells. An analysis of publicly available genomic data, including those from The Cancer Genome Atlas (TCGA 2014), shows messenger ribonucleic acid (mRNA) overexpression for PDGFRα and platelet-derived growth factors (PDGFs) in sarcoma, further implicating this autocrine loop in the pathogenesis of soft tissue sarcoma (STS) (data on file). Preclinical studies of olaratumab as a single agent or in combination with chemotherapy have demonstrated antitumor activity in human sarcoma xenograft models.

The PDGFR pathway has also been implicated in several pediatric tumors such as gliomas (Paugh et al. 2013), sarcomas including rhabdomyosarcoma (Ehnman et al. 2013), osteosarcoma (McGary et al. 2002), and Ewing sarcoma (Dubois et al. 2010). In pediatric sarcomas and gliomas, several types of genetic alterations, including gene amplification, translocations, and activating mutations, resulted in ligand and/or receptor overexpression. PDGFR gene expression in pediatric rhabdomyosarcoma demonstrated decreased failure-free survival for patients with tumors that overexpressed either PDGFRα or PDGFRβ mRNA (DuBois and Demetri 2007).

Olaratumab (LY3012207) is a recombinant human immunoglobulin subclass G1 (IgG1) monoclonal antibody (mAb) that specifically binds to PDGFRα and has demonstrated activity in in vitro and in vivo systems on cancer models known to be driven by a PDGF-PDGFRα autocrine loop (Gerber et al. 2012; ImClone Report 4881-10, and data on file). Once bound to PDGFRα, olaratumab blocks PDGF binding and PDGF-induced PDGFRα activation (Loizos et al. 2005). Olaratumab as a single agent has demonstrated in vivo antitumor activity in human sarcoma xenograft models. In addition, the combination of olaratumab plus doxorubicin had statistically significant antitumor activity compared to the effects of either monotherapy in leiomyosarcoma (LMS) and osteosarcoma xenograft models (ImClone Report 3276-05, ImClone Report 3521-05). The benefit of the doxorubicin plus olaratumab treatment was associated with increased tumor cell apoptosis in SKLMS-1 and KHOS/NP xenograft models (LMS and osteosarcoma) as compared to both agents on their own (ImClone Report 3764-06, ImClone Report 3614-06). Additional preclinical data (Section 5.3.1) indicated that olaratumab showed antitumor activity in pediatric xenografts models, both as a single agent and in combination with doxorubicin.

The importance of PDGFRα activity in sarcomas and the preclinical evidence of activity of olaratumab in sarcoma (as a single agent or in combination with chemotherapy) provided the

rationale for evaluating the clinical efficacy and safety of olaratumab plus doxorubicin in the treatment of patients with advanced STS in the Phase 1b/2 Study I5B-IE-JGDG (JGDG). Patients with Kaposi's sarcoma and gastrointestinal stromal tumor were not included in the study.

As of 22 August 2015, a total of 497 adult patients had been treated with olaratumab. In the randomized portion of Study JGDG (doxorubicin alone or in combination with olaratumab), a total of 129 patients with advanced STS were treated. Interim efficacy and safety data available from this study demonstrate a positive benefit-risk assessment for olaratumab treatment (discussed in Section 5.3).

Altogether, preclinical and clinical data support exploring olaratumab in combination with standard chemotherapy regimens for patients with sarcomas and other pediatric tumors. The present Phase 1 study (JGDN) has been developed based on regulatory input and advice from external experts, who recommended minimizing the exposure to single-agent therapy in pediatrics prior to continuing on standard combination chemotherapy regimens commonly used for specific tumor subtypes. In this regard, the proposed study intends to enroll pediatric patients aged from 0 to less than 18 years of age with solid tumors for 1 cycle of olaratumab monotherapy and subsequently move to standard therapies with either doxorubicin, or vincristine/irinotecan, or high-dose ifosfamide. Olaratumab monotherapy will start at 15 mg/kg, a dose which was efficacious in adults (Study JGDG). A dose of 15 mg/kg olaratumab is expected to achieve a similar serum exposure level in both the pediatric and adult populations (see Section 5.4). Furthermore, in 2 previous Phase 1 dose-escalation trials (I5B-IE-JGDC [JGDC] and I5B-IE-JGDF [JGDF]) and in the 2 Phase 2 monotherapy studies (I5B-IE-JGDE [JGDE] and I5B-IE-JGDH [JGDH]) in adults, single-agent olaratumab has consistently been well tolerated, with no dose-limiting toxicities (DLTs) observed up to a dose of 16 mg/kg weekly times 4 doses in a 6 week cycle, 20 mg/kg administered every 2 weeks, and up to a dose of 15 mg/kg administered of Day 1 and Day 8 of a 21-day cycle.

The primary objective in Study JGDN will be to assess the safety profile of olaratumab as a single agent and in combination with either doxorubicin, vincristine/irinotecan, or high-dose ifosfamide. The secondary objectives will include the pharmacokinetic (PK) profile of olaratumab as a single agent and in combination with doxorubicin, vincristine/irinotecan, or high-dose ifosfamide and the antitumor activity of the combination chemotherapies. These regimens are recommended according to standard clinical practice in pediatric patients (Sandler et al. 2001; Carli et al. 2003; Mascarenhas et al. 2010).

The study consists of 3 parts. Part A will consist of approximately 12 evaluable pediatric patients treated for 1 cycle (21 days) of olaratumab monotherapy at 15 mg/kg on Day 1 and Day 8. If the patient does not experience a DLT in the first cycle of monotherapy, or meet any other criteria for discontinuation, the patient will then receive olaratumab (15 mg/kg) plus one of 3 standard chemotherapy regimens (doxorubicin or vincristine/irinotecan or high-dose ifosfamide per investigator discretion). Part B patients will be treated for 1 cycle of olaratumab monotherapy at 20 mg/kg on Day 1 and Day 8 then receive olaratumab (20 mg/kg) plus one of 3 standard chemotherapy regimens described in Part A. Part B will be complete when at least 10 patients (regardless of assigned chemotherapy arm) are evaluable for safety of olaratumab 20 mg/kg monotherapy. Part C will be initiated after confirmation of safety of olaratumab 20 mg/kg from Part B. Part C patients will receive olaratumab (20 mg/kg) in combination with any of the 3 chemotherapy regimens (per investigator discretion) from Cycle 1 onward (i.e no olaratumab monotherapy in Cycle 1 of Part C). Parts B and C together will enroll up to 45 patients (15 per chemotherapy arm). Treatment will continue until disease progression or other discontinuation criteria are met.

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. Objectives

5.2.1. Primary Objective

The primary objective of this study is to determine a recommended dose of olaratumab in combination with at least one of the studied chemotherapy regimens in pediatric patients based on any DLTs as well as olaratumab serum exposure-matching between the adult and pediatric populations.

5.2.2. Secondary Objectives

The secondary objectives of this study are:

- to investigate the PK of olaratumab as monotherapy and in combination with either doxorubicin, vincristine/irinotecan, or high-dose ifosfamide in pediatric patients;
- to assess the possible development of antibodies against olaratumab (immunogenicity) in pediatric patients; and
- to document any antitumor activity (including progression-free survival [PFS] and objective response rate [ORR]) observed with olaratumab in combination with either doxorubicin, vincristine/irinotecan, or high-dose ifosfamide in pediatric patients.

5.2.3. Exploratory Objectives

The exploratory objective of this study is:

- to identify exploratory biomarkers associated with tumor response and/or safety.

5.3. General Introduction to Olaratumab

Olaratumab is a recombinant human mAb of the IgG1 subclass. It is composed of 4 polypeptide chains, 2 identical heavy (γ) chains consisting of 457 amino acids each and 2 identical light (κ) chains consisting of 214 amino acids each. The heavy chain subunit contains 2 consensus sequences for potential N-linked glycosylation. Olaratumab selectively binds to PDGFRα.

Olaratumab has been studied in adult patients with advanced and metastatic cancer. As of 30 June 2015, adverse event (AE) information is available for 497 adult patients administered olaratumab from 2 Phase 1 monotherapy studies in patients with advanced solid tumors and 6 Phase 2 studies, including monotherapy and combination therapy studies. Olaratumab was well tolerated in Phase 1 monotherapy dose-escalation trials (JGDC and JGDF) (dose ranging from 4 to 20 mg/kg administered as 1-hour intravenous [IV] infusions once a week, once every 2 weeks, or on Day 1 and Day 8 of a 21-day cycle) and no DLTs were observed.

In the Phase 2 trials, olaratumab was given both as a single agent and in combination with other chemotherapeutic agents (Table JGDN.5.1) in adult patients with various solid tumor types. In general, olaratumab was well tolerated, with an acceptable and monitorable toxicity profile. The observed safety profile in the combination trials was generally consistent with the safety profile of combination chemotherapeutic agents. No hepatic or renal safety issues were identified in the clinical development program either as olaratumab monotherapy or in combination with other chemotherapies.

Table JGDN.5.1. Chemotherapeutic Agents Used in Combination with Olaratumab

Tumor Type	Chemotherapy
Ovarian	Liposomal doxorubicin
Non-small cell lung	Paclitaxel and carboplatin
Prostate	Mitozantren and prednisone
Soft tissue sarcoma	Doxorubicin

In Study JGDG (adult STS), olaratumab in combination with doxorubicin has an acceptable and monitorable safety profile and supports a positive benefit-risk profile in light of the efficacy data.

Lilly has identified infusion-related reactions (IRR) as an important identified risk of olaratumab. As with other mAbs, hypersensitivity reactions have been reported with olaratumab administration. IRRs have been primarily Grade 1-2.

Study JGDG was an open-label, randomized Phase 1b/2 study that enrolled doxorubicin-naïve patients with advanced STS not amenable to treatment with surgery or radiotherapy. The investigational Arm A received olaratumab (15 mg/kg) on Day 1 and Day 8 plus doxorubicin (75 mg/m²) on Day 1 of each 21-day cycle for up to 8 cycles. The control Arm B received doxorubicin (75 mg/m^2) on Day 1 of each 21-day cycle for up to 8 cycles.

The primary analysis of this trial (based on 103 PFS events observed as of the 15 August 2014 cutoff date) showed that the predefined, statistical, primary endpoint for PFS was met over doxorubicin alone, with a stratified PFS hazard ratio (HR) of 0.67 (p=0.0615 relative to the

protocol-defined two-sided significance level of alpha=0.1999]). Based on investigator assessment, the median PFS was 28.6 weeks (6.6 months) for the investigational arm and 18.0 weeks (4.1 months) for the control arm. At the time of this analysis, a total of 84 overall survival (OS) events were observed. The combination of olaratumab and doxorubicin provided a highly statistically significant improvement of 11.8 months over doxorubicin alone (HR=0.463; p = 0.0003); the median OS was 26.5 months in the investigational arm and 14.7 months in the control arm.

Adverse events of Grade ≥ 3 were reported in 76.6% of patients in the investigational arm and 66.2% of patients in the control arm (Table JGDN.5.2). The Grade ≥3 AEs in Arm A observed with highest incidence were neutropenia (consolidated term), anemia (consolidated term), febrile neutropenia, thrombocytopenia, and fatigue. In the control arm, the Grade ≥ 3 AEs observed with highest incidence were neutropenia (consolidated term), febrile neutropenia, and anemia (consolidated term). The incidence of neutropenia was higher in the investigational arm; however, the incidences of febrile neutropenia and infections were similar between arms.

Table JGDN.5.2. Summary of Common Adverse Events (Grade 3 and Grade ≥4)
Study JGDG
Safety Population (Phase 2)

Preferred Term	Arm A N = 64 n (%) Median no. of doxorubicin infusions=7		Arm B N = 65 n (%) Median no. of doxorubicin infusions=4	
	Grade 3	Grade ≥ 4	Grade 3	Grade ≥ 4
Patients with any AE	**24 (37.5)**	**27 (42.2)**	**25 (38.5)**	**20 (30.8)**
Neutropenia[a]	12 (18.8)	23 (35.9)	5 (7.7)	17 (26.2)
Anemia[d]	8 (12.5)	0	6 (9.2)	0
Febrile Neutropenia	7 (10.9)	1 (1.6)	9 (13.8)	0
Fatigue	6 (9.4)	0	2 (3.1)	0
Thrombocytopenia	5 (7.8)	2 (3.1)	3 (4.6)	2 (3.1)
Infections and Infestations[c]	5 (7.8)	0	4 (6.2)	3 (4.6)
Mucositis[b]	2 (3.1)	0	3 (4.6)	0
Hypokalemia	2 (3.1)	0	2 (3.1)	0
Lymphopenia	2 (3.1)	0	1 (1.5)	0
Diarrhea	2 (3.1)	0	0	0
Abdominal Pain[g]	2 (3.1)	0	0	0
Musculoskeletal Pain[f]	5 (7.8)	0	0	0
Infusion-Related Reaction[e]	0	2 (3.1)	0	0
Nausea	1 (1.6)	0	2 (3.1)	0
Decreased Appetite	1 (1.6)	0	0	0
Dry Mouth	1 (1.6)	0	0	0
Dehydration	1 (1.6)	0	0	0
Constipation	0	0	1 (1.5)	0
Dyspnea	0	0	1 (1.5)	0
Cardiac arrhythmias	0	0	1 (1.5)	0
Cardiac dysfunctions	1 (1.6)	0	0	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of randomized patients; n = number of patients with given event.
Data cut-off date: 16 May 2015.
[a] Consolidated term comprising the following preferred terms: leukopenia, neutropenia, neutrophil count decreased, white blood cell count decreased.
[b] Consolidated term comprising the following preferred terms: mucosal inflammation, oropharyngeal pain, stomatitis.
[c] Includes all preferred terms within the MedDRA system organ class of Infections and Infestations.
[d] Consolidated term comprising the following preferred terms: anemia, hemoglobin decreased.
[e] Consolidated term comprising the following preferred terms: hypersensitivity, infusion-related reaction, infusion site erythema, injection site pain.
[f] Consolidated term comprising the following preferred terms: back pain, musculoskeletal chest pain, musculoskeletal pain.
[g] Consolidated term comprising the following preferred terms: abdominal pain upper, abdominal pain.
Note. Arm A = Olaratumab + Doxorubicin; Arm B = Doxorubicin.
Source: JGDG CSR Table JGDG 12.16

More information about the known and expected benefits, risks, and reasonably anticipated AEs may be found in the Investigator's Brochure (IB).

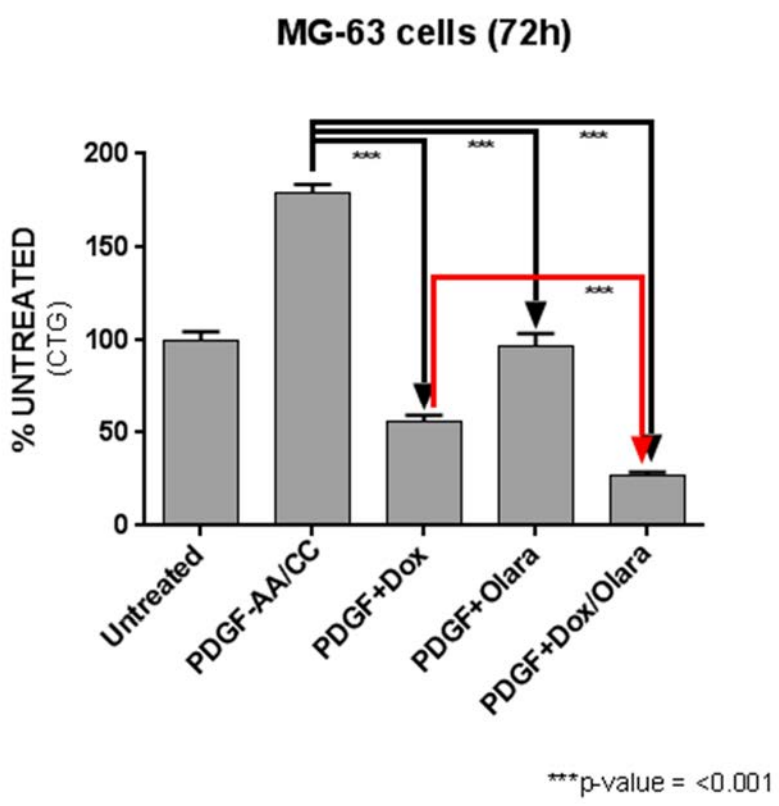
5.3.1. Mechanism of Action and In Vitro/In Vivo Activity

Olaratumab is a recombinant human IgG1-type monoclonal antibody that binds to PDGFRα. This antibody possesses high affinity binding for PDGFRα and blocks PDGF-AA, -BB, and -CC from binding to the receptor. In addition to blocking ligand-induced cell mitogenesis and receptor autophosphorylation, olaratumab inhibits ligand-induced phosphorylation of the downstream signaling molecules Akt and mitogen-activated protein kinase.

PDGF/PDGFRα signaling plays a role in both organ and tissue development, as well as in pathogenesis of nonmalignant diseases (for example, pulmonary fibrosis) and malignant cancers (Östman and Heldin 2007). Many cancer types have been shown to consistently express PDGFRα on tumor tissues, including osteosarcoma, chondrosarcoma, prostate cancer, breast cancer, ovarian cancer, and others (Fleming et al. 1992; de Jong et al. 1998; Östman and Heldin 2007). In malignant disease, the PDGF/PDGFRα axis is effective in promoting tumor growth and proliferation through both autocrine and paracrine mechanisms (Forsberg et al. 1993; Östman and Heldin 2007). PDGFRα is expressed on stromal cells, as well as the cancer cells themselves, within certain tumors. Furthermore, studies have shown that PDGF/PDGFRα signaling affects tumor vasculature through paracrine mediation of vascular endothelial growth factor production (Shah et al. 2010).

Olaratumab has demonstrated activity on cancer models known to be driven by exogenous PDGF stimulation as well as a PDGF-PDGFRα autocrine loop in both *in vitro* and *in vivo* systems (Gerber et al. 2012; Study Reports 4881-10 and C-3G3-1). PDGFRα autocrine signaling has been implicated in the pathogenesis of sarcomas (Fleming et al. 1992), which are hypothesized to originate from PDGFR-positive mesenchymal cells. An analysis of publicly available genomic data, including those from TCGA, shows mRNA overexpression for PDGFRα and PDGFs in sarcoma, further implicating this autocrine loop in the pathogenesis of STS (Study Report BIX-PDGFRA-1).

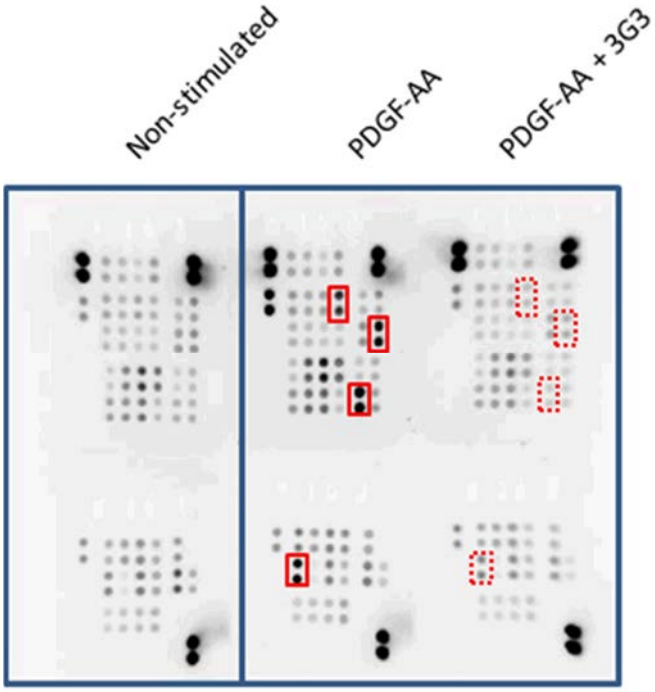
In vitro olaratumab treatment blocks PDGF-dependent proliferation of the MG-63 human osteosarcoma cell line and enhances the antiproliferative effects of doxorubicin (Figure JGDN.5.1).



Abbreviations: Dox = doxorubicin; Olara = olaratumab;
PDGF-AA/CC = platelet-derived growth factor(s) AA and/or CC.

Figure JGDN.5.1. Olaratumab significantly reduces proliferation in the MG-63 Human Osteosarcoma cell line as a single agent and in combination with doxorubicin.

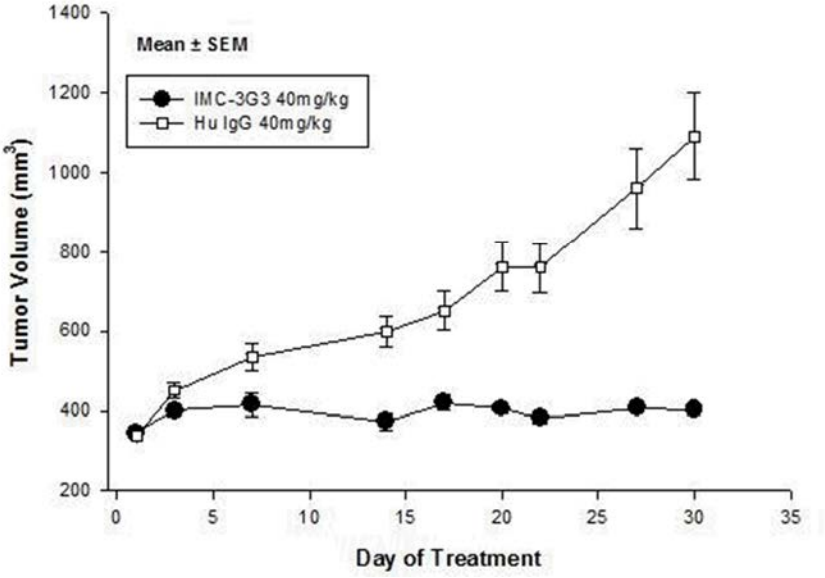
Furthermore, in this same cell line olaratumab treatment completely blocks downstream signaling through a variety of PDGF-activated signaling molecules such as AKT, ERK, and CREB (Figure JGDN.5.2).



Abbreviations: 3G3 = olaratumab; PDGF-AA = platelet-derived growth factor-AA.

Figure JGDN.5.2. Olaratumab blocks PDGF-dependent activation of downstream signaling proteins in the MG-63 human osteosarcoma cell line using Western blot detection. Phospho protein order (red rectangles, top to bottom): pCREB, pERK, pAKT, pWNK1.

Olaratumab as a single agent has demonstrated *in vivo* antitumor activity in a human (SKLMS-1; adult) leiomyosarcoma (LMS) xenograft model (Loizos et al. 2005) and the A-204 human (pediatric) rhabdoid mouse xenograft model (Figure JGDN.5.3). In addition, the combination of olaratumab plus doxorubicin had statistically significant antitumor activity compared to the effects of either monotherapy in LMS and osteosarcoma (KHOS/NP; pediatric) xenograft models (ImClone Report 3276-05; ImClone Report 3521-05 and Figure JGDN.5.4 Graph A, $p < 0.0001$ vs. control). The combination of olaratumab plus doxorubicin was also tested in a patient-derived xenograft (PDX) model ("TTX") established from a tumor tissue harvested from an osteosarcoma patient biopsy (adult) (Bruheim et al. 2004). In this osteosarcoma PDX model, antitumor activity of olaratumab plus doxorubicin (T/C% = 2, $p<0.0001$ vs. control) was significantly enhanced compared to doxorubicin alone (Study Report OPDX3G3-1, and Figure JGDN.5.4 Graph B). Olaratumab as a single agent has demonstrated *in vivo* antitumor activity in a human alveolar rhabdomyosarcoma PDX model ST162 (Figure JGDN.5.5).



Abbreviations: IgG = immunoglobulin G; SEM = standard error of measure.

Figure JGDN.5.3. Activity of olaratumab in the A-204 human rhabdoid mouse xenograft model. Note that "3G3" is the internal designation for olaratumab.

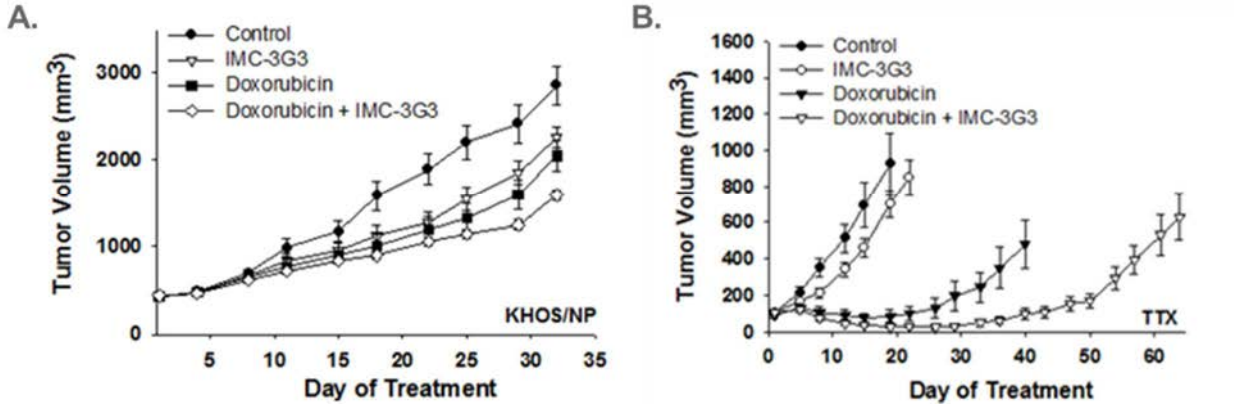
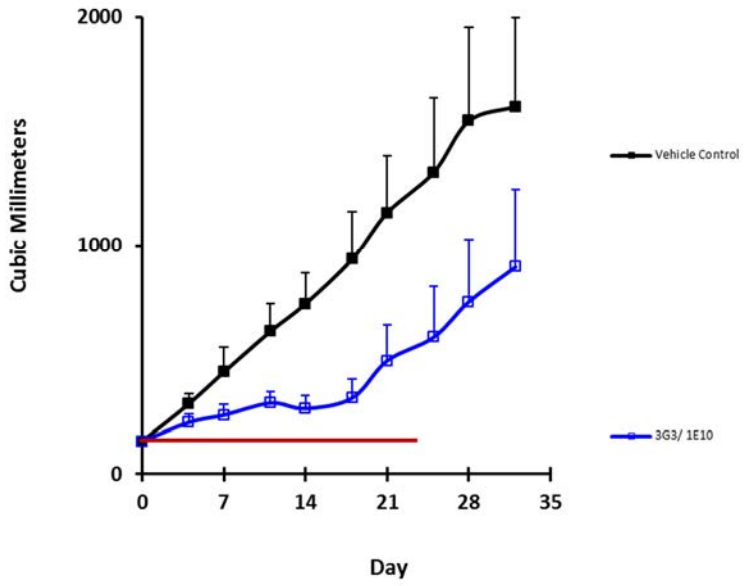


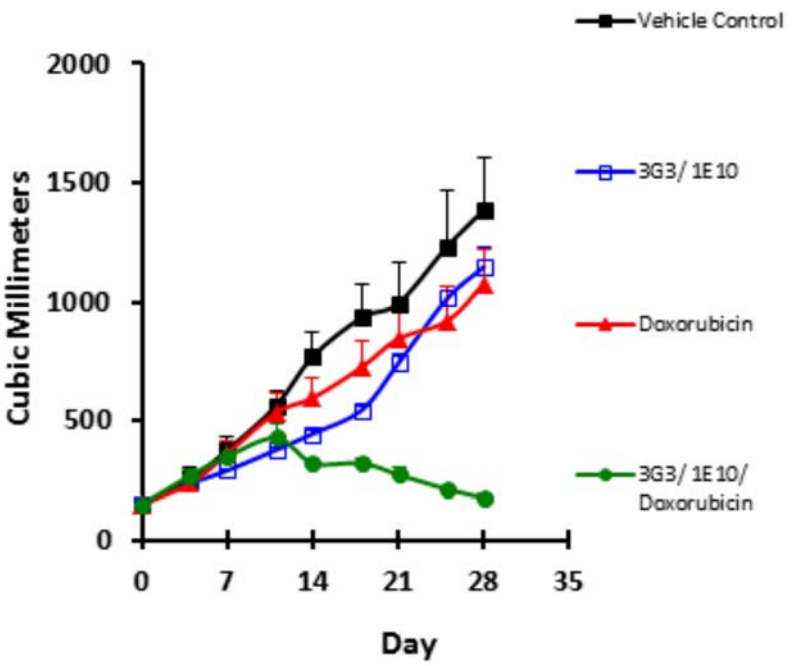
Figure JGDN.5.4. Activity of olaratumab as a single agent and in combination with doxorubicin in 2 mouse models of human osteosarcoma. Note that IMC-3G3 is the internal designation for olaratumab.



Abbreviation: PDGFRα = platelet-derived growth factor receptor alpha.
Note that "3G3" is the original designation for olaratumab and is specific for human PDGFRα; 1E10 is an anti-mouse PDGFRα monoclonal antibody and targets mouse stromal PDGFRα. Combined the 2 antibodies are used to mimic the effects of olaratumab on human patients

Figure JGDN.5.5. Activity of olaratumab in the ST162 human rhabdomyosarcoma patient-derived mouse xenograft model. Note that the red bar indicates the dosing period.

Olaratumab in combination with doxorubicin significantly impairs the growth of the ST1547 patient-derived LMS xenograft model, which is known to express PDGFRα and PDGF-C (Figure JGDN.5.6).



Abbreviation: PDGFRα = platelet-derived growth factor receptor alpha.
Note that "3G3" is the original designation for olaratumab and is specific for human PDGFRα; 1E10 is an anti-mouse PDGFRα monoclonal antibody and targets mouse stromal PDGFRα. Combined the 2 antibodies are used to mimic the effects of olaratumab on human patients.

Figure JGDN.5.6. Activity of olaratumab and doxorubicin on ST1547 human leiomyosarcoma xenograft model.

5.3.2. Nonclinical Pharmacokinetics/Pharmacodynamics

The PK profile of olaratumab was characterized in mice and the pharmacokinetics 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 and clearance and a volume of distribution 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.

5.3.3. Nonclinical Toxicology

The nonclinical safety of olaratumab has been adequately assessed in 3 repeat-dose Good Laboratory Practice studies in cynomolgus monkeys. It was not possible to directly assess crossreactivity in tissue-binding experiments, as olaratumab could not be used for the purposes of immunohistochemical staining (Study IM1236P). However, in addition to immunoprecipitation of PDGFRα in several cynomolgus tissues and the ability to block PDGFRα signaling in cynomolgus skin fibroblasts, direct binding of olaratumab to the

extracellular domain of cynomolgus PDGFRα, with similar affinity to human PDGFRα, has been demonstrated. The toxicity, TK, and immunogenicity of olaratumab were investigated after administration by IV infusion over 5, 13, or 39 weeks to male and female monkeys. In the 5-week toxicity study, olaratumab was administered at dose levels of 5, 16, and 50 mg/kg at Weeks 1, 3, 4, and 5. In the 13- and 39-week studies, olaratumab was administered once per week at dose levels of 7.5, 24, and 75 mg/kg. Mortality, clinical signs, body weight, and food consumption were monitored throughout the treatment and recovery periods. Hematology, coagulation, clinical chemistry, urinalysis, ophthalmology, electrocardiograms (ECGs), heart rate, and blood pressure recordings were analyzed during the treatment and recovery phases. The 13-week and 39-week studies included an immunophenotyping analysis of lymphocyte subsets. Terminal procedures included a full macroscopic examination, organ weight determination, and a comprehensive histopathological evaluation. Development and reproductive toxicity studies of olaratumab in animals have not been conducted.

No clear olaratumab treatment-related adverse effects were noted in any study. A single female treated for 39 weeks with 75 mg/kg was noted with mildly to moderately increased alanine aminotransferase, minimal individual cell necrosis, and moderate infiltrates in the liver, but this effect was not considered clearly attributable to treatment nor was it considered adverse. Therefore, the no-observable-adverse-effects levels (NOAELs) 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.

In summary, weekly administration of olaratumab by IV infusion for up to 39 weeks was well tolerated and not associated with the development of any adverse effects. The monkey serum minimum concentration (C_{min}; 1164 µg/mL) at the 75-mg/kg NOAEL in the 39-week study was approximately 4.5-fold greater than the threshold C_{min} believed to be needed for antitumor activity based on tumor xenograft models (260 µg/mL). The area under the concentration curve from time 0 to 168 hours ($AUC_{[0\text{-}168hr]}$) following the last infusion of 75 mg/kg in the 39-week study (284976 hr•µg/mL) 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 ($AUC_{[0\text{-}96hr]}$ = 17184 hr•µg/mL). Therefore, the 39-week 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. Rationale for Selection of Dose

The current dose-selection strategy for the pediatric population is based on the efficacy, safety, and PK data for olaratumab across previous Phase 1 and Phase 2 studies in adults.

During clinical development, in Phase 1 dose-escalation trials (JGDC and JGDF) and in Phase 2 monotherapy studies (JGDE and JGDH), olaratumab has been consistently well tolerated, with no DLTs observed in the dose-escalation studies up to a dose of 16 mg/kg weekly times 4 doses in a 6-week cycle, 20 mg/kg administered every 2 weeks, and up to a dose of 15 mg/kg administered on Day 1 and Day 8 of a 21-day cycle. When used in combination with other therapeutic agents, an increase of toxicities such as neutropenia and infections were observed in combination with liposomal doxorubicin (olaratumab dose of 20 mg/kg every 2 weeks) and with

paclitaxel/carboplatin (olaratumab dose of 15 mg/kg on Day 1 and Day 8 every 3 weeks). In Study JGDG (15 mg/kg on Day 1 and Day 8 of a 21-day cycle), an increase in neutropenia and mucositis, but not in neutropenic sepsis or febrile neutropenia, have been observed. These toxicities are acceptable and monitorable and are consistent with the toxicity profile of doxorubicin.

Results from a currently ongoing population PK (PopPK) modeling analysis indicate that the serum levels of olaratumab obtained at the dose of 15 mg/kg are best described by a 2-compartment model with linear clearance. This suggests that the dose of 15 mg/kg used in Study JGDG provides serum concentrations such that target-mediated drug disposition is maintained at its near maximum throughout the course of treatment once steady state is reached. Survival data from Study JGDG show that the combination of olaratumab 15 mg/kg with doxorubicin 75 mg/m^2 provides a significant benefit compared to single-agent doxorubicin in patients with advanced metastatic STS, without an increase in serious toxicity. A matched case-control analysis per exposure quartiles based on the trough olaratumab serum concentration at the end of Cycle 1 ($C_{min,1}$) suggests that only patients in the lowest exposure 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, do not show PFS or OS improvement. In addition, a PopPK analysis performed on PK data collected from adult cancer patients indicates that body weight is the main covariate to olaratumab clearance. A dose of 15 mg/kg olaratumab is thus expected to achieve a similar serum exposure level in the pediatric population compared to the adult populations. However, as the relationship between body weight and olaratumab clearance is less than fully proportional, potentially sub-therapeutic olaratumab serum exposures might be observed in patients with very low body weight. Study JGDN therefore manages this possibility by escalating olaratumab to a dose of 20 mg/kg in order to ensure that the pediatric population be exposed to olaratumab serum levels previously associated with clinical benefit. The decision to dose escalate will be based on safety data collected during the first 2 cycles of treatment of JGDN Part A.

6. Investigational Plan

6.1. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Individuals may be re-screened 1 time. The interval before re-screening should be at least 2 weeks. When re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, 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] The patient must have histological or cytological evidence of a diagnosis of solid tumor, excluding lymphomas and melanoma, but including central nervous system (CNS) tumors, that is relapsed or refractory, not be amenable to curative treatment, and for whom chemotherapy with doxorubicin, vincristine/irinotecan, or ifosfamide is deemed appropriate by the investigator. For patients with CNS tumors, neurologic deficits in patients with CNS tumors must have been stable for at least 7 days prior to study enrollment.

[2] The patient has the presence of measurable and/or nonmeasurable but evaluable disease as defined by the Response Evaluation Criteria In Solid Tumors (RECIST Version 1.1) (Eisenhauer et al. 2009; refer to Attachment 8). Response Assessment in Neuro-Oncology (RANO) Criteria (Wen et al. 2010) or Macdonald Criteria (Macdonald et al. 1990) should be used for CNS tumors.

[3] The patient is <18 years of age at the time of first dose of study drug.

[4] The patient, or patient's parent/guardian, has given written informed consent and authorization for release of health information for research prior to any study-specific procedures being performed.

[5] The patient has a Lansky (<16 years of age; Lansky et al. 1987) or Karnofsky (≥16 years of age; Karnofsky et al. 1948) performance score of at least 50.

[6] The patient has adequate hematologic, organ, and coagulation function ≤2 weeks (14 days) prior to first dose of study drug:

- Absolute neutrophil count (ANC) ≥750/mm^3. Granulocyte colony-stimulating factor (G-CSF) cannot be administered ≤1 week (7 days) prior to first dose of study drug. Pegfilgrastim cannot be administered ≤2 weeks (14 days) prior to first dose of study drug.

- Platelets ≥75,000/mm^3. Platelet transfusion to meet this enrollment criterion is not allowed within the preceding 5 days of first dose of study drug.
- Hemoglobin ≥8 g/dL. Transfusions with packed red blood cells is allowed.
- Total bilirubin (sum of conjugated + unconjugated) ≤ 1.5 X upper limit of normal (ULN) for age.
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 times ULN. If the liver has tumor involvement, AST and ALT equaling ≤5.0 times ULN are acceptable.
- Serum creatinine is based on age/gender as follows:

Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1.0	1.0
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating glomerular filtration rate (Attachment 6).

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

[7] Female patients of child-bearing potential must have a negative serum pregnancy test within 7 days prior to Cycle 1 Day 1.

[8] Both female and male patients of child-bearing potential must agree to use highly effective contraceptive precautions during the trial and up to 3 months following the last dose of olaratumab, or longer if appropriate for other study drugs according to their label. A highly effective method of birth control is defined as one that results in a low failure rate (that is, <1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices, sexual abstinence, or a vasectomized partner.

[9] Patients must have fully recovered from the acute toxic effects of all prior anticancer therapies or must adhere to post-treatment conditions as follows:

- Myelosuppressive chemotherapy: at least 21 days after the last dose of myelosuppressive chemotherapy (or 42 days if prior nitrosourea)
- Hematopoietic growth factors: at least 14 days after the last dose of a long-acting growth factor (for example, Neulasta®) or 7 days for short-acting growth factor. For agents that have known adverse events (AEs) occurring beyond 7 days after administration, this period must be extended beyond the time during which AEs are known to occur. The duration of this interval must be discussed with Lilly clinical research physician or clinical research scientist (CRP/CRS).
- Biologic (anti-neoplastic agent): at least 7 days after the last dose of a biologic agent
- Antibody therapy: at least 3 half-lives after the last treatment
- Radiation: 14 days since local palliative radiation therapy (RT) (small port); 150 days if patient has had prior total body irradiation (TBI), craniospinal RT, or 50% or greater pelvic radiation; 42 days for other substantial radiation (such as metaiodobenzylguanidine therapy)
- Stem Cell Infusion without TBI: at least 84 days must have elapsed after transplant or stem cell infusion
- Corticosteroids: for patients with CNS lesions, the dose of corticosteroids should be stable for at least 1 week.

6.1.2. Exclusion Criteria

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

[10] 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) or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[11] Patients that have had bone marrow or solid organ transplant are excluded.

[12] The patient has uncontrolled intercurrent illness including, but not limited to, an ongoing/active infection requiring parenteral antibiotics, symptomatic congestive heart failure (CHF), severe myocardial insufficiency, cardiac arrhythmia, cardiomyopathy, or a psychiatric illness/social situation that would limit compliance with study requirements.

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

[14] Female patients who are pregnant or breastfeeding are excluded.

[15] If the patient is to be enrolled in the doxorubicin combination arm, a left ventricular dysfunction (LVEF < 50%) or shortening fraction of <27% by echocardiogram (either multigated acquisition [MUGA] or echocardiogram [ECHO] are required, not both).

[16] Patients that have received prior anthracycline therapy if the patient is to be enrolled in the doxorubicin combination arm.

[17] The patient has a corrected QT interval of >480 msec on screening ECG if the patient is to be enrolled in the doxorubicin combination arm.

6.2. Summary of Study Design

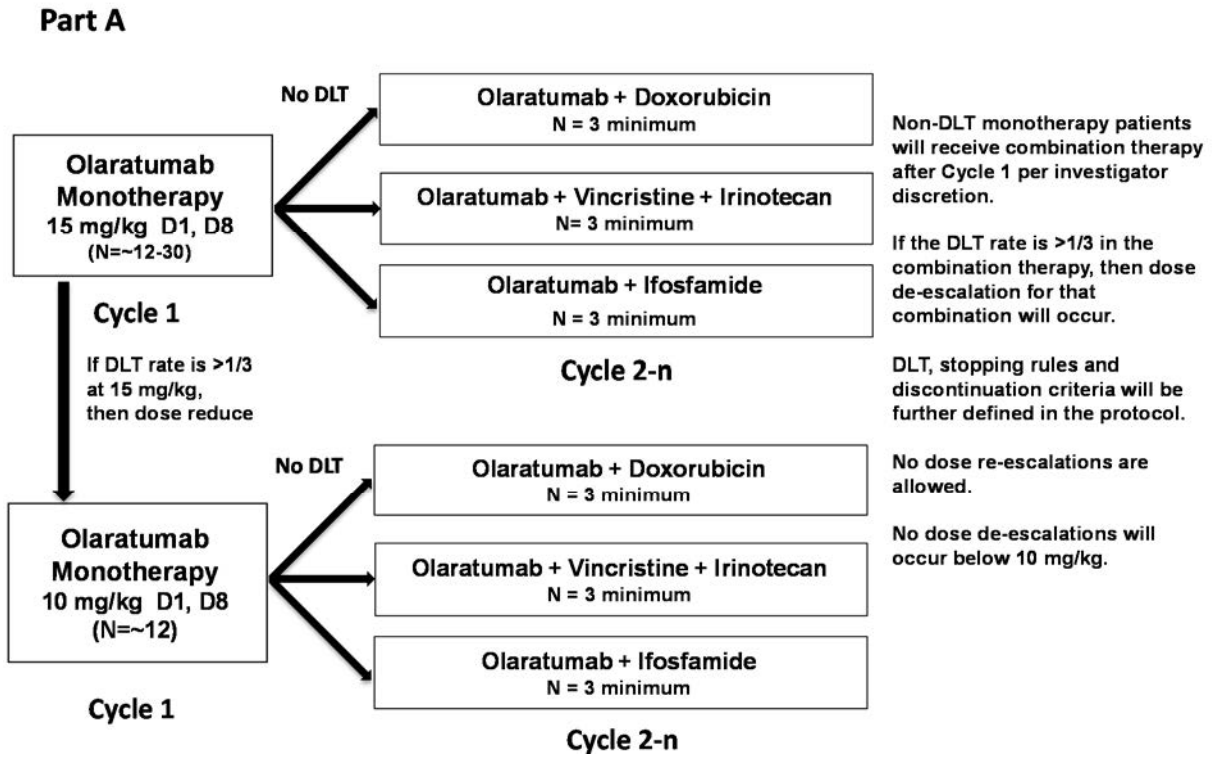
Study JGDN is a multicenter, dose-escalation, open-label Phase 1 pediatric safety clinical trial with 3 distinct components, Part A, Part B, and Part C.

Part A will consist of at least 12 evaluable pediatric patients. Given the expected diversity of age and body weight in the study population, this sample size is expected to provide the necessary amount of PK information in order to characterize the disposition of olaratumab in the pediatric population.

Patients will be treated for 1 cycle (21 days) of olaratumab monotherapy at 15 mg/kg on Day 1 and Day 8 (adult dose for which efficacy was observed in Study JGDG). If the patient does not experience a DLT in the first cycle of monotherapy, or meet any other criteria for discontinuation, the patient will then receive olaratumab (15 mg/kg) plus one of 3 standard chemotherapy regimens (doxorubicin or vincristine/irinotecan or high-dose ifosfamide per investigator discretion). Treatment will continue until disease progression or other discontinuation criteria are met.

During Cycle 1 monotherapy, if the DLT rate is >1/3 (that is, greater than 4 out of 12 patients), then the dose of olaratumab will be reduced to 10 mg/kg. If the DLT rate is >1/3 in the first cycle (Cycle 2) of any of the combination therapy arms, then appropriate dose de-escalation of olaratumab for that combination will occur. Another cohort with at least 3 patients will be studied for that combination with olaratumab at 10 mg/kg.

Part A of the study design is illustrated in Figure JGDN.6.1.



Abbreviations: D = day; DLT = dose-limiting toxicity; N = number of patients; n = number of cycles.

Figure JGDN.6.1. Illustration of Part A of the study design.

Part B will be initiated after the following criteria have been met:

- Acceptable safety results, which must include a minimum of 6 evaluable patients, and the PK profile from Part A monotherapy.
- At least one of the 15 mg/kg combination arms has met the following DLT criteria: less than one-third (that is, approximately ~33.3% [minimum of 3 patients]) DLT rate. Only the combination arms in Part A that have met these criteria may be studied in Part B.

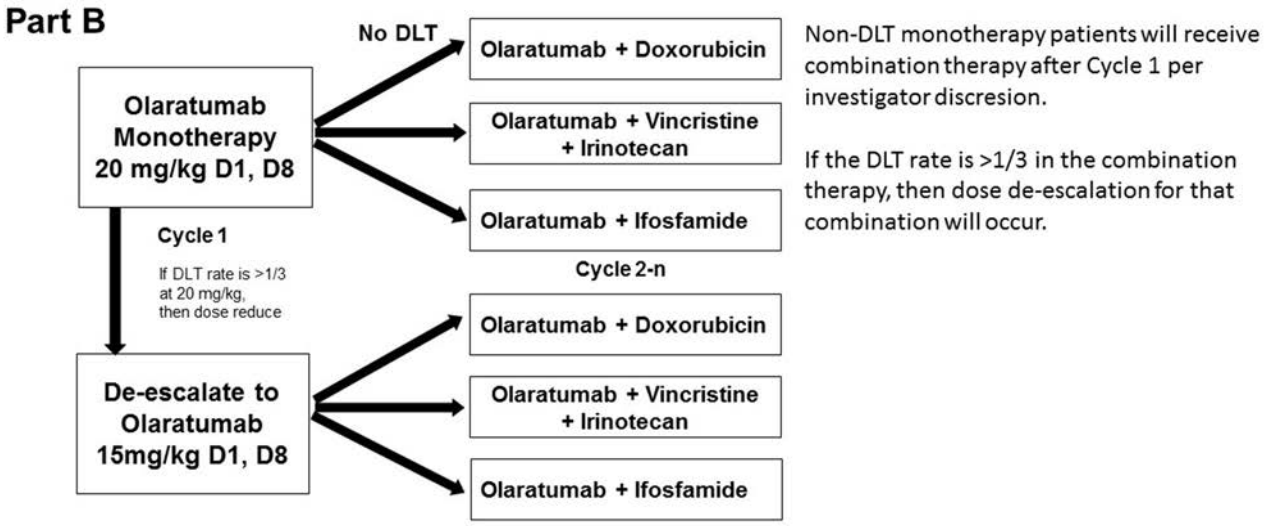
Part B patients will be treated for 1 cycle (21 days) of olaratumab monotherapy at 20 mg/kg on Day 1 and Day 8 then receive olaratumab (20 mg/kg) plus one of 3 standard chemotherapy regimens described in Part A. Part B will be complete when at least 10 patients (regardless of assigned chemotherapy arm) are evaluable for safety of olaratumab 20 mg/kg monotherapy. Treatment will continue until disease progression or other discontinuation criteria are met.

In Part B, if a patient has a DLT during the Cycle 1 monotherapy, the subsequent olaratumab dose will be reduced to 15 mg/kg, and the patient will receive combination therapy in Cycle 2.

During Cycle 1 monotherapy, if the DLT rate is >1/3 (that is, greater than 4 out of 12 patients), then the dose of olaratumab will be reduced to 15 mg/kg for patients subsequently enrolled. If

the DLT rate is >1/3 in any of combination therapy arms, then appropriate dose de-escalation of olaratumab for that combination will occur.

Part B is illustrated in Figure JGDN.6.2.

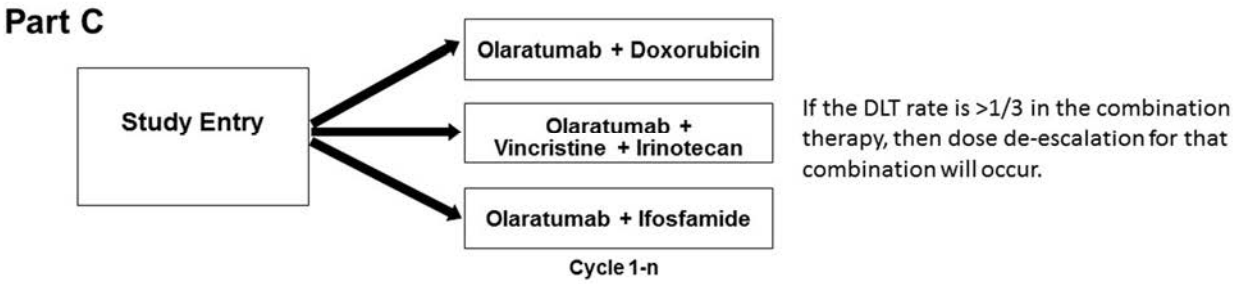


Abbreviations: D = day; DLT = dose-limiting toxicity; N = number of patients; n = number of cycles.

Figure JGDN.6.2. Illustration of Part B of the study design.

Part C will receive olaratumab (20 mg/kg) in combination with any of the 3 chemotherapy regimens from Cycle 1 onwards (ie. no olaratumab monotherapy in Cycle 1). Treatment will continue until disease progression or other discontinuation criteria are met.

Part C is illustrated in Figure JGDN.6.3.



Abbreviations: DLT = dose-limiting toxicity; n = number of cycles.

Figure JGDN.6.3. Illustration of Part C of the study design.

Parts B and C together will enroll up to 45 patients (15 per chemotherapy arm).

The planned duration of treatment is not fixed; patients will remain on study until they fulfill one of the criteria for study discontinuation (Section 6.3). Patients on study treatment who continue to experience clinical benefit and no undue risks may continue olaratumab monotherapy after completion of chemotherapy until one of the criteria for discontinuation is met if deemed medically appropriate in the opinion of the investigator and following discussion and agreement by the medical monitor. This study will enroll a minimum of 24 (maximum of 79) pediatric patients, including a minimum of 10 osteosarcoma patients and 10 rhabdomyosarcoma patients across all treatment arms, if possible. The goal will be to enroll approximately 20 evaluable patients in each combination arm (across Parts A, B, and C) to characterize the safety and PK profile of olaratumab and the respective chemotherapeutic agents, and to inform dose choice for potential later-phase studies.

Refer to Attachment 1 for the Study Schedule.

6.2.1. Primary Endpoint

Primary endpoint is defined as DLT and PK data exposure matching. The primary endpoint analysis will occur after the final patient enrolled has been evaluated for at least 2 cycles.

6.2.2. Study Completion and End of Trial

Any patient enrolled in Part A or Part B that has completed at least 1 cycle of treatment or discontinued due to an AE (during Cycle 1), and completed the required post-treatment safety assessment, will be considered to have completed the monotherapy portion of the study. Patients in Part A or Part B completing Cycle 1 who do not continue to Cycle 2 will be considered evaluable for monotherapy DLTs and PK. Any patient enrolled in Part A or Part B that has completed at least 2 cycles of treatment or discontinued due to an AE (during Cycle 2), and completed the required post-treatment safety assessment, will be considered to have completed the study. Any patient enrolled in Part C that has completed 1 cycle of treatment or discontinued due to an AE (during Cycle 1), and completed the required post-treatment safety assessment, will be considered to have completed the study. However, in all parts of the study, additional cycles of therapy may continue as long as the patient is receiving benefit and no criteria for discontinuation have been met. All secondary and exploratory endpoint analyses will be updated at study completion.

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

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 CRP or CRS 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 or CRS 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 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, parent or legal guardian decision
    - the patient or the patient's designee (for example, parents or legal guardian) requests to be discontinued from the study or study drug
- Sponsor Decision
    - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- The patient has radiographic progressive disease or significant symptomatic disease deterioration characterized as progression of disease, in the opinion of investigator, in the absence of radiographic evidence of progressive disease.
- The patient experiences unacceptable toxicity (for example, a persistent moderate toxicity that is intolerable to the patient).
- The patient is noncompliant with study procedures and/or treatment (Section 7.6).

The reason for 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 electronic case report form (eCRF). 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 (ERB) 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 provided to the sites by Lilly.

Olaratumab for injection is supplied in single-use 500 mg/50 mL vials containing 10 mg/mL of olaratumab in histidine buffer, administered to patients as an IV infusion at 10, 15, or 20 mg/kg.

Other drug products (i.e. doxorubicin hydrochloride, dexrazoxane, vincristine sulfate, irinotecan hydrochloride, and ifosfamide) to be used in Study JGDN will be supplied by Lilly, but commercially available supply may be used as directed by Lilly for cases of regional restrictions or supply limitations.

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

7.2. Study Drug Administration

The investigator or designee is responsible for the following:

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

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

Patients or the parent/guardian 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. Premedication

Infusion-related reactions (IRR), including Grade 3/4 IRR events, have been observed with olaratumab. To date, Grade 3/4 IRR have only been reported during the first cycle of olaratumab treatment. Therefore, in Cycle 1 (both Day 1 and Day 8 doses) all patients should receive premedication with dexamethasone (or equivalent medication) and an H1 antagonist intravenously 30 to 60 minutes prior to olaratumab infusion. Additional premedication may be provided at investigator discretion.

For all subsequent cycles, <u>all</u> patients should receive premedication with an H1 antagonist (for example, diphenhydramine) intravenously 30 to 60 minutes prior to each dose of olaratumab. Additional premedication may be provided at investigator discretion.

Patients with a prior Grade 1 or Grade 2 olaratumab IRR must receive antihistamine and additional premedication (described in Section 7.2.4.1.1). All premedication administered must be adequately documented in the eCRF.

Doxorubicin

Given the emetogenic potential of doxorubicin, premedication with antiemetics per institutional guidelines is recommended.

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

Dexrazoxane may be administered at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion via IV injection, beginning within 30 minutes prior to each doxorubicin infusion for the prevention of cardiotoxicity. It is recommended that all patients receiving doxorubicin also receive dexrazoxane.

Vincristine

Laxatives and/or stool softeners may be used preemptively during vincristine-containing cycles.

Irinotecan

A prophylactic treatment with antiemetics is recommended before each treatment with irinotecan. Nausea and vomiting have been frequently reported. For patients with vomiting associated with delayed diarrhea, hospitalization should be considered.

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

Ifosfamide

When the treatment includes ifosfamide, mesna should be administered at a minimum dose equal to 60% of the ifosfamide dose according to institutional guidelines, including divided dose or continuous infusion. .

Ifosfamide is associated with moderate emetic potential, antiemetics are recommended to prevent nausea or vomiting.

Ifosfamide should be given with extensive hydration consisting of oral or intravenous fluid (2 L/m^2 IV) to prevent bladder toxicity or according to institutional guidelines. The criteria to start chemotherapy may also include a urine-specific gravity < 1.010 or according to institutional guidelines.

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

premedication may be administered immediately following the end of the observation period (if applicable) or after the completion of the olaratumab infusion.

7.2.2. Dosing Schedule

If any study drug is discontinued (olaratumab or chemotherapy), the patient will be discontinued from the trial. A change of body weight ≥10% (increase or decrease) from baseline will result in re-calculation of dose to be administered.

The following treatments will be administered in this study every 3-week (21-day) ± 3 day cycle (Table JGDN.7.1 and Table JGDN.7.2).

Part A:

Cycle 1

Olaratumab as IV infusion on Day 1 and Day 8 (at 15 mg/kg)

Cycle 2 and beyond

Olaratumab as IV infusion on Day 1 and Day 8 (at 15mg/kg, or 10 mg/kg if de-escalated),

AND

Doxorubicin as IV infusion on Day 1 and Day 2 (at 37.5 mg/m^2; up to 6 cycles or a cumulative dose of 450 mg/m^2)

OR

Vincristine as IV on Day 1 and Day 8 (patients ≥ 10 kg: 1.5 mg/m^2, patients <10 kg: 0.05 mg/kg. Dose is capped at 2 mg) plus irinotecan as IV on Days 1, 2, 3, 4, 5 (at 50 mg/m^2),

OR

Ifosfamide as IV on Days 1, 2, 3, 4, and 5 (at 2.8 g/m^2; up to 6 cycles or a cumulative dose of 84 g/m^2). Treatment beyond 84 g/m^2 requires consultation with the Lilly CRP/CRS.

Part B:

Cycle 1

Olaratumab as IV infusion on Day 1 and Day 8 (at 20 mg/kg)

Cycle 2 and beyond

Olaratumab as IV infusion on Day 1 and Day 8 (at 20 mg/kg),

AND

Doxorubicin as IV infusion on Day 1 and Day 2 (at 37.5 mg/m^2; up to 6 cycles or a cumulative dose of 450 mg/m^2)

OR

Vincristine as IV on Day 1 and Day 8 (patients ≥ 10 kg: 1.5 mg/m^2, patients <10 kg: 0.05 mg/kg. Dose is capped at 2 mg) plus irinotecan as IV on Days 1, 2, 3, 4, 5 (at 50 mg/m^2),

OR

Ifosfamide as IV on Days 1, 2, 3, 4, and 5 (at 2.8 g/m^2; up to 6 cycles or a cumulative dose of 84 g/m^2). Treatment beyond 84 g/m^2 requires consultation with the Lilly CRP/CRS.

Part C:

<u>All Cycles</u>

Olaratumab as IV infusion on Day 1 and Day 8 (at 20 mg/kg),

AND

Doxorubicin as IV infusion on Day 1 and Day 2 (at 37.5 mg/m^2; up to 6 cycles or a cumulative dose of 450 mg/m^2)

OR

Vincristine as IV on Day 1 and Day 8 (patients ≥ 10 kg: 1.5 mg/m^2, patients <10 kg: 0.05 mg/kg. Dose is capped at 2 mg) plus irinotecan as IV on Days 1, 2, 3, 4, and 5 (at 50 mg/m^2),

OR

Ifosfamide as IV on Days 1, 2, 3, 4, and 5 (at 2.8 g/m^2; up to 6 cycles or a cumulative dose of 84 g/m^2). Treatment beyond 84 g/m^2 requires consultation with the Lilly CRP/CRS.

Table JGDN.7.1. Treatment Regimens/Dosing Schedule (Parts A and B)

	Study Drug		Dose	Route	Timing
Cycle 1	Olaratumab[a]	Part A	15 mg/kg	IV	approximately 1 hour infusion on Day 1 and Day 8 of each 21-day cycle
		Part B	20 mg/kg		
Cycle 2-n	Olaratumab[a]	Part A	15 mg/kg	IV	approximately 1 hour infusion Day 1 and Day 8 of each 21-day cycle
		Part B	20 mg/kg		
	1-hour observation period[b] followed by				
	Doxorubicin[c,dg]	Parts A and B	37.5 mg/m^2	IV	Day 1 and Day 2 of each 21-day cycle
			OR		
	Vincristine[e]	Parts A and B	1.5 mg/m^2	IV	Day 1 and Day 8 of each 21-day cycle
	Irinotecan[g]	Parts A and B	50 mg/m^2	IV	Days 1, 2, 3, 4, and 5 of each 21-day cycle
			OR		
	Ifosfamide[fg]	Parts A and B	2.8 g/m^2	IV	approximately 2 to 3 hour infusion on Days 1, 2, 3, 4, and 5 of each 21-day cycle

Abbreviations: eCRF = electronic case report form; IV = intravenous.

a Administer premedication prior to infusion of olaratumab. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at the investigator's discretion. Premedication must be provided in the setting of a prior Grade 1-2 infusion-related reaction, as detailed in Section 7.2.4.1. All premedication administered must be adequately documented in the eCRF.

b A 1-hour observation period is required after the administration of the first and second doses of olaratumab. If there is no evidence of an infusion-related reaction during the initial 2 cycles of olaratumab, then no observation period is required for subsequent treatment cycles. In the event an infusion-related reaction occurs thereafter, then the 1-hour observation period should be reinstituted; see Section 7.2.4.1.

c Administer doxorubicin for up to 6 cycles only or cumulative dose of 450 mg/m^2.

d Administer doxorubicin according to institutional guidelines and/or clinical practice as an IV injection or as an infusion in less than 60 minutes (+10 minutes). Decrease the rate of doxorubicin administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occurs.

e For patients weighing less than 10 kg, the dose of vincristine should be 0.05 mg/kg. The dose is capped at 2 mg for all patients.

f Administer ifosfamide for up to 6 cycles only or a cumulative dose of 84 g/m^2. Treatment beyond 84 g/m^2 requires consultation with the Lilly clinical research physician/clinical research scientist.

g For sequential day chemotherapy, it is recommended to allow a minimum of 20 hours between dosing, unless institutional standard varies.

Table JGDN.7.2 Treatment Regimens/Dosing Schedule (Part C)

	Study Drug	Dose	Route	Timing
Cycle 1-n	Olaratumab[a]	20 mg/kg	IV	approximately 1 -hour infusion on Day 1 and Day 8 of each 21-day cycle
	1-hour observation period[b] followed by			
	Doxorubicin[c,d,g]	37.5 mg/m^2	IV	Day 1 and Day 2 of each 21-day cycle
	OR			
	Vincristine[e]	1.5 mg/m^2	IV	Day 1 and Day 8 of each 21-day cycle
	Irinotecan[g]	50 mg/m^2	IV	Days 1, 2, 3, 4, and 5 of each 21-day cycle
	OR			
	Ifosfamide[f,g]	2.8 g/m^2	IV	approximately 2- to 3 -hour infusion on Days 1, 2, 3, 4, and 5 of each 21-day cycle

Abbreviations: eCRF = electronic case report form; IV = intravenous.

a Administer premedication prior to infusion of olaratumab. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at the investigator's discretion. Premedication must be provided in the setting of a prior Grade 1-2 infusion-related reaction, as detailed in Section 7.2.4.1. All premedication administered must be adequately documented in the eCRF.

b A 1-hour observation period is required after the administration of the first and second doses of olaratumab. If there is no evidence of an infusion-related reaction during the initial 2 cycles of olaratumab, then no observation period is required for subsequent treatment cycles. In the event an infusion-related reaction occurs thereafter, then the 1-hour observation period should be reinstituted; see Section 7.2.4.1.

c Administer doxorubicin for up to 6 cycles only or cumulative dose of 450 mg/m^2.

d Administer doxorubicin according to institutional guidelines and/or clinical practice as an IV injection or as an infusion in less than 60 minutes (+10 minutes). Decrease the rate of doxorubicin administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occurs.

e For patients weighing less than 10 kg, the dose of vincristine should be 0.05 mg/kg. The dose is capped at 2 mg for all patients.

f Administer ifosfamide for up to 6 cycles only or a cumulative dose of 84 g/m^2. Treatment beyond 84 g/m^2 requires consultation with the Lilly clinical research physician/clinical research scientist.

g For sequential day chemotherapy, it is recommended to allow a minimum of 20 hours between dosing, unless institutional standard varies.

7.2.3. Dose Progression through Study Parts

Safety will be the primary criteria for the dose escalation or de-escalation of both olaratumab monotherapy and the combination regimens. No dose escalation can occur without prior discussion and agreement between the investigators and the Lilly CRP/CRS/Lilly study team; the decision will be documented in writing. Sites will be notified of this decision in writing.

Based on the ongoing safety reviews, modifications to the dose-escalation strategy or other design elements may be made via protocol amendment to ensure patient safety.

Part B will be initiated after acceptable safety results from Part A, including a minimum of 6 evaluable patients, and the PK profile from Part A monotherapy. Part B will be complete when at least 10 patients (regardless of assigned chemotherapy arm) are evaluable for safety of olaratumab 20 mg/kg monotherapy.

Part C will open for enrollment after a complete safety review of the first 10 patients (regardless of chemotherapy arm) to complete Part B monotherapy (olaratumab 20 mg/kg). This safety review will be performed by the Lilly CRP/CRS/Lilly study team and investigators and documented in writing. Sites will be notified of this decision in writing.

7.2.3.1. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition

A DLT is defined as an adverse event (AE) during the first 21 days that is possibly related to the study drug and fulfills any one of the following criterion using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0:

- CTCAE Grade ≥3 nonhematologic toxicity. Exceptions will be made for:
  - Grade 3 febrile neutropenia without complications,
  - Grade 3 events of nausea, vomiting, diarrhea, transient electrolyte abnormalities, and constipation that can be controlled with optimal medical management within 48 hours, and
  - transient Grade 3 elevations of ALT and/or AST lasting fewer than 8 days, without evidence of other hepatic injury may not be considered a DLT if agreed by the study investigator and Lilly CRP/CRS.
- Grade 4 neutropenia that lasts longer than 2 weeks
- Grade ≥3 thrombocytopenia complicated by hemorrhage
- Any hematologic toxicity that causes a cycle delay of >14 days
- Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (for example, any toxicity that is possibly related to the study medication that requires the withdrawal of the patient from the study during Cycle 1)

7.2.3.2. Dose-Escalation Method

Part B will be initiated after the following criteria have been met:

- Acceptable safety results, which must include a minimum of 6 evaluable patients, and the PK profile from Part A monotherapy
- At least one of the 15 mg/kg combination arms has met the following DLT criteria: less than one third (that is, approximately 33.3% [minimum of 3 patients]) DLT rate. Only the combination arms in Part A that have met these criteria may be studied in Parts B and C.

In Part A, if the DLT rate is >1/3 (that is, greater than 4 out of 12 patients) during Cycle 1 monotherapy, then the dose of olaratumab will be reduced to 10 mg/kg. In Part B, if the DLT rate is >1/3 during Cycle 1 monotherapy, then the dose of olaratumab will be reduced to

15 mg/kg. In Part C, if the DLT rate is >1/3 during Cycle 1 combination therapy, then the dose of olaratumab will be reduced to 15 mg/kg.

If the DLT rate is >1/3 in the first cycle (Parts A and B Cycle 2, or Part C Cycle 1) of any of the chemotherapy arms, then appropriate dose de-escalation (Table JGDN.7.3) of olaratumab for that combination will occur.

7.2.4. Dose Adjustments and Delays

In the event that a patient experiences a DLT or a DLT-equivalent (a DLT occurring in Cycle 3 or later of Parts A and B or Cycle 2 or later of Part C), treatment will be interrupted. Dosing can be resumed after resolution of the toxicity to baseline levels at the next lower dose level (Table JGDN.7.3) already deemed safe upon discussion with the Lilly CRP/CRS. For Grade 3/4 toxicities that are not dose-limiting, see Section 7.2.4.1.2 for hematologic toxicities and Section 7.2.4.1.3 for nonhematologic toxicities.

Table JGDN.7.3. Olaratumab Dose Levels and Adjustments for Olaratumab-related Toxicities

		Dose Reduction		
Dose at Enrollment		**First**	**Second**	**Third**
Dose level 3	20 mg/kg	15 mg/kg	10 mg/kg	discontinue olaratumab
Dose level 2	15 mg/kg	10 mg/kg	discontinue olaratumab	
Dose level 1	10 mg/kg	discontinue olaratumab		

In the event of alteration of olaratumab therapy due to an olaratumab-related toxicity, chemotherapy need not be altered, and the planned chemotherapy schedule should be maintained. In the event that olaratumab treatment is discontinued for reason of toxicity, the patient should be discontinued from the study.

Similarly, olaratumab therapy should not be altered for chemotherapy-related toxicity, even if the chemotherapy dose is modified. In the event that chemotherapy is discontinued for reason of toxicity, the patient should be discontinued from the study.

To begin dosing at each cycle, the following criteria must be fulfilled:

- ANC $\geq$750/mm^3
- Platelets $\geq$75,000/mm^3
- Hemoglobin $\geq$8 g/dL
- Total bilirubin $\leq$ 1.5 x ULN
- AST and ALT $\leq$3.0 x ULN, or $\leq$5 x ULN if the transaminase elevation is due to liver metastases
- Any nonhematologic toxicity that are NCI-CTCAE, v4.0 Grade <2 or equivalent severity to baseline

Treatment may be delayed for up to 14 days to allow a patient sufficient time for recovery from study drug-related toxicity.

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

- IRR (see Section 7.2.4.1.1)
- Hematologic toxicity (see Section 7.2.4.1.2)
- Nonhematologic toxicity (see Section 7.2.4.1.3)

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

- Hematologic toxicity (see Section 7.2.4.2.1)
- Cardiovascular toxicity (see Section 7.2.4.2.2)
- Hepatic impairment (see Section 7.2.4.2.3)

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

- Hematologic toxicity (see Section 7.2.4.3.1)
- Nonhematologic toxicity (see Section 7.2.4.3.2)

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

- Hematologic toxicity (see Section 7.2.4.4.1)
- Diarrhea and cholinergic reactions (see Section 7.2.4.4.2)

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

- Urotoxic effects (see Section 7.2.4.5.1)
- Proximal tubular damage (see Section 7.2.4.5.2)
- Central nervous system (see Section 7.2.4.5.3)
- Other Toxicities (see Section 7.2.4.5.4)

7.2.4.1. Olaratumab

7.2.4.1.1. Infusion-Related Reactions

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

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

Olaratumab infusion reactions will be defined according to the NCI-CTCAE Version 4.0 definition of infusion-related reactions.

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

In general, if a patient experiences a Grade 1 or 2 IRR, the infusion should stop and the patient should be treated with an antihistamine (for example, diphenhydramine hydrochloride), glucocorticoid (for example, dexamethasone), acetaminophen (or equivalent), and oxygen (as indicated), according to standard medical practices. After recovery, the infusion rate should be decreased 50% for the duration of the infusion. If subsequent infusions are then tolerated with the use of premedications as above and a 50% decrease in infusion rate, the infusion rate may be increased to a rate deemed appropriate by the investigator, as long as it does not exceed 25 mg/min.

A Grade 3 or 4 IRR will require immediate treatment, including, but not limited to, 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.

For a patient who has had a Grade 1 or 2 olaratumab infusion reaction in a previous cycle, patients should be premedicated with antihistamine and glucocorticoid (for example dexamethasone) intravenously 30 to 60 minutes prior to olaratumab infusion, and acetaminophen (or equivalent) for all subsequent infusions. Additional premedication may be provided at investigator discretion.

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

7.2.4.1.2. Hematologic Toxicity

Table JGDN.7.4 summarizes the olaratumab dose modifications required in case of olaratumab-related hematologic toxicities during any cycle.

Table JGDN.7.4. General Guidelines for Olaratumab Dose Modification Due to Hematologic Toxicity Deemed Related to Olaratumab

Toxicity	Required Dose Modification
Neutropenia	
ANC Grade 1-3	No dose modification required
ANC <500/mm^3 (Grade ≥4)	No treatment administered; treatment cycle delayed
At retreatment:	
If Grade ≥3 neutropenic fever/infection has occurred	Withhold dose until ANC is ≥ 750/mm^3; for the 15-mg/kg cohort (Part A), reduce dose to 10 mg/kg; for the 20-mg/kg cohort (Part B and Part C), reduce dose to 15 mg/kg.
If Grade 4 neutropenia lasting >1 week has occurred	Withhold dose until ANC is ≥ 750/mm^3; for the 15-mg/kg cohort (Part A), reduce dose to 10 mg/kg; for the 20-mg/kg cohort (Part B and Part C), reduce dose to 15 mg/kg.
Grade 4 ANC without fever/infection lasting ≤ 1 week	Administer the next olaratumab at full dose at investigator's discretion with recommended use of prophylactic G-CSFs
Second incidence of either: 1) Grade ≥3 neutropenic fever/infection 2) Grade 4 neutropenia lasting > 1 week	For the 15-mg/kg cohort (Part A) that have been reduced to 10-mg/kg, discontinue olaratumab; for the 20-mg/kg cohort (Part B and Part C) that have been reduced to 15-mg/kg, a second dose level reduction to 10 mg/kg
Thrombocytopenia	
Platelets <75,000/mm^3	No treatment administered; treatment delayed until resolved to ≥75,000/mm^3
Anemia	
Hemoglobin <8 g/dL	No treatment administered; treatment delayed until resolved to ≥8 g/dL, transfusion with packed red blood cells allowed

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

7.2.4.1.3. Nonhematologic Toxicity

Specific guidelines for dose adjustments in patients who experience olaratumab IRRs may be found in Section 7.2.4.1.1.

General guidelines for dose modification for other nonhematologic toxicities related to olaratumab are shown in Table JGDN.7.5.

Table JGDN.7.5. 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.
Grade 3	For a Grade 3 toxicity not adequately controlled with appropriate supportive care, the dose must be withheld until toxicity is ≤ Grade 1 or has returned to pretreatment baseline; then treatment may resume at a reduced dose of 10 mg/kg for the 15-mg/kg cohort (Part A) and reduced dose of 15 mg/kg for the 20-mg/kg cohort (Part B and Part C). If toxicity recurs after therapy resumes, then treatment should be discontinued for the 15-mg/kg cohort (Part A) or the dose reduced to 10 mg/kg for the 20-mg/kg cohort (Part B and Part C).
Grade 4	The dose must be withheld until dose toxicity is ≤ Grade 1 or has returned to baseline. Permanent discontinuation should be considered for any patient experiencing Grade 4 non-hematologic toxicity assessed as related to olaratumab. However, if resumption of dosing is deemed appropriate by the investigator, treatment may resume only after consultation with the Lilly study physician, with the dose reduced to 10 mg/kg for the 15-mg/kg cohort (Part A); dose reduced to 15 mg/kg for the 20-mg/kg cohort (Part B and Part C). If Grade 4 toxicity recurs after therapy resumes, treatment with olaratumab will be discontinued.

7.2.4.2. Doxorubicin Dose Adjustments

The dose adjustments and delays for doxorubicin apply to patients treated with olaratumab plus doxorubicin.

7.2.4.2.1. Hematologic Toxicity

Doxorubicin will not be administered if the patient's ANC is <750/mm^3 or if the platelet count is <75,000/mm^3. When necessary, the next treatment cycle should be delayed until the ANC is ≥750/mm^3 and the platelet count is ≥75,000/mm^3 and nonhematologic toxicities have resolved. For patients who experience Grade ≥3 neutropenic fever or infection, doxorubicin should be held until resolved and doxorubicin should be administered at the full dose at investigator's discretion with recommended use of prophylactic G-CSFs. If a patient experiences a second incidence of neutropenic fever/infection, then doxorubicin should be reduced to 28 mg/m2 on Day 1 and Day 2 will be necessary (75% of the starting dose). If used, dexrazoxane should be adjusted to maintain a 10:1 ratio with doxorubicin. Therapeutic and prophylactic use of Neulasta® (pegfilgrastim) or other G-CSFs will be allowed per current American Society of Clinical Oncology (ASCO; Smith et al. 2006) and National Comprehensive Cancer Network (NCCN 2015) guidelines or at the investigator's discretion. For patients with Grade 4 ANC without fever/infection, retreatment will be allowed at the investigator's discretion with the full dose of doxorubicin (37.5 mg/m^2 on Day 1 and Day 2) with recommended use of G-CSFs per current ASCO guidelines (Smith et al. 2006). See Table JGDN.7.6 for doxorubicin dose modification for neutropenia.

Table JGDN.7.6. General Guidelines for Doxorubicin Dose Modification Due to Neutropenia

Toxicity	Required Dose Modification[a]
ANC <750/mm^3	No doxorubicin administered; treatment cycle delayed
At retreatment:	
If Grade ≥3 neutropenic fever/infection has occurred Grade 4 ANC without fever/infection	Retreatment with doxorubicin at full dose at investigator's discretion with recommended use of prophylactic G-CSFs
Second incidence of either: 1) Grade ≥3 neutropenic fever/infection 2) Grade 4 neutropenia lasting longer than 1 week	Reduce to approximately 28 mg/m^2 doxorubicin on Day 1 and Day 2

Abbreviations: ANC = absolute neutrophil count; G-CSFs = granulocyte colony-stimulating factors.
a Dexrazoxane should be adjusted to maintain a 10:1 ratio with doxorubicin.

7.2.4.2.2. Cardiac Monitoring for Doxorubicin-Associated Cardiotoxicity

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

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

An ECHO/MUGA scan is required within 28 days prior to first dose of study drug for all patients receiving doxorubicin. Thereafter, ECHO or MUGA scans must be performed at the end of Cycles 2, 4, and 6 and when clinically indicated. If doxorubicin cardiotoxicity has been observed, an ECHO or MUGA should be performed at the 30-day follow-up visit. Additional ECHO/MUGA may be performed if clinically indicated or at the investigator's discretion.

If there is a decrease in LVEF to or below 40% or an absolute decrease of 20%, then doxorubicin will be discontinued. If there is an absolute decrease in the shortening fraction of >10% or the shortening fraction is below 29%, then doxorubicin will be discontinued. Doxorubicin should also be discontinued if the patient develops Grade 3 or 4 left ventricular systolic dysfunction (symptomatic CHF). If doxorubicin is discontinued for the above changes in LVEF, olaratumab should also be discontinued.

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

7.2.4.2.3. Hepatic Impairment

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

Decrease the dose of doxorubicin in patients with elevated serum total bilirubin concentrations as noted in Table JGDN.7.7.

Table JGDN.7.7. General Guidelines for Doxorubicin Dose Modification Due to Elevated Serum Total Bilirubin Concentrations

Serum Bilirubin Concentration	Doxorubicin Dose Reduction
>1.5 to 3 mg/dL	50% of initial dose
3.1 to 5 mg/dL	25% of initial dose
Greater than 5 mg/dL	Do not initiate doxorubicin Discontinue doxorubicin

7.2.4.3. Vincristine Dose Adjustments

The dose adjustments and delays for vincristine apply to patients treated with olaratumab plus vincristine and irinotecan.

7.2.4.3.1. Hematologic Toxicity

Vincristine does not appear to have any constant or significant effect upon the platelets or the red blood cells; however, anemia and thrombocytopenia have been reported. Due to concerns of neurotoxicity, the ASCO guideline recommends that vincristine be capped at a maximum dose of 2 mg. No dose adjustment is required. Therapeutic and prophylactic use of Neulasta (pegfilgrastim) or other G-CSFs will be allowed according to the current ASCO (Smith et al. 2006) and NCCN guidelines (NCCN 2015) or at the investigator's discretion.

7.2.4.3.2. Nonhematologic Toxicity

Table JGDN.7.8 provides the general guidelines for dose modifications of vincristine due to toxicity.

7.2.4.3.2.1. Neurologic Toxicity

Vincristine-related sensory and motor neuropathies are common and are cumulative. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, hyporeflexia, areflexia, neuralgia, jaw pain, decreased vibratory sense, cranial neuropathy, ileus, burning sensation, arthralgia, myalgia, muscle spasm, or weakness, both before and during treatment. Orthostatic hypotension may occur. The risk of neurologic toxicity is greater if vincristine is administered to patients with preexisting neuromuscular disorders or when other drugs with risk of neurologic toxicity are being given. The most frequent manifestations of nervous system toxicity are as follows:

Peripheral neuropathy, the earliest indication of which is the depression of the Achilles reflex. Later loss of other deep tendon reflexes occurs and is accompanied by peripheral paresthesias, pain, and tingling. If therapy is prolonged or high doses are administered, wrist and foot drop, ataxia, a slapping gait, and difficulty in walking may occur. Young children may refuse to walk due to extremity pain.

Cranial nerve neuropathy may lead to vocal cord paresis or paralysis (hoarseness, weak voice), ocular motor nerve dysfunction (ptosis, strabismus), bilateral facial nerve palsies, or jaw pain. Severe jaw pain can occur within a few hours of the first dose of vincristine. Cranial nerve toxicities tend to be bilateral and reversible when treatment with vincristine is discontinued.

Autonomic neuropathy is manifested as constipation (which can be severe), abdominal pain, urinary retention, and paralytic ileus. Laxatives or stool softeners should be considered routinely to prevent constipation. These symptoms resolve with time and may not occur with subsequent treatment. If bladder atony occurs, vincristine should be held until symptoms resolve. Worsening neuropathy requires dose delay, reduction, or discontinuation.

Table JGDN.7.8. General Guidelines for Dose Modification of Vincristine due to Toxicity

Toxicity/Worst Counts in Cycle	Vincristine Dose Reduction
Neurotoxicity	
Grade 1 or 2	Full dose
Grade 3 or 4	Hold until Grade ≤1 then 50% of initial dose [a]
Severe paralytic ileus	Hold until normal bowel movement then 50% of initial dose
Grade 3 other related nonhematologic/organ toxicity	Hold
Grade 4 other related nonhematologic/organ toxicity	Discontinue

[a] Reescalation to 75% or full dose should be considered at the start of each vincristine containing cycle based on patient's symptoms.

7.2.4.3.2.2. Hepatic Toxicity

Fatal liver toxicity and elevated levels of aspartate aminotransferase have occurred with vincristine use. Monitor hepatic function tests. Reduce or interrupt vincristine for hepatic toxicity (Table JGDN.7.9).

Table JGDN.7.9. General Guidelines for Vincristine Dose Modification Due to Elevated Serum Total Bilirubin Concentrations

Serum Bilirubin Concentration	Vincristine Dose Reduction
<2.1 mg/dL	Full dose
2.1 to 4 mg/dL	50% of initial dose
4.1 to 6 mg/dL	25% of initial dose
Greater than 6 mg/dL	Do not initiate vincristine Discontinue vincristine

7.2.4.4. Irinotecan Dose Adjustments

Dose levels and adjustments for irinotecan are shown in Table JGDN.7.10. General guidelines for irinotecan dose modifications are shown in Table JGDN.7.11.

7.2.4.4.1. Hematologic Toxicities

Irinotecan may cause severe myelosuppression and deaths due to sepsis following severe myelosuppression. Therapy should be temporarily discontinued if neutropenic fever occurs or if the ANC is <750/mm^3. The dose of irinotecan should be reduced according to Table JGDN.7.11. Patients with abnormal glucuronidation of bilirubin, such as Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving irinotecan. A new cycle of therapy should not begin until the granulocyte count has recovered to ≥750/mm^3 and the platelet count has recovered to ≥75,000/mm^3. Treatment should be delayed 1 to 2 weeks to

allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing irinotecan.

7.2.4.4.2. Diarrhea and Cholinergic Reactions

Irinotecan may cause severe, dose-limiting, and potentially fatal diarrhea. Early diarrhea has occurred during or shortly after infusion and may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and abdominal cramping. Atropine 0.01 mg/kg IV (maximum dose: 0.4 mg) may be used to prevent or treat symptoms of early diarrhea. Late diarrhea has occurred >24 hours after irinotecan administration and can be prolonged, leading to life-threatening dehydration and electrolyte imbalance. Treat late diarrhea promptly with loperamide until a normal pattern of bowel movements returns; fluid and electrolyte replacement may be needed for dehydration. Provide antibiotic support (cefixime has been used in children whose diarrhea persisted >24 hours despite loperamide) if patient develops persistent diarrhea, ileus, fever, or severe neutropenia. Interrupt or reduce subsequent irinotecan doses if NCI CTCAE Grade 3 (increase of 7-9 stools daily, or incontinence, or severe cramping) or Grade 4 (increase ≥10 stools daily, grossly bloody stool, or need for parenteral support) late diarrhea occurs. Cases of colitis complicated by ulceration, bleeding, ileus, and infection have been reported. Renal impairment and acute renal failure have been reported, possibly due to dehydration secondary to diarrhea. A new cycle of therapy should not begin until treatment-related diarrhea is fully resolved. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing irinotecan.

Table JGDN.7.10. Dose Levels and Adjustments for Irinotecan

	Dose Reduction		
Dose at Enrollment	-1 dose level	-2 dose levels	3 dose levels
50 mg/m²/d	25% reduction	50% reduction	discontinue irinotecan

Table JGDN.7.11. General Guidelines for Dose Modification of Irinotecan due to Toxicity

Toxicity	During a Cycle of Therapy
Neutropenia	
Grade 3 (500 to 749/mm^3)	Hold dose until resolved to ≥750/mm^3; no dose reduction
Grade 4 (<500/mm^3)	Hold dose until resolved to ≥750/mm^3 and then decrease by 1 dose level
Neutropenic fever	Hold dose until resolved
Diarrhea	
Grade 2 (4–6 stools/day > pretreatment)	Hold dose; no dose reduction
Grade 3 (7–9 stools/day > pretreatment)	Hold dose until resolved to ≤2 and then decrease by 1 dose level
Grade 4 (≥10 stools/day > pretreatment)	Hold dose until resolved to ≤2 and then decrease by 2 dose levels
Other nonhematologic toxicities	
Grade 2	Hold dose; no dose reduction
Grade 3	Hold dose until resolved to ≤2 and then decrease by 1 dose level
Grade 4	Hold dose until resolved to ≤2 and then decrease by 2 dose levels

7.2.4.5. Ifosfamide Dose Adjustments

7.2.4.5.1. Urotoxic Effects

The incidence of urotoxic effects without an uroprotector can be up to 40% and is dose dependent; coadministration with mesna and adequate hydration are mandatory. Patients may present with hematuria, symptomatic cystitis, or bladder fibrosis. Past or concomitant radiation of the bladder or busulfan treatment may increase the risk of hemorrhagic cystitis. Several methods of treatment for established hematuria have been described: bladder irrigation with water or normal saline, intravesical instillation of astringents (alum, silver nitrate), systemic administration of antifibrinolytics (aminocaproic acid, tranexamic acid), cystoscopy to evacuate the bladder of clots, continuous bladder irrigation, and intravesical prostaglandins. For severe or refractory hematuria**,** intravesical formalin, phenol, or prostaglandin has been used ± surgical intervention (electrocautery, cryosurgery, diversion of urine flow, hypogastric artery ligation, or cystectomy). Ifosfamide should be discontinued or dose reduced for macroscopic hematuria.

7.2.4.5.2. Proximal Tubular Damage

Glomerular, proximal, or distal tubular impairment may all occur, often in combination and may progress even after ifosfamide has been discontinued. Proximal tubular damage often presents as Fanconi syndrome with low serum bicarbonate, proteinuria, glucosuria, aminoaciduria, and hypochloremic metabolic acidosis. Risk factors for the development of nephrotoxicity include age less than 5 years; preexisting renal impairment; prior treatment with cisplatin; concurrent use of nephrotoxic drugs, reduced renal reserve (unilateral nephrectomy, renal radiation); hydronephrosis; and total cumulative dose. Renal impairment may increase the risk of myelosuppression and possibly, cardiotoxicity. Mesna does not appear to be protective against

the proximal tubular abnormalities induced by ifosfamide. Dose modifications of ifosfamide due to renal impairment are shown in Table JGDN.7.12.

Table JGDN.7.12. Dose Modification of Ifosfamide due to Renal Impairment

Creatinine Clearance (mL/Min)	Ifosfamide Dose Reduction
>60	Full dose
40-60	75% of initial dose
20-40	50% of initial dose
<20	Discontinue

7.2.4.5.3. Central Nervous System

Central nervous system toxicity appears to be dose dependent, and is variable in onset, but usually resolves when ifosfamide is discontinued. Incidence is higher with higher doses, concomitant use of aprepitant, electrolyte imbalances, renal/ hepatic impairment or preexisting CNS disorders. It may manifest as transient mental status changes (somnolence, confusion, hallucination, disorientation, and lethargy), cerebellar dysfunction, extrapyramidal symptoms, transient weakness, cranial nerve dysfunction or seizure activity. Methylene blue, which may act as an electron acceptor or decrease chloracetaldehyde formation, has been suggested as treatment or prophylaxis of ifosfamide induced encephalopathy.

7.2.4.5.4. Other Toxicities

General guidelines for ifosfamide dose modification are shown in Table JGDN.7.13. Dose modifications of ifosfamide due to hepatic impairment are shown in Table JGDN.7.14.

Table JGDN.7.13. General Guidelines for Dose Modification of Ifosfamide due to Toxicity

Worst Toxicity /Counts in Previous Cycle	Ifosfamide Dose Reduction[a]
Febrile neutropenia	First episode: maintain full dose and include GCSF at subsequent cycles. Subsequent episodes: Decrease 20%
Platelets <75,000/mm^3	If less than 1 week duration: maintain full dose If greater than 1 week duration: Decrease 20%
Thrombocytopenic bleeding	Decrease 20%
Somnolence or other signs of encephalopathy	Hold; methylene blue 50 mg intravenous every 4 hours until resolution. Consider prophylactic methylene blue for subsequent cycles. Consider discontinuing or dose reduction for next cycle.
Grade 3 related organ / nonhematologic	Decrease 20%
Grade 3 or 4 neurotoxicity	Discontinue
Grade 4 related organ / nonhematologic	Discontinue

a Do not retreat until absolute neutrophil count ≥ 750/mm^3, platelets ≥ 75,000/mm^3 and toxicity recovered to ≤ Grade 2.

Table JGDN.7.14. Dose Modification of Ifosfamide due to Hepatic Impairment

Bilirubin		AST/ALT	Ifosfamide Dose Reduction*
1-2 X ULN		<2 X ULN	Full dose
2-4 X ULN	And/or	2-5 X ULN	75% of initial dose
>4 X ULN		>5 ULN	Discontinue

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

a Based on clinical judgment – less conservative adjustments can be considered if hepatic changes are secondary to metastases rather than hepatic cirrhosis or hepatitis.

7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive olaratumab in this study. Before each patient's enrollment into the study, an eligibility check must be conducted between the investigational site and the Lilly clinical research personnel to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the site will register the patient by assigning the patient a unique study identification number via the Interactive Web Response System (IWRS), which is accessible 24 hours a day. Study drug will be allocated to patients using the IWRS. No dose escalations (that is, initiating Parts B and C for a chemotherapy combination) can occur without prior discussion and agreement with the responsible Lilly CRP or CRS.

In Part A, if investigators have eligible patients who have consented concurrently, more than 3 patients may be entered for a particular chemotherapy combination provided that accrual has not ceased due to excessive toxicity. This enrollment procedure is allowed because of the advanced disease state of this patient population and the screening involved in defining eligibility. This event should be approved by the sponsor following discussions with the investigators.

7.4. Blinding

This is an open-label study.

7.5. Concomitant Therapy

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

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

With the exceptions listed in the sections below, no other chemotherapy, investigational medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, or surgery for cancer will be permitted while patients are on study treatment. Palliative radiotherapy (of ≤14 calendar days, e.g., for a solitary skeletal metastasis) after Cycle 7 may be allowed as long as the patient has not developed another reason for study discontinuation and other sites of disease are available for response assessment. Palliative radiation may not occur prior to discussion with the study medical monitor and written approval.

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

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

7.5.1. Supportive Care

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

7.5.1.1. Dexrazoxane

For patients in the doxorubicin combination arm, dexrazoxane may be administered starting with the first dose of doxorubicin at the investigator's discretion according to instructions provided in the Pharmacy Manual for this study, beginning within 30 minutes prior to each doxorubicin infusion for the prevention of cardiotoxicity. It is recommended that all patients receiving doxorubicin receive dexrazoxane. Investigators should consult the dexrazoxane information provided in the Pharmacy Manual for this study for administration information (including warnings, precautions, contraindications, adverse reactions, and dose modifications).

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

7.5.1.2. Mesna

For patients in the ifosfamide arm, mesna should be administered at a minimum dose equal to 60% of the ifosfamide dose according to institutional guidelines, including divided dose or continuous infusion.

Note that as the dose of mesna administered is dependent on the dose of ifosfamide administered, any dose modifications to ifosfamide will require a corresponding dose modification to mesna in order to maintain the correct dosage (mesna = minimum 60% ifosfamide).

7.5.1.3. Hydration

Ifosfamide should be given with extensive hydration consisting of oral or intravenous fluid (2 L/m^2 IV) to prevent bladder toxicity or according to institutional guidelines. The criteria to start chemotherapy may also include a urine-specific gravity < 1.010 or according to institutional guidelines.

7.5.1.4. Granulocyte-Colony Stimulating Factors and Erythroid Growth Factors

Following the first dose of combination chemotherapy , the use of G-CSFs such as Neulasta® (pegfilgrastim) and erythroid stimulating factors (for example, erythropoietin) are permitted,

including prophylactic use, during investigational therapy at the discretion of the investigator or according to ASCO guidelines (Smith et al. 2006) and NCCN guidelines (NCCN 2015).

7.5.1.5. Transfusion of Blood Products

Transfusions of red blood cells, platelets, or other blood products are permitted at the investigator's discretion, but may not be used to meet hematologic criteria for inclusion in the study (refer to Section 6.1.1, Inclusion Criterion [6]).

7.5.1.6. Antiemetic Therapy

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

7.5.2. Prohibited Therapies

Additional concurrent chemotherapy, radiation therapy, biologic response modifiers, or other investigational or approved anticancer agents may not be administered to patients on this study. Palliative radiotherapy (of ≤14 calendar days, e.g., for a solitary skeletal metastasis) after Cycle 7 may be allowed as long as the patient has not developed another reason for study discontinuation and other sites of disease are available for response assessment. Palliative radiation may not occur prior to discussion with the study medical monitor and written approval.

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

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

7.6. Treatment Compliance

Study drugs will be administered intravenously at the investigational site, 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 eCRF.

7.6.1. Evaluable Patients

Patients who withdraw from the study before receiving study drug(s) will be replaced and will not be included in the safety or efficacy assessments. Safety analyses will be conducted on all patients who have been exposed to study drug, regardless of whether they are deemed evaluable for other assessments.

Any patient from Parts A or B who is discontinued from the study before completing 1 cycle of olaratumab treatment will be deemed non-evaluable for assessment of olaratumab monotherapy, unless the patient experiences a DLT prior to withdrawal. Any patient who is discontinued from the study before completing 1 cycle of combination chemotherapy treatment (Cycle 2 for Parts A or B or Cycle 1 for Part C) will be deemed non-evaluable for assessment of a combination chemotherapy, unless the patient experiences a DLT or DLE-equivalent prior to withdrawal.

If a patient from Parts A or B is noncompliant during Cycle 1 due to reasons other than drug-related toxicity, he or she will be considered non-evaluable for olaratumab monotherapy and may be replaced. If a patient from Parts A or B is noncompliant during Cycle 2 or a patient from Part C is noncompliant during Cycle 1 due to reasons other than drug-related toxicity, he or she will be considered non-evaluable for combination chemotherapy and may be replaced.

Nonevaluable patients may be replaced to ensure that enough patients complete 1 cycle of olaratumab monotherapy or combination chemotherapy, unless accrual to that cohort has stopped due to a DLT.

Patients who are not evaluable for pharmacokinetics, but who complete 1 cycle of olaratumab monotherapy or 1 cycle of combination chemotherapy, may be replaced to ensure adequate PK data, unless accrual to that cohort has stopped due to a DLT.

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

8.1. Safety Evaluations

The safety and tolerability of olaratumab have been assessed in nonclinical toxicology and clinical 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 pediatric 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 serum 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 serious adverse event (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 JGDN.8.1 presents a summary of AE and SAE reporting guidelines. Table JGDN.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 it is 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 v 4.0.

The NCI-CTCAE v 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. All AEs observed will be graded using CTCAE v 4.0. Any minor version of CTCAE v 4.0 (for example, version 4.0X) may be used for this study. Minor CTCAE v 4.0 updates from the NCI will not necessitate a protocol amendment. For AEs without matching terminology within the NCI-CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the eCRF. 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 condition(s), 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, study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terminologies are defined:

- **Related**: a direct cause and effect relationship between the study treatment and the AE is likely.

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

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

8.1.2.1. Serious Adverse Events

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

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

Planned 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 (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

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

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

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

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

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This

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

If an investigator becomes aware of SAEs occurring after the patient's participation in the trial has ended, and the investigator believes that the SAEs are 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.

For recommendations on reporting SAEs, see Attachment 5.

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 ICF. For patients who do not enroll in the trial (that is, have not received at least 1 dose of olaratumab), only AEs and SAEs related to protocol procedures are required to be reported.

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 (Visit 801) must be reported to Lilly or its designee. The follow-up visit (Visit 801) starts one day after the decision is made to discontinue the patient from the study. At the end of the follow-up visit, the patient will be required to have specific safety assessments (Attachment 1). The timing of these safety assessments is 30 days ± 7 days after the decision is made to discontinue the patient from the study.

Following the safety assessments, which mark the end of the follow-up visit (Visit 801), 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 followed in subsequent long-term 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 (Visit 801), AEs are not required to be reported unless the investigator feels the AEs were related to either study drug, drug delivery system, or a protocol procedure. If an investigator becomes aware of an SAE 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 serious adverse events 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. The United States 21 CFR 312.32, the European Union Clinical Trial Directive 2001/20/EC, and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulatory regulations and the associated detailed guidances.

8.1.2.4. Summary of AE/SAE Reporting Guidelines

The AE and SAE reporting guidelines for enrolled patients are summarized in Table JGDN.8.1.

Table JGDN.8.1. Adverse Event and Serious Adverse Reporting Guidelines for Patients Enrolled in Study JGDN

Timing	Types of AEs/SAEs Reported	Collection Database	Lilly Safety System
Prestudy (baseline assessments) (Starts at the signing of informed consent and ends just before the first dose of study drug)	Preexisting conditions All AEs 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 All SAEs regardless of relatedness	x x	 x
Follow-up Visit (Visit 801) (Starts one day after the decision is made to discontinue patient from study and ends when end of study safety assessments are completed [approximately 30 days later])	All AEs All SAEs regardless of relatedness	x x	 x
Subsequent Follow-up visits, if necessary for patient monitoring	Ongoing AEs possibly related to study drug(s), or protocol procedures All SAEs related to protocol procedures or study drug	x x	 x
Patient no longer on study	All SAEs related to protocol procedures or study drug that the investigator becomes aware of		x

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

8.1.3. Other Safety Measures

8.1.3.1. Electrocardiograms

For each patient, a 12-lead digital ECG will be collected according to the Study Schedule (Attachment 1).

Consecutive replicate ECGs (3 readings) will be obtained, whenever feasible for the patient, 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 first dose of study drug, the investigator will assess the patient for symptoms (for example, 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 site. 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 are 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.

8.1.3.2. Echocardiograms and Multigated Acquisition (MUGA) Scan

Refer to Section 7.2.4.2.2.

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 analytes
- adverse events
- If a study patient experiences elevated ALT >5X ULN and elevated total bilirubin >2X ULN, clinical and laboratory monitoring should be initiated by the investigator.
- For patients entering the study with ALT >3X ULN, monitoring should be triggered at ALT >2X baseline.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3).

8.1.5. Complaint Handling

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

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 adverse events 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 7 provides a summary of the estimated maximum number and volume of invasive samples, for all sampling, during the 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 and include a determination of the clinical significance of abnormal labs.

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. Pharmacokinetic Samples

At the visits and times specified in the Pharmacokinetic and Immunogenicity Sampling Schedule (Attachment 4), venous blood samples will be collected to determine the serum concentrations of

olaratumab and plasma concentrations of doxorubicin and doxorubicinol, vincristine, irinotecan (and its active metabolite SN-38), and ifosfamide. A maximum of 6 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. Doxorubicin and doxorubicinol, vincristine, irinotecan, SN-38, and ifosfamide concentrations in plasma will be analyzed using specific liquid chromatography with tandem mass spectrometry assays.

The PK samples will be stored at a facility designated by the sponsor. The remaining plasma from the samples collected for pharmacokinetics 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 year following last patient visit for the study.

8.2.3. Samples for Tailoring Genetics Biomarkers

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology, and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis as specified in the Sampling Schedule (Attachment 1). These samples **are not** being collected to create a biobank for conducting unspecified disease or population genetic research either now or in the future.

Samples may be used to investigate variable response to study treatment and to investigate genetic variants thought to play a role in cancer. Assessment of variable response may include evaluation of AEs or differences in efficacy. These studies may include but are not limited to the PGDFRα pathway to evaluate their association with observed response to study treatment.

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

Samples will be retained for a maximum of 15 years after the last patient visit, or as local regulations and ERBs allow, for the study at a facility selected by the sponsor. This retention

period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

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

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

8.2.4. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected at the visits and times specified in the Pharmacokinetic and Immunogenicity Sampling Schedule (Attachment 4) to determine antibody production against olaratumab. Immunogenicity will be assessed by a validated serum assay designed to detect anti-drug antibodies in the presence of olaratumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of olaratumab. Immunogenicity may be further characterized by performing additional related assays. In the event of an IRR, additional samples will be evaluated (see Attachment 4).

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

8.2.5. Tailoring Biomarker Samples

Collection of samples for other biomarker research is also part of this study. Tumor tissue and plasma samples will be collected.

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

- plasma

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

- tumor tissue (archival or new biopsy)

Samples will be collected for potential non-pharmacogenetic biomarker research. Tumor tissue and plasma samples will be collected at the times specified in the Sampling Schedule (Attachment 1).

Samples may be used for research on the drug target, disease process, pathways associated with cancer, mechanism of action of olaratumab, and/or research method or in validating diagnostic tools or assays related to cancer.

Where local regulations and ERBs allow, these samples will be collected for biomarker research as discussed below and specified in the Sampling Schedule (Attachment 1).

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

8.3. Efficacy Evaluations

A secondary objective of the study is to document any antitumor activity. Imaging studies and tumor assessments are to be obtained every 2 cycles (±7 days), until documented progression for patients with complete response (CR), partial response (PR), or stable disease (SD).

For patients who have discontinued study treatment due to toxicity or reasons other than progressive disease, imaging studies and tumor assessments are to be obtained every 6 weeks (±7 days) until progression. For these patients, details on subsequent anticancer treatment (start/stop dates and treatments administered) and first post-study treatment disease progression date should be recorded.

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

- Computed tomography (CT) scan
- Magnetic resonance imaging (MRI)
- Chest x-ray

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

- Tumor measurement by RECIST v1.1 (Eisenhauer et al. 2009) should be used for all tumors with the exception of CNS tumors. RANO (Wen et al. 2010) or Macdonald (Macdonald et al. 1990) criteria should be used for CNS tumors.
- Evaluation of tumor markers, if indicated
- Evaluation of performance status (Lansky [Lansky et al. 1987] or Karnofsky [Karnofsky et al. 1948] scale)

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 6 weeks (2 cycles) following the initial observation of an objective response, using the sample method that was used at baseline. 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, pharmacodynamics (PD) samples, and efficacy measurements are given as targets, to be achieved within reasonable limits. The scheduled time points may be subject to minor alterations; however, the actual collection time must be correctly recorded on the eCRF.

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

9. Data Management Methods

9.1. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and/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 institutional review board/ERBs 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.

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

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

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

9.2.2. Ancillary Data

Data managed by a central vendor will be stored electronically in the central laboratory's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

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 data warehouse.

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

10. Data Analyses

10.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company.

The interpretation of the study results will be the responsibility of Lilly CRP, CRS, pharmacokineticist, and statistician. The CRP, CRS, 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.

10.2. Patient Disposition

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

10.3. Patient Characteristics

Patient characteristics will include a summary/listing of the following:

- patient demographics
- baseline disease characteristics
- prior disease-related therapies
- concomitant medications

Other patient characteristics will be summarized as deemed appropriate.

10.4. Safety Analyses

All patients who receive at least 1 dose of olaratumab will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE, Version 4.0. Adverse events will be characterized by the frequency of observed toxicities (treatment-emergent adverse events, SAEs, deaths, and discontinuations due to AEs).

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- dose adjustments
- laboratory values
- vital signs
- DLTs at each dose level
- ECG readings
- ECHO/MUGA scanning
- immunogenicity data

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.

Mean population PK parameters for olaratumab in serum (clearance, volume of distribution) and inter-individual PK variability will be computed for this study using nonlinear mixed-effect modeling implemented in [redacted] in order to describe the dose-concentration relationship in the target population. Covariate effects (such as age, weight, and sex) on the PK parameters of olaratumab in serum will also be investigated.

Pharmacokinetic data collected for doxorubicin and doxorubicinol, vincristine, irinotecan, and ifosfamide will be analyzed using descriptive statistics.

Additional analyses such as exposure-response using appropriate efficacy or safety clinical endpoints may be performed, if warranted by the data.

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

The population PK and PK/PD analyses will be reported as separate standalone reports for this study.

10.6. Immunogenicity Analyses

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

In the event of an IRR, the immunogenicity and olaratumab serum concentrations will be tabulated.

10.7. Efficacy Analyses

Exploratory efficacy analysis will be performed to investigate antitumor activity within each combination arm. Progression-free survival curves and the median with 90% confidence interval (CI) will be estimated using Kaplan-Meier method (Kaplan and Meier 1958). The objective response rate (ORR=CR+PR) and disease control rate (DCR=CR+PR+SD) and the 90% exact CI will be tabulated for each cohort. Additional analyses may be performed as necessary. The details will be outlined in the statistical analysis plan (SAP).

10.8. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the sponsor will determine if it is necessary to amend the protocol.

Since this is a dose-finding study, data will be reviewed on a cohort-by-cohort basis during the study, until the maximum-tolerated dose (MTD) is determined. The purpose of these cohort-by-cohort reviews is to evaluate the safety data at each dose level and determine if a DLT has been observed that would suggest MTD has been met or exceeded. The investigators and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data as described in this protocol.

10.9. Biomarker Analyses

Exploratory biomarker assay results will be summarized and correlated with clinical outcomes.

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.

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

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

11.2. Ethical Review

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

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

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

- the current IB 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 International Ethical Guidelines
2) the ICH GCP Guideline [E6]
3) applicable laws and regulations

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

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

An identification code assigned 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 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 JGDN Study Schedule

JGDN Study Schedule, Screening and Baseline Assessments (All Parts)

Relative Day Prior to Cycle 1 Day 1	≤28	≤14	≤7	Comments
Eligibility Assessments				
Informed Consent	X			Written informed consent must be obtained prior to any study-specific screening evaluations.
Medical History		X		
Lansky/Karnofsky performance status		X		To be assessed by the investigator.
ECG	X			Consecutive replicate ECGs (3 readings) will be obtained, whenever feasible for the patient, at approximately 1-minute intervals.
ECHO or MUGA	X			For patients that will receive doxorubicin, ECHO or MUGA must be performed within 28 days prior to C1D1.
Safety Assessments				
Physical Exam		X		Physical exam includes height, weight, and BSA measurement.
Vital Signs		X		Vital sign measurements include temperature, pulse rate, and blood pressure.
Concomitant Medication Assessment		X		Concomitant medications will be recorded including any taken within 30 days prior to study medication.
Laboratory Assessments (See Attachment 2 for details)				
Hematology Profile		X		Screening evaluations done within 7 days prior to C1D1 do not have to be repeated unless otherwise specified.
Coagulation Profile		X		
Chemistry Profile		X		
Urinalysis			X	Includes a routine urinalysis, and if clinically indicated, a microscopic analysis. If routine analysis indicates > 2+ proteinuria, then a 24-hour urine must be collected and must demonstrate ≤ 1000 mg of protein in 24 hours, or urine protein/creatinine ratio < 1, prior to proceeding to treatment. Screening evaluations done within 7 days prior to C1D1 do not have to be repeated unless otherwise specified.
Pregnancy Test			X	Serum β-HCG pregnancy test (women of childbearing potential only) within 7 days prior to C1D1. If the serum pregnancy test performed for inclusion purposes is positive, confirm by repeating the serum and performing a urine pregnancy test.
Genetic (whole blood) Sample)		X		See Section 8.2.3 (whole blood sample).

Relative Day Prior to Cycle 1 Day 1	≤28	≤14	≤7	Comments
Efficacy Assessments				
Imaging Studies (CT/MRI/chest x-ray)	X			For rapidly growing tumors, scans should be performed ≤14 days prior to C1D1. Scans performed prior to the date of consent may be used provided they are within 28 days of C1D1. RECIST v1.1 should be used for all tumors with the exception of CNS tumors; RANO or Macdonald criteria should be used for CNS tumors.
RECIST v1.1, RANO, or Macdonald Tumor Assessments	X			
Other Assessments				
Biomarker Sampling		X		
Biopsy/Tumor Tissue Submission	X			Optional sample from archived or new tumor tissue

Abbreviations: BSA = body surface area; C1D1 = Cycle 1 Day 1; CNS = central nervous system; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; HCG = human chorionic gonadotropin; MRI = magnetic resonance imaging; MUGA = multigated acquisition; RANO = Response Assessment in Neuro-Oncology; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors Version 1.1.

JGDN Study Schedule, Treatment Period for Olaratumab in Combination with Doxorubicin (Parts A and B)

All evaluations must be done on the day of study drug administration. In case of dose interruption, these evaluations will also be done at minimum frequency every 21 days (±3 days).

	Treatment Period 21-Day Cycles						
	Cycle 1		Cycle 2-n				
Day	Day 1 (±3)	Day 8 (±3)	Day 1 (±3)	Day 2 (±3)	Day 8 (±3)	Day 15 (±3)	Comments
Eligibility Assessments							
Lansky/Karnofsky performance status	X		X				
ECG	X		X				Consecutive replicate ECGs will be obtained (3 readings), whenever feasible for the patient, at approximately 1-minute intervals.
ECHO or MUGA			X				ECHO or MUGA scans must be performed at the **end of** Cycles 2, 4, and 6 and when clinically indicated. Additional ECHO/MUGA may be performed at the investigator's discretion.
Safety Assessments							
Physical Exam	X	X	X		X		Physical exam includes weight and BSA measurement.
Vital Signs	X	X	X	X	X		Vital sign measurements include temperature, pulse rate, and blood pressure. **Cycle 1:** Obtain vital signs prior to and after the completion of the olaratumab infusion. In **Cycle 2 and later:** On Day 1, obtain vital signs prior to and after the completion of the olaratumab infusion (prior to dexrazoxane, if used; or if not used, then prior to doxorubicin) and within 1 hour after completion of the doxorubicin infusion. On Day 2, obtain vital signs prior to dexrazoxane infusion (patients receiving dexrazoxane and doxorubicin) or prior to doxorubicin infusion (patients receiving doxorubicin only) and within 1 hour after completion of the doxorubicin infusion. On Day 8, obtain vital signs prior to and after the completion of the olaratumab infusion.
Adverse Event Assessment	X	X	X	X	X		All AEs considered at least possibly-related to study treatment will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.
Concomitant Medication Assessment	X	X	X	X	X		

Day	Treatment Period 21-Day Cycles						Comments
	Cycle 1		Cycle 2-n				
	Day 1 (±3)	Day 8 (±3)	Day 1 (±3)	Day 2 (±3)	Day 8 (±3)	Day 15 (±3)	
Laboratory Assessments (See Attachment 2 for details)							
Hematology Profile	X	X	X		X	X	Hematology measurements must be collected on Day 15 only during Cycle 2 and Cycle 3.
Coagulation Profile			X				Perform every other cycle beginning at Cycle 2 Day 1.
Chemistry Profile	X		X				
Urinalysis			X				Includes a routine urinalysis, and if clinically indicated, a microscopic analysis. If routine analysis indicates > 2+ proteinuria, then a 24-hour urine must be collected and must demonstrate ≤ 1000 mg of protein in 24 hours or urine protein/creatinine ratio < 1, prior to proceeding to the next cycle.
Pregnancy Test	X		X				Urine pregnancy test on Day 1 of every cycle or per local practice (whichever is of shorter duration) and at short-term follow-up visit. If the urine pregnancy test performed on Day 1 of the cycle is positive, confirm with a serum pregnancy test.
Immunogenicity	See Attachment 4 for specific time points.						When possible, an immunogenicity sample will be collected at the same time as the PK sample. If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
Efficacy Assessments							
Imaging Studies (CT/MRI)			X				Imaging studies and tumor assessments are be obtained every 2 cycles (±7 days) until documented progression for patients with CR, PR, or SD. RECIST v1.1 should be used for all tumors with the exception of CNS tumors; RANO or Macdonald criteria should be used for CNS tumors.
RECIST v1.1, RANO, or Macdonald Tumor Assessments			X				
Other Assessments							
PK Sampling	See Attachment 4 for specific time points						
Biomarker Sampling			X				During treatment, a single sample will be collected prior to dosing at Cycle 3 Day 1.
Biopsy/Tumor Tissue Submission			X				Optional tumor tissue from biopsy for biomarkers and tumor type. May be collected any time during or after Cycle 2 Day 1.

Day	Treatment Period 21-Day Cycles						Comments
	Cycle 1		Cycle 2-n				
	Day 1 (±3)	Day 8 (±3)	Day 1 (±3)	Day 2 (±3)	Day 8 (±3)	Day 15 (±3)	
Premedication							
Premedication prior to olaratumab administration	X	X	X		X		In Cycle 1 (both Day 1 and Day 8 doses), all patients should receive premedication with dexamethasone (or equivalent medication) and an H1 antagonist intravenously 30–60 minutes prior to olaratumab infusion. Additional premedication may be provided at investigator discretion. For all subsequent cycles, all patients should receive premedication with an H1 antagonist (for example, diphenhydramine) intravenously 30–60 minutes prior to each dose of olaratumab. Additional premedication may be provided at investigator discretion. For a patient who has had a Grade 1 or 2 olaratumab infusion reaction in a previous cycle, patients should be premedicated with antihistamine and glucocorticoid (for example, dexamethasone) intravenously 30–60 minutes prior to olaratumab infusion, and acetaminophen (or equivalent) for all subsequent infusions. Additional premedication may be provided at investigator discretion.
Administer dexrazoxane			X	X			Dexrazoxane may be given at 10:1 ratio (dexrazoxane to doxorubicin) prior to doxorubicin on Day 1 and Day 2 at the investigator' discretion. Dexrazoxane is recommended for all patients receiving doxorubicin.
Clinical Drug Supplies							
Administer olaratumab	X	X	X		X		When the maximum dose of doxorubicin has been reached, olaratumab will not be continued and the patient should be discontinued from the study.
Administer doxorubicin			X	X			Doxorubicin to be administered at 37.5 mg/m^2 on Day 1 and Day 2 to be continued for 6 Cycles or a cumulative dose of 450 mg/m^2

Abbreviations: AE = adverse event; BSA = body surface area; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; IRR = infusion-related reaction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PK = pharmacokinetics; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors Version 1.1; SD = stable disease.

JGDN Study Schedule, Treatment Period for Olaratumab in Combination with Doxorubicin (Part C)

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 8[a]	Day 15[a]	Comments
Eligibility Assessments					
Lansky/Karnofsky performance status	X				
ECG	X				Baseline ECG can be used for C1D1 if completed within 7 days. Consecutive replicate ECGs will be obtained (3 readings), whenever feasible for the patient, at approximately 1-minute intervals.
ECHO or MUGA	X				ECHO or MUGA scans must be performed PRIOR to Cycles 1, 3, and 5 and results must be available prior to doxorubicin administration for those cycles. Additional ECHO/MUGA may be performed at the investigator's discretion as clinically indicated.
Safety Assessments					
Physical Exam	X		X		Physical exam includes weight and BSA measurement.
Vital Signs	X	X	X		Vital sign measurements include temperature, pulse rate, and blood pressure. On Day 1, obtain vital signs prior to and after the completion of the olaratumab infusion (prior to dexrazoxane, if used; or if not used, then prior to doxorubicin) and within 1 hour after completion of the doxorubicin infusion. On Day 2, obtain vital signs prior to dexrazoxane infusion (patients receiving dexrazoxane and doxorubicin) or prior to doxorubicin infusion (patients receiving doxorubicin only) and within 1 hour after completion of the doxorubicin infusion. On Day 8, obtain vital signs prior to and after the completion of the olaratumab infusion.
Adverse Event Assessment	X	X	X		All AEs considered at least possibly related to study treatment will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.
Concomitant Medication Assessment	X	X	X		
Laboratory Assessments (See Attachment 2 for details)					
Hematology Profile	X		X	X	Hematology measurements must be collected on Day 15 only during Cycle 1 and Cycle 2.
Coagulation Profile	X				Perform every other cycle beginning at Cycle 1 Day 1. Baseline value can be used for C1D1 if completed within 7 days.
Chemistry Profile	X				
Urinalysis	X				Includes a routine urinalysis, and if clinically indicated, a microscopic analysis. If routine

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 8[a]	Day 15[a]	Comments
					analysis indicates > 2+ proteinuria, then a 24-hour urine must be collected and must demonstrate ≤1000 mg of protein in 24 hours or urine protein/creatinine ratio <1, prior to proceeding to the next cycle.
Pregnancy Test	X				Urine pregnancy test on Day 1 of every cycle or per local practice (whichever is of shorter duration) and at short-term follow-up visit. If the urine pregnancy test performed on Day 1 of the cycle is positive, confirm with a serum pregnancy test.
Immunogenicity	See Attachment 4 for specific time points.				When possible, an immunogenicity sample will be collected at the same time as the PK sample. If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
Efficacy Assessments					
Imaging Studies (CT/MRI)	X				Imaging studies and tumor assessments are to be obtained every 2 cycles (-7 days) until documented progression for patients with CR, PR, or SD. RECIST v1.1 should be used for all tumors with the exception of CNS tumors; RANO or Macdonald criteria should be used for CNS tumors.
RECIST v1.1, RANO, or Macdonald Tumor Assessments	X				
Other Assessments					
PK Sampling	See Attachment 4 for specific time points				
Biomarker Sampling	X				During treatment, a single sample will be collected prior to dosing at Cycle 3 Day 1.
Biopsy/Tumor Tissue Submission	X				Optional tumor tissue from biopsy for biomarkers and tumor type. May be collected any time during or after Cycle 1 Day 1.

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 8[a]	Day 15[a]	Comments
Premedication					
Premedication prior to olaratumab administration	X		X		In Cycle 1 (both Day 1 and Day 8 doses), all patients should receive premedication with dexamethasone (or equivalent medication) and an H1 antagonist intravenously 30–60 minutes prior to olaratumab infusion. Additional premedication may be provided at investigator discretion. For all subsequent cycles, all patients should receive premedication with an H1 antagonist (for example, diphenhydramine) intravenously 30–60 minutes prior to each dose of olaratumab. Additional premedication may be provided at investigator discretion. For a patient who has had a Grade 1 or 2 olaratumab infusion reaction in a previous cycle, patients should be premedicated with antihistamine and glucocorticoid (for example, dexamethasone) intravenously 30–60 minutes prior to olaratumab infusion, and acetaminophen (or equivalent) for all subsequent infusions. Additional premedication may be provided at investigator discretion.
Administer dexrazoxane	X	X			Dexrazoxane may be given at 10:1 ratio (dexrazoxane to doxorubicin) prior to doxorubicin on Day 1 and Day 2 at the investigator discretion. Dexrazoxane is recommended for all patients receiving doxorubicin.
Clinical Drug Supplies					
Administer olaratumab	X		X		
Administer doxorubicin	X	X			Doxorubicin to be administered at 37.5 mg/m^2 on Day 1 and Day 2 to be continued for 6 Cycles or a cumulative dose of 450 mg/m^2.

Abbreviations: AE = adverse event; BSA = body surface area; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; IRR = infusion-related reaction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PK = pharmacokinetics; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors Version 1.1; SD = stable disease.

[a] A delay of up to 3 days will be permitted due to holidays, weekends, inclement weather, or other unforeseen circumstances, including unexpected changes in patient schedules, and will not count as a protocol deviation. However, assessments must be done prior to treatments and the interval between cycles may not be less than 21 days. In later cycles, longer delays may be allowed in consultation with Lilly medical representative.

JGDN Study Schedule, Treatment Period for Olaratumab in Combination with Vincristine and Irinotecan (Parts A and B)

All evaluations must be done on the day of study drug administration. In case of dose interruption, these evaluations will also be done at minimum frequency every 21 days (±3 days).

	Treatment Period 21-Day Cycles									
	Cycle 1		Cycle 2-n							
Day	Day 1 (±3)	Day 8 (±3)	Day 1 (±3)	Day 2 (±3)	Day 3 (±3)	Day 4 (±3)	Day 5 (±3)	Day 8 (±3)	Day 15 (±3)	Comments
Eligibility Assessments										
Lansky/Karnofsky performance status	X		X							
ECG	X		X							Consecutive replicate ECGs will be obtained (3 readings), whenever feasible for the patient, at approximately 1-minute intervals.
Safety Assessments										
Physical Exam	X	X	X					X		Physical exam includes weight and BSA measurement.
Vital Signs	X	X	X	X	X	X	X	X		Vital sign measurements include temperature, pulse rate, and blood pressure. **Cycle 1:** Obtain vital signs prior to and after the completion of the olaratumab infusion. In **Cycle 2 and later:** On Day 1, obtain vital signs prior to and after the completion of the olaratumab infusion (prior to vincristine) and within 1 hour after completion of the irinotecan infusion. On Days 2-5, obtain vital signs prior to irinotecan infusion and within 1 hour after completion of the infusion. On Day 8, obtain vital signs prior to and after the completion of the olaratumab infusion (prior to vincristine) and within 1 hour after completion of the vincristine infusion.

Day	Treatment Period 21-Day Cycles									Comments
	Cycle 1		Cycle 2-n							
	Day 1 (±3)	Day 8 (±3)	Day 1 (±3)	Day 2 (±3)	Day 3 (±3)	Day 4 (±3)	Day 5 (±3)	Day 8 (±3)	Day 15 (±3)	
Adverse Event Assessment	X	X	X	X	X	X	X	X		All AEs considered at least possibly-related to study treatment will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.
Concomitant Medication Assessment	X	X	X	X	X	X	X	X		
Laboratory Assessments (See Attachment 2 for details)										
Hematology Profile	X	X	X					X	X	Hematology measurements must be collected on Day 15 only during Cycle 2 and Cycle 3.
Coagulation Profile			X							Perform every other cycle beginning at Cycle 2 Day 1.
Chemistry Profile	X		X							
Urinalysis			X							Includes a routine urinalysis, and if clinically indicated, a microscopic analysis. If routine analysis indicates > 2+ proteinuria, then a 24-hour urine must be collected and must demonstrate ≤ 1000 mg of protein in 24 hours, or urine protein/creatinine ratio < 1, prior to proceeding to the next cycle.
Pregnancy Test	X		X							Urine pregnancy test on Day 1 of every cycle or per local practice (whichever is of shorter duration) and at short-term follow-up visit. If the urine pregnancy test performed on Day 1 of the cycle is positive, confirm with a serum pregnancy test.

Day	Treatment Period 21-Day Cycles									Comments
	Cycle 1		Cycle 2-n							
	Day 1 (±3)	Day 8 (±3)	Day 1 (±3)	Day 2 (±3)	Day 3 (±3)	Day 4 (±3)	Day 5 (±3)	Day 8 (±3)	Day 15 (±3)	
Immunogenicity	See Attachment 4 for specific time points.									When possible, an immunogenicity sample will be collected at the same time as the PK sample. If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
Efficacy Assessments										
Imaging Studies (CT/MRI)			X							Imaging studies and tumor assessments are be obtained every 2 cycles (±7 days) until documented progression for patients with CR, PR, or SD. RECIST v1.1 should be used for all tumors with the exception of CNS tumors; RANO or Macdonald criteria should be used for CNS tumors.
RECIST v1.1, RANO, or Macdonald Tumor Assessments			X							
Other Assessments										
PK Sampling	See Attachment 4 for specific time points.									
Biomarker Sampling			X							During treatment, a single sample will be collected prior to dosing at Cycle 3 Day 1.
Biopsy/Tumor Tissue Submission			X							Optional tumor tissue from biopsy for biomarkers and tumor type. May be collected any time during or after Cycle 2 Day 1.

Day	Treatment Period 21-Day Cycles									Comments
	Cycle 1		Cycle 2-n							
	Day 1 (±3)	Day 8 (±3)	Day 1 (±3)	Day 2 (±3)	Day 3 (±3)	Day 4 (±3)	Day 5 (±3)	Day 8 (±3)	Day 15 (±3)	
Premedication										
Premedication prior to olaratumab administration	X	X	X					X		In Cycle 1 (both Day 1 and Day 8 doses), all patients should receive premedication with dexamethasone (or equivalent medication) and an H1 antagonist intravenously 30–60 minutes prior to olaratumab infusion. Additional premedication may be provided at investigator discretion. For all subsequent cycles, all patients should receive premedication with an H1 antagonist (for example, diphenhydramine) intravenously 30–60 minutes prior to each dose of olaratumab. Additional premedication may be provided at investigator discretion. For a patient who has had a Grade 1 or 2 olaratumab infusion reaction in a previous cycle, patients should be premedicated with antihistamine and glucocorticoid (for example dexamethasone) intravenously 30–60 minutes prior to olaratumab infusion, and acetaminophen (or equivalent) for all subsequent infusions. Additional premedication may be provided at investigator discretion.
Vincristine Premedication			X					X		Laxatives and/or stool softeners should be used preemptively during vincristine containing cycles.

Day	Treatment Period 21-Day Cycles									Comments
	Cycle 1		Cycle 2-n							
	Day 1 (±3)	Day 8 (±3)	Day 1 (±3)	Day 2 (±3)	Day 3 (±3)	Day 4 (±3)	Day 5 (±3)	Day 8 (±3)	Day 15 (±3)	
Irinotecan Premedication			X	X	X	X	X			A prophylactic treatment with antiemetics is recommended before each treatment with irinotecan.
Clinical Drug Supplies										
Administer olaratumab	X	X	X					X		
Administer vincristine			X					X		
Administer irinotecan			X	X	X	X	X			

Abbreviations: AE = adverse event; BSA = body surface area; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; IRR = infusion-related reaction; MRI = magnetic resonance imaging; PK = pharmacokinetics; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors Version 1.1; SD = stable disease.

JGDN Study Schedule, Treatment Period for Olaratumab in Combination with Vincristine and Irinotecan (Part C)

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 3[a]	Day 4[a]	Day 5[a]	Day 8[a]	Day 15[a]	Comments
Eligibility Assessments								
Lansky/Karnofsky performance status	X							
ECG	X							Consecutive replicate ECGs will be obtained (3 readings), whenever feasible for the patient, at approximately 1-minute intervals.
Safety Assessments								
Physical Exam	X					X		Physical exam includes weight and BSA measurement.
Vital Signs	X	X	X	X	X	X		Vital sign measurements include temperature, pulse rate, and blood pressure. On Day 1, obtain vital signs prior to and after the completion of the olaratumab infusion (prior to vincristine) and within 1 hour after completion of the irinotecan infusion. On Days 2-5, obtain vital signs prior to irinotecan infusion and within 1 hour after completion of the infusion. On Day 8, obtain vital signs prior to and after the completion of the olaratumab infusion (prior to vincristine) and within 1 hour after completion of the vincristine infusion.
Adverse Event Assessment	X	X	X	X	X	X		All AEs considered at least possibly related to study treatment will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.
Concomitant Medication Assessment	X	X	X	X	X	X		
Laboratory Assessments (See Attachment 2 for details)								
Hematology Profile	X					X	X	Hematology measurements must be collected on Day 15 only during Cycle 1 and Cycle 2.
Coagulation Profile	X							Perform every other cycle beginning at Cycle 1 Day 1. Baseline value can be used for C1D1 if completed within 7 days.
Chemistry Profile	X							

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 3[a]	Day 4[a]	Day 5[a]	Day 8[a]	Day 15[a]	Comments
Urinalysis	X							Includes a routine urinalysis, and if clinically indicated, a microscopic analysis. If routine analysis indicates > 2+ proteinuria, then a 24-hour urine must be collected and must demonstrate ≤1000 mg of protein in 24 hours, or urine protein/creatinine ratio <1, prior to proceeding to the next cycle.
Pregnancy Test	X							Urine pregnancy test on Day 1 of every cycle or per local practice (whichever is of shorter duration) and at short-term follow-up visit. If the urine pregnancy test performed on Day 1 of the cycle is positive, confirm with a serum pregnancy test.
Immunogenicity	See Attachment 4 for specific time points.							When possible, an immunogenicity sample will be collected at the same time as the PK sample. If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
Efficacy Assessments								
Imaging Studies (CT/MRI)	X							Imaging studies and tumor assessments are to be obtained every 2 cycles (±7 days) until documented progression for patients with CR, PR, or SD. RECIST v1.1 should be used for all tumors with the exception of CNS tumors; RANO or Macdonald criteria should be used for CNS tumors.
RECIST v1.1, RANO, or Macdonald Tumor Assessments	X							
Other Assessments								
PK Sampling	See Attachment 4 for specific time points.							
Biomarker Sampling	X							During treatment, a single sample will be collected prior to dosing at Cycle 3 Day 1.
Biopsy/Tumor Tissue Submission	X							Optional tumor tissue from biopsy for biomarkers and tumor type. May be collected any time during or after Cycle 1 Day 1.

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 3[a]	Day 4[a]	Day 5[a]	Day 8[a]	Day 15[a]	Comments
Premedication								
Premedication prior to olaratumab administration	X					X		In Cycle 1 (both Day 1 and Day 8 doses), all patients should receive premedication with dexamethasone (or equivalent medication) and an H1 antagonist intravenously 30–60 minutes prior to olaratumab infusion. Additional premedication may be provided at investigator discretion. For all subsequent cycles, all patients should receive premedication with an H1 antagonist (for example, diphenhydramine) intravenously 30–60 minutes prior to each dose of olaratumab. Additional premedication may be provided at investigator discretion. For a patient who has had a Grade 1 or 2 olaratumab infusion reaction in a previous cycle, patients should be premedicated with antihistamine and glucocorticoid (for example, dexamethasone) intravenously 30–60 minutes prior to olaratumab infusion, and acetaminophen (or equivalent) for all subsequent infusions. Additional premedication may be provided at investigator discretion.
Clinical Drug Supplies								
Administer olaratumab	X					X		
Administer vincristine	X					X		
Administer irinotecan	X	X	X	X	X			

Abbreviations: AE = adverse event; BSA = body surface area; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; IRR = infusion-related reaction; MRI = magnetic resonance imaging; PK = pharmacokinetics; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors Version 1.1; SD = stable disease.

[a] A delay of up to 3 days will be permitted due to holidays, weekends, inclement weather, or other unforeseen circumstances, including unexpected changes in patient schedules, and will not count as a protocol deviation. However, assessments must be done prior to treatments and the interval between cycles may not be less than 21 days. In later cycles, longer delays may be allowed in consultation with Lilly medical representative.

JGDN Study Schedule, Treatment Period for Olaratumab in Combination with Ifosfamide (Parts A and B)

All evaluations must be done on the day of study drug administration. In case of dose interruption, these evaluations will also be done at minimum frequency every 21 days (±3 days).

	Treatment Period 21-Day Cycles									
	Cycle 1		Cycle 2-n							
Day	Day 1 (±3)	Day 8 (±3)	Day 1 (±3)	Day 2 (±3)	Day 3 (±3)	Day 4 (±3)	Day 5 (±3)	Day 8 (±3)	Day 15 (±3)	Comments
Eligibility Assessments										
Lansky/Karnofsky performance status	X		X							
ECG	X		X							Consecutive replicate ECGs will be obtained (3 readings), whenever feasible for the patient, at approximately 1-minute intervals.
Safety Assessments										
Physical Exam	X	X	X					X		Physical exam includes weight and BSA measurement.
Vital Signs	X	X	X	X	X	X	X	X		Vital sign measurements include temperature, pulse rate, and blood pressure. **Cycle 1:** Obtain vital signs prior to and after the completion of the olaratumab infusion. In **Cycle 2 and later:** On Day 1, obtain vital signs prior to and after the completion of the olaratumab infusion (prior to ifosfamide) and within 1 hour after completion of the ifosfamide infusion. On Days 2-5, obtain vital signs prior to ifosfamide infusion and within 1 hour after completion of the infusion. On Day 8, obtain vital signs prior to and after the completion of the olaratumab infusion.
Adverse Event Assessment	X	X	X	X	X	X	X	X		All AEs considered at least possibly-related to study treatment will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.

Day	Treatment Period 21-Day Cycles									Comments
	Cycle 1		Cycle 2-n							
	Day 1 (±3)	Day 8 (±3)	Day 1 (±3)	Day 2 (±3)	Day 3 (±3)	Day 4 (±3)	Day 5 (±3)	Day 8 (±3)	Day 15 (±3)	
Concomitant Medication Assessment	X	X	X	X	X	X	X	X		
Laboratory Assessments (See Attachment 2 for details)										
Hematology Profile	X	X	X					X	X	Hematology measurements must be collected on Day 15 only during Cycle 2 and Cycle 3.
Coagulation Profile			X							Perform every other cycle beginning at Cycle 2 Day 1.
Chemistry Profile	X		X							
Urinalysis			X							Includes a routine urinalysis, and if clinically indicated, a microscopic analysis. If routine analysis indicates > 2+ proteinuria, then a 24-hour urine must be collected and must demonstrate ≤ 1000 mg of protein in 24 hours, or urine protein/creatinine ratio < 1, prior to proceeding to the next cycle.
Pregnancy Test	X		X							Urine pregnancy test on Day 1 of every cycle or per local practice (whichever is of shorter duration) and at short-term follow-up visit. If the urine pregnancy test performed on Day 1 of the cycle is positive, confirm with a serum pregnancy test.
Immunogenicity	See Attachment 4 for specific time points.									When possible, an immunogenicity sample will be collected at the same time as the PK sample. If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.

Day	Treatment Period 21-Day Cycles									Comments
	Cycle 1		Cycle 2-n							
	Day 1 (±3)	Day 8 (±3)	Day 1 (±3)	Day 2 (±3)	Day 3 (±3)	Day 4 (±3)	Day 5 (±3)	Day 8 (±3)	Day 15 (±3)	
Efficacy Assessments										
Imaging Studies (CT/MRI)			X							Imaging studies and tumor assessments are be obtained every 2 cycles (±7 days) until documented progression for patients with CR, PR, or SD. RECIST v1.1 should be used for all tumors with the exception of CNS tumors; RANO or Macdonald criteria should be used for CNS tumors.
RECIST v1.1, RANO, or Macdonald Tumor Assessments			X							
Other Assessments										
PK Sampling	See Attachment 4 for specific time points									
Biomarker Sampling			X							During treatment, a single sample will be collected prior to dosing at Cycle 3 Day 1.
Biopsy/Tumor Tissue Submission			X							Optional tumor tissue from biopsy for biomarkers and tumor type. May be collected any time during or after Cycle 2 Day 1.
Premedication										
Premedication prior to olaratumab administration	X	X	X					X		In Cycle 1 (both Day 1 and Day 8 doses), all patients should receive premedication with dexamethasone (or equivalent medication) and an H1 antagonist intravenously 30–60 minutes prior to olaratumab infusion. Additional premedication may be provided at investigator discretion. For all subsequent cycles, all patients should receive premedication with an H1 antagonist (for example, diphenhydramine) intravenously 30–60 minutes prior to each dose of olaratumab. Additional premedication may be provided at investigator discretion.

Day	Treatment Period 21-Day Cycles									Comments
	Cycle 1		Cycle 2-n							
	Day 1 (±3)	Day 8 (±3)	Day 1 (±3)	Day 2 (±3)	Day 3 (±3)	Day 4 (±3)	Day 5 (±3)	Day 8 (±3)	Day 15 (±3)	
										For a patient who has had a Grade 1 or 2 olaratumab infusion reaction in a previous cycle, patients should be premedicated with antihistamine and glucocorticoid (for example, dexamethasone) intravenously 30–60 minutes prior to olaratumab infusion, and acetaminophen (or equivalent) for all subsequent infusions. Additional premedication may be provided at investigator discretion.
Mesna Administration			X	X	X	X	X			Administer at a minimum 60% of the ifosfamide dose according to institutional guidelines.
Clinical Drug Supplies										
Administer olaratumab	X	X	X					X		When the maximum dose of ifosfamide has been reached (or has been discontinued), olaratumab will not be continued and the patient should be discontinued from the study.
Administer ifosfamide			X	X	X	X	X			Administer ifosfamide for up to 6 cycles or a cumulative dose of 84 g/m^2. Treatment beyond 84 g/m^2 requires consultation with the Lilly CRP/CRS.

Abbreviations: AE = adverse event; BSA = body surface area; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; IRR = infusion-related reaction; MRI = magnetic resonance imaging; PK = pharmacokinetics; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria In Solid Tumors; SD = stable disease.

JGDN Study Schedule, Treatment Period for Olaratumab in Combination with Ifosfamide (Part C)

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 3[a]	Day 4[a]	Day 5[a]	Day 8[a]	Day 15[a]	Comments
Eligibility Assessments								
Lansky/Karnofsky performance status	X							
ECG	X							Consecutive replicate ECGs will be obtained (3 readings), whenever feasible for the patient, at approximately 1-minute intervals.
Safety Assessments								
Physical Exam	X					X		Physical exam includes weight and BSA measurement.
Vital Signs	X	X	X	X	X	X		Vital sign measurements include temperature, pulse rate, and blood pressure. On Day 1, obtain vital signs prior to and after the completion of the olaratumab infusion (prior to ifosfamide) and within 1 hour after completion of the ifosfamide infusion. On Days 2-5, obtain vital signs prior to ifosfamide infusion and within 1 hour after completion of the infusion. On Day 8, obtain vital signs prior to and after the completion of the olaratumab infusion.
Adverse Event Assessment	X	X	X	X	X	X		All AEs considered at least possibly related to study treatment will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.
Concomitant Medication Assessment	X	X	X	X	X	X		
Laboratory Assessments (See Attachment 2 for details)								
Hematology Profile	X					X	X	Hematology measurements must be collected on Day 15 only during Cycle 1 and Cycle 2.
Coagulation Profile	X							Perform every other cycle beginning at Cycle 1 Day 1.
Chemistry Profile	X							
Urinalysis	X							Includes a routine urinalysis, and if clinically indicated, a microscopic analysis. If routine analysis indicates > 2+

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 3[a]	Day 4[a]	Day 5[a]	Day 8[a]	Day 15[a]	Comments
								proteinuria, then a 24-hour urine must be collected and must demonstrate ≤1000 mg of protein in 24 hours, or urine protein/creatinine ratio <1, prior to proceeding to the next cycle.
Pregnancy Test	X							Urine pregnancy test on Day 1 of every cycle or per local practice (whichever is of shorter duration) and at short-term follow-up visit. If the urine pregnancy test performed on Day 1 of the cycle is positive, confirm with a serum pregnancy test.
Immunogenicity	See Attachment 4 for specific time points.							When possible, an immunogenicity sample will be collected at the same time as the PK sample. If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
Efficacy Assessments								
Imaging Studies (CT/MRI)	X							Imaging studies and tumor assessments are to be obtained every 2 cycles (±7 days) until documented progression for patients with CR, PR, or SD. RECIST v1.1 should be used for all tumors with the exception of CNS tumors; RANO or Macdonald criteria should be used for CNS tumors.
RECIST v1.1, RANO, or Macdonald Tumor Assessments	X							
Other Assessments								
PK Sampling	See Attachment 4 for specific time points							
Biomarker Sampling	X							During treatment, a single sample will be collected prior to dosing at Cycle 3 Day 1.
Biopsy/Tumor Tissue Submission	X							Optional tumor tissue from biopsy for biomarkers and tumor type. May be collected any time during or after Cycle 1 Day 1.
Premedication								
Premedication prior to olaratumab administration	X					X		In Cycle 1 (both Day 1 and Day 8 doses), all patients should receive premedication with dexamethasone (or equivalent medication) and an H1 antagonist intravenously 30–60 minutes prior to olaratumab infusion. Additional premedication may be

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 3[a]	Day 4[a]	Day 5[a]	Day 8[a]	Day 15[a]	Comments
								provided at investigator discretion. For all subsequent cycles, all patients should receive premedication with an H1 antagonist (for example, diphenhydramine) intravenously 30–60 minutes prior to each dose of olaratumab. Additional premedication may be provided at investigator discretion. For a patient who has had a Grade 1 or 2 olaratumab infusion reaction in a previous cycle, patients should be premedicated with antihistamine and glucocorticoid (for example, dexamethasone) intravenously 30–60 minutes prior to olaratumab infusion, and acetaminophen (or equivalent) for all subsequent infusions. Additional premedication may be provided at investigator discretion.
Mesna Administration	X	X	X	X	X			Administer at a minimum 60% of the ifosfamide dose according to institutional guidelines.
Clinical Drug Supplies								
Administer olaratumab	X					X		
Administer ifosfamide	X	X	X	X	X			Administer ifosfamide for up to 6 cycles or a cumulative dose of 84 g/m^2. Treatment beyond 84 g/m^2 requires consultation with the Lilly CRP/CRS.

Abbreviations: AE = adverse event; BSA = body surface area; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; IRR = infusion-related reaction; MRI = magnetic resonance imaging; PK = pharmacokinetics; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria In Solid Tumors; SD = stable disease.

[a] A delay of up to 3 days will be permitted due to holidays, weekends, inclement weather, or other unforeseen circumstances, including unexpected changes in patient schedules, and will not count as a protocol deviation. However, assessments must be done prior to treatments and the interval between cycles may not be less than 21 days. In later cycles, longer delays may be allowed in consultation with Lilly medical representative.

JGDN Study Schedule, Follow-up Assessments (All Parts)

Day	Follow-up		Comments
	Short-Term[a]	Long-Term[b]	
	30 days (±7) after discontinuation date		
Eligibility Assessments			
Lansky/Karnofsky performance status	X		
ECG	X		Consecutive replicate ECGs will be obtained (3 readings), whenever feasible for the patient, at approximately 1-minute intervals.
ECHO or MUGA	X		**For patients on the doxorubicin arm:** if doxorubicin cardiotoxicity has been observed, an ECHO or MUGA should be performed at the 30-day follow-up visit. Additional ECHO/MUGA may be performed at the investigator's discretion.
Safety Assessments			
Physical Exam	X		Physical exam includes weight.
Vital Signs	X		Vital sign measurements include temperature, pulse rate, and blood pressure.
Adverse Event Assessment	X		All AEs considered at least possibly-related to study treatment will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.
Concomitant Medication Assessment	X		
Laboratory Assessments (See Attachment 2 for details)			
Hematology Profile	X		
Coagulation Profile	X		
Chemistry Profile	X		
Urinalysis	X		Includes a routine urinalysis, and if clinically indicated, a microscopic analysis.
Pregnancy Test	X		If the urine pregnancy test is positive, confirm with a serum pregnancy test.
Immunogenicity	X		See Attachment 4 for details.

Day	Follow-up		Comments
	Short-Term[a]	Long-Term[b]	
	30 days (±7) after discontinuation date		
Efficacy Assessments			
Imaging Studies (CT/MRI)	X (if applicable)	X	For patients who have discontinued study treatment due to toxicity or reasons other than progressive disease, imaging studies and tumor assessments are to be obtained every 6 weeks (±7 days) until progression or initiation of other anticancer therapy. RECIST v1.1 should be used for all tumors with the exception of CNS tumors; RANO or Macdonald criteria should be used for CNS tumors.
RECIST v1.1, RANO, or Macdonald Tumor Assessments	X (if applicable)	X	
Subsequent Anti-Cancer Treatments, and Associated Disease Progression Date		X	For all patients, details on subsequent anticancer treatment (start/stop dates and treatments administered) and first post-study treatment disease progression date should be recorded.
Other Assessments			
PK Sampling	X		See Attachment 4 for details.
Biomarker Sampling	X		

Abbreviations: AE = adverse event; CNS = central nervous system; CRF = case report form; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; IRR = infusion-related reaction; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; PK = pharmacokinetics; RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria In Solid Tumors.

a **Short-term follow-up** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (±7 days). The date of this agreement is to be reported on the CRF as the date of discontinuation from study treatment.

b **Long-term follow-up** begins the day after short-term follow-up is completed. Patients that discontinue study treatment for reasons other than progression will be followed every 6 weeks (±7 days) until progression.

Attachment 2. Protocol JGDN Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	Clinical Chemistry[a]
Hemoglobin	**Serum Concentrations of the following:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Total bilirubin
Mean cell hemoglobin concentration (MCHC)	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT)
Neutrophils	Aspartate aminotransferase (AST)
Lymphocytes	Gamma glutamyl transferase (GGT)
Monocytes	Blood urea nitrogen (BUN) or Blood Urea
Eosinophils	Creatinine
Basophils	Urate
Platelets	Calcium
	Glucose, random
Coagulation Test[a]	Albumin
Prothrombin time (PT)	Total protein
International normalized ratio (INR)	Chloride
Partial thromboplastin time (PTT or aPTT)	Thyroid-stimulating hormone
	Direct bilirubin
Urinalysis[a,c]	Bicarbonate
Specific gravity	Magnesium
pH	Phosphate
Protein	
Glucose	**Pregnancy test[a,d]**
Ketones	
Blood	**Exploratory Biomarker Tests[b]**
Urine leukocyte esterase	
Other[b]	
Immunogenicity samples	
PK samples	

Abbreviations: CRP = clinical research physician; PK = pharmacokinetics; RBC = red blood cells; UPC = urine protein/creatinine; WBC = white blood cells.

a Assayed by local or investigator-designated laboratory.

b Samples will be assayed by Lilly-designated laboratory.

c If urinary protein is ≥2+ at evaluations, a 24-hour urine collection (to assess protein) must be collected and must be ≤1000 mg of protein in 24 hours, or alternatively, a urine protein/creatinine ratio ≤ 1, prior to proceeding to the next cycle. Note: UPC ratio of spot urine is an estimation of the 24-hour urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1000 mg. UPC ratio is calculated using one of the following formulae:

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

d Serum pregnancy test will be performed at screening in female patients of childbearing potential only (if the baseline serum test is positive, a repeat serum and urine pregnancy test will be done; if those results are positive, the investigator is to consult with the Lilly CRP regarding if dosing should occur and which follow-up laboratory tests are performed). While on-study, urine pregnancy test will be performed in female patients of childbearing potential only on Day 1 of every cycle or per local practice (whichever is of shorter duration) and at short-term follow-up visit. If the serum pregnancy test performed for inclusion purposes is positive confirm by repeating the serum and performing a urine pregnancy test. If the urine pregnancy test performed on Day 1 of each cycle is positive, confirm with a serum pregnancy test.

Attachment 3. Protocol JGDN Hepatic Monitoring Tests for Treatment Emergent Abnormality

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

Hepatic Monitoring Tests

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

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma glutamyl transferase; Ig = immunoglobulin; INR = International Normalised Ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by local or investigator-designated laboratory.

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

Attachment 4. Protocol JGDN Pharmacokinetic and Immunogenicity Sampling Schedule

Pharmacokinetic and Immunogenicity Sampling (Parts A and B)

Sample Number	Cycle	Day	Sampling Time	Olaratumab PK[a]	Combination agents PK[b]	Immunogenicity[c]
1	1	1	Prior to olaratumab infusion	X		X
2		8	Within 5 min post olaratumab infusion	X		
3	2	1	Within 15 min prior to olaratumab infusion	X		X
4		1	Within 5 min post chemotherapy infusion	X	X	
5		8	Within 5 min post olaratumab infusion	X		
6	3 and then every other cycle	1	Within 15 min prior to olaratumab infusion	X		X
7	30-day follow-up (Visit 801)		Any time	X		X

Abbreviation: PK = pharmacokinetics.

a A 2.5-mL (~1 mL if patient has <19kg) blood sample will be collected (to generate serum for bioanalysis).

b A 2-mL (~1 mL if patient has <19kg) blood sample will be collected (to generate plasma for bioanalysis).

c A 3.5-mL blood sample will be collected (to generate serum for anti-olaratumab antibody analysis).

Pharmacokinetic and Immunogenicity Sampling (Part C)

Sample Number	Cycle	Day	Sampling Time	Olaratumab PK[a]	Combination agents PK[b]	Immunogenicity[c]
1	1	1	Prior to olaratumab infusion	X		X
2		1	Within 5 min post chemotherapy infusion	X	X	
3		8	Within 5 min post olaratumab infusion	X		
4	2	1	Within 15 min prior to olaratumab infusion	X		X
5		8	Within 5 min post olaratumab infusion	X		
6	3 and then every other cycle	1	Within 15 min prior to olaratumab infusion	X		X
7	30-day follow-up (Visit 801)		Any time	X		X

Abbreviation: PK = pharmacokinetics.

[a] A 2.5-mL (~1 mL if patient has <19 kg) blood sample will be collected (to generate serum for bioanalysis).

[b] A 2-mL (~1 mL if patient has <19 kg) blood sample will be collected (to generate plasma for bioanalysis).

[c] A 3.5-mL blood sample will be collected (to generate serum for anti-olaratumab antibody analysis).

Attachment 5. Protocol JGDN Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events

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

Patient Demographics

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

Study Identification

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

Study Drug

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

Adverse Event

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

Relationship to Study Drug & Protocol Procedures

Concomitant Drug Therapy

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

In Case of Death

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

Attachment 6. Protocol JGDN Creatinine Clearance Formula

Protocol JGDN will use the Schwartz formula for the determination of creatinine clearance.

All Females and Pre-adolescent Males:

C_{cr} (mL/min/1.73 m^2) = 0.55 x Height (cm)/S_{cr} (mg/dL)

Adolescent Males:

C_{cr} (mL/min/1.73 m^2) = 0.70 x Height (cm)/S_{cr} (mg/dL)

Note: C_{cr} = creatinine clearance and S_{cr} = serum creatinine

Source: Schwartz et al. 1976; Schwartz and Gauthier 1985.

Attachment 7. Protocol JGDN Sampling Summary

This table summarizes the maximum number of samples (venipunctures, biopsies), volumes for all sampling, and tests (study qualification, health monitoring, drug concentration, tailoring biomarkers, immunogenicity, and exploratory) during the study. The summary below provides estimates. More samples could be required in the case of retests, additional health monitoring (if needed), or for patients continuing treatment beyond the protocol-specified number of cycles in the study. Fewer samples may actually be taken (for example, patients who discontinue from the study).

Protocol I5B-MC-JGDN Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Study qualification[a]	Blood	5 mL	4	10 mL
Health Monitoring (may be more than 1 tube)[b]	Blood	5 mL	33	98 mL
	Tissue Biopsy	5 mm 0.5 oz 1 cc	1	5 mm 0.5 oz 1 cc
Drug concentration	Blood	2-2.5 mL (~1 mL if patient has <19kg)	11	27 mL (13 mL if patient has <19kg)
Tailoring biomarkers	Blood	4 mL	3	12 mL
	Tumor tissue	FFPE block or slides	1	FFPE block or slides
Pharmacogenetic (DNA) Sample	Blood	0.5 mL	1	0.5 mL
Immunogenicity	Blood	3.5 mL	7	24.5 mL
Hepatic Monitoring[b]	Blood	3 - 30 mL	-	-
Total blood per patient completing 9 cycles and Short-term follow up visit	Blood			172 mL (158 mL if patient has <19kg)

Abbreviations: DNA = deoxyribonucleic acid; FFPE = formalin-fixed, paraffin-embedded.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with the designated medical monitor.

Attachment 8. Protocol JGDN RECIST Criteria 1.1

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

Measurability of Tumor at Baseline

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

Measurable

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

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

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

Nonmeasurable

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

Special Considerations for Lesion Measurability

Bone lesions:

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

Cystic lesions:

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

Lesions with Prior Local Treatment:

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

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

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

Nontarget Lesions

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

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

Specifications by Methods of Measurement

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

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

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

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

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

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

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

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

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

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

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

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

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

Response Criteria

Evaluation of Target Lesions

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

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

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

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

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

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

Evaluation of Nontarget Lesions

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

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

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

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

Evaluation of Best Overall Response

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

Time Point Response

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

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

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

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

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

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

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

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

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

Frequency of Tumor Re-Evaluation

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

Confirmatory Measurement/Duration of Response

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

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

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

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

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

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

Independent Review of Response and Progression

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

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

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

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

Attachment 10. Protocol JGDN Protocol Amendment I5B-MC-JGDN(b) Summary A Phase 1, Open-Label, Dose-Escalation Study of Olaratumab as a Single Agent and in Combination with Doxorubicin, Vincristine/Irinotecan, or High-Dose Ifosfamide in Pediatric Patients with Relapsed or Refractory Solid Tumors

Overview

Protocol I5B-MC-JGDN "A Phase 1, Open-Label, Dose-Escalation Study of Olaratumab as a Single Agent and in Combination with Doxorubicin, Vincristine/Irinotecan, or High-Dose Ifosfamide in Pediatric Patients with Relapsed or Refractory Solid Tumors" has been amended. 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 protocol was amended to allow the addition of Part C and allow site sourcing of non-investigational study drugs. In Part C, patients will not receive olaratumab monotherapy and will directly enter into combination chemotherapy. This will occur after documentation for safety of olaratumab 20mg/kg monotherapy in Part B. The rationale for this is to improve the risk-benefit ratio for patients by allowing known active therapy in combination with olaratumab at study entry.

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

- Part C was added to the study design and updated throughout the protocol.
- An update to the number of planned patients as well as the planned last patient visit was updated due to adding Part C.
- The duration of treatment was updated to allow patients with clinical benefit to continue on monotherapy until one of the criteria for discontinuation is met.
- Contraceptive language was clarified in the inclusion criteria (Section 6.1.1).
- Comparator drug language was updated, in Section 7.1, to account for potential supply shortage and product availability.
- Premedication language was updated in Section 7.2.1 to reflect current standard practice.
- A clarification to Section 7.5 regarding concomitant palliative radiotherapy was added.
- A clarification to the premedication timing language in Section 7.5 was made to ensure premedications are given appropriately.
- Mesna language was better clarified to reflect current standard practice.
- Palliative radiotherapy language was better explained in Section 7.5.2.

- The schedule of events (baseline, treatment, and follow-up) was updated to reflect clarifications, standard practices, and the addition of Part C.
- The PK sample schedule was updated to reflect the addition of Part C.
- Other minor editorial changes were made to add clarity.

Revised Protocol Sections

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

Clinical Protocol Synopsis: Study I5B-MC-JGDN

Name of Investigational Product: Olaratumab (LY3012207)

Title of Study: A Phase 1, Open-Label, Dose-Escalation Study of Olaratumab as a Single Agent and in Combination with Doxorubicin, Vincristine/Irinotecan, or High-Dose Ifosfamide in Pediatric Patients with Relapsed or Refractory Solid Tumors

Number of Planned Patients:	**Phase of Development:** 1
Entered/Screened: Approximately 1~~00~~10 Enrolled: Minimum 24 Maximum 7~~0~~9	

Length of Study:
Planned first patient visit: 11 February 2016
Planned last patient visit: ~~11~~05 June~~February~~ 2019

Objectives:
The primary objective of this study is to determine a recommended dose of olaratumab in combination with at least one of the studied chemotherapy regimens in pediatric patients based on any dose-limiting toxicities (DLTs) as well as olaratumab serum exposure-matching between the adult and pediatric populations.

The secondary objectives of this study are:

- to investigate the pharmacokinetics (PK) of olaratumab as monotherapy and in combination with either doxorubicin, vincristine/irinotecan, or high-dose ifosfamide in pediatric patients;
- to assess the possible development of antibodies against olaratumab (immunogenicity) in pediatric patients; and
- to document any antitumor activity (including progression-free survival and objective response rate [ORR]) observed with olaratumab in combination with either doxorubicin, vincristine/irinotecan, or high-dose ifosfamide in pediatric patients.

The exploratory objective of this study is:

- to identify exploratory biomarkers associated with tumor response and/or safety.

Study Design: Study JGDN is a multicenter, dose-escalation, open-label Phase 1 pediatric safety clinical trial with 3 distinct components, Part A, Part B, and Part ~~B~~C.

Part A will consist of at least 12 evaluable pediatric patients. These patients will be treated for 1 cycle (21 days) of olaratumab monotherapy at 15 mg/kg on Day 1 and Day 8 (adult dose for which efficacy was observed in Study I5B-IE-JGDG). If the patient does not experience a DLT in the first cycle of monotherapy, or meet any other criteria for discontinuation, the patient will then receive olaratumab (15 mg/kg) plus one of 3 standard chemotherapy regimens (doxorubicin or vincristine/irinotecan or high-dose ifosfamide per investigator discretion). Treatment will continue until disease progression or other discontinuation criteria are met.

Part B and Part C will be initiated after the following criteria have been met:

- Acceptable safety results, which must include a minimum of 6 evaluable patients, and the PK profile from Part A monotherapy.
- At least one of the 15 mg/kg combination arms has met the following DLT criteria: less than one-third (that is, approximately 33.3% [minimum of 3 patients]) DLT rate. Only the combination arms in Part A that have met these criteria may be studied in Parts B and C.

Part B ~~will consist of at least 12 evaluable pediatric patients. These~~ patients will be treated for 1 cycle (21 days) of olaratumab monotherapy at 20 mg/kg on Day 1 and Day 8~~. If the patient does not experience a DLT in the first~~

~~cycle of monotherapy, or meet any other criteria for discontinuation,~~ then ~~patient will then~~ receive olaratumab (20mg/kg) plus one of 3 standard chemotherapy regimens described in Part A ~~that have successfully passed the DLT criteria described above for Part A (doxorubicin or vincristine/irinotecan or high-dose ifosfamide per investigator discretion)~~. Part B will be complete when at least 10 patients (regardless of assigned chemotherapy arm) are evaluable for safety of olaratumab 20mg/kg monotherapy. Part C will be initiated when at least 10 patients (regardless of chemotherapy arm) are evaluable for safety of olaratumab 20 mg/kg monotherapy from Part B. Part C patients will receive olaratumab (20 mg/kg) in combination with any of the 3 chemotherapy regimens (per investigator discretion) from Cycle 1 onward (i.e. no olaratumab monotherapy will be given in Part C). Part B and C together will enroll up to 45 patients (15 per chemotherapy arm). Treatment will continue until disease progression or other discontinuation criteria are met.

Diagnosis and Main Criteria for Inclusion and Exclusions: Eligible patients will be <18 years of age with a diagnosis of relapsed or refractory solid tumors not amenable to curative treatment, for whom chemotherapy with doxorubicin, vincristine/irinotecan, or high-dose ifosfamide is deemed appropriate by the investigator. In addition, the patient must have adequate performance status by Lansky or Karnofsky and adequate hematologic, organ, and coagulation function. The patient must not have a hematologic malignancy, uncontrolled intercurrent illness, or active infection.

Test Product, Dosage, and Mode of Administration:

Olaratumab: for intravenous (IV) use, supplied in single-use 500 mg/50 mL vials containing 10 mg/mL of product in histidine buffer, administered to patients as an IV infusion at 15 or 20 mg/kg on Day 1 and Day 8 of each cycle. Cycles are 21 days in length.

Doxorubicin: will be ~~supplied by Lilly and~~ administered intravenously. Doxorubicin (37.5 mg/m^2) is to be administered on Day 1 and Day 2 of each 21-day cycle, for up to 6 cycles or a cumulative dose of 450 mg/m^2.

Dexrazoxane: ~~will be supplied by Lilly and~~ may be administered at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion via IV injection, beginning 30 minutes prior to ~~the~~each doxorubicin infusion for the prevention of cardiotoxicity. ~~and its use~~It is recommended ~~in~~that all patients receiving 5 or more cycles of doxorubicin also receive dexrazoxane. Dexrazoxane should be administered after completion of the olaratumab infusion, prior to administration of doxorubicin. ~~Doxorubicin should be administered within approximately 30 minutes of receiving dexrazoxane.~~

Vincristine: will be ~~supplied by Lilly and~~ administered intravenously. Vincristine (patients ≥ 10 kg: 1.5 mg/m^2, patients <10 kg: 0.05mg/kg. Dose is capped at 2 mg) is to be administered on Day 1 and Day 8 of each 21-day cycle.

Irinotecan: will be ~~supplied by Lilly and~~ administered intravenously. Irinotecan (50 mg/m^2) is to be administered on Days 1, 2, 3, 4, and 5 of each 21-day cycle.

Ifosfamide: will be ~~supplied by Lilly and~~ administered intravenously. Ifosfamide (2.8 g/m^2) is to be administered on Days 1, 2, 3, 4, and 5 of each 21-day cycle, for up to 6 cycles or a cumulative dose of 84 g/m^2. Mesna: commercial formulations will be used and administered intravenously. Mesna should be administered at a minimum dose equal to 60% of the ifosfamide dose according to institutional guidelines. ~~The mesna dose should be divided equally between 3 infusions given together with the ifosfamide infusion, 4 hours after the ifosfamide infusion, and 8 hours after the infusion.~~

Planned Duration of Treatment:

The planned duration of treatment is not fixed; patients will remain on study until they fulfill one of the criteria for study discontinuation.

Follow-up in post-treatment discontinuation: 30 days (±7 days) for patients with disease progression. For patients who have discontinued study treatment due to toxicity or reasons other than progressive disease, follow-up will continue ~~imaging studies and tumor assessments are to be obtained~~ every 6 weeks (±7 days) until progression.

Criteria for Evaluation:

Efficacy:

Radiographic assessments will be performed at baseline and then every 2 cycles (±7 days) until radiographic documentation of progressive disease. Response Evaluation Criteria In Solid Tumors, Version 1.1 criteria should be used for all solid tumors with the exception of central nervous system tumors. Response Assessment in Neuro-Oncology Criteria or Macdonald Criteria should be used for central nervous system tumors.

Safety: The safety and tolerability of the study treatment is determined by reported adverse events (AEs), physical exam including vital signs, clinical laboratory tests, electrocardiograms, and results of echocardiogram / multigated acquisition scans. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 and summarized by System Organ Class and preferred term.

Pharmacokinetic/Pharmacodynamic:

Blood samples will be collected at various time points for PK assessment for olaratumab levels and the levels of the combination chemotherapies. Blood samples will be collected at various time points for immunogenicity analysis.

Tailoring Genetics and Biomarkers:

Samples will be collected at various time points for nonpharmacogenomic biomarker research. A whole blood sample will be collected for pharmacogenomics analysis.

Tumor Tissue Biomarker:

Patients may provide a previously archived primary or metastatic tumor tissue sample (paraffin block or unstained slides). Additional voluntary pre- and post-treatment tumor tissue samples may be requested for further biomarker research.

Statistical Methods:

The primary objective of this study is to determine a safe dose of olaratumab alone or in combination with chemotherapy regimens that can be administered to pediatric patients. The study will enroll a minimum of 12 patients in Part A. ~~A s~~Safety reviews will be performed prior to ~~moving~~opening ~~into~~ Parts B and C of the study.

Safety:

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

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

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

Efficacy: Exploratory efficacy analysis will be performed to investigate antitumor activity within each combination arm. Progression-free survival curves and the median with 90% confidence interval (CI) will be estimated using Kaplan-Meier method. The objective response rate (ORR = complete response [CR] + partial response [PR]) and disease control rate (DCR=CR + PR + stable disease) and the 90% exact CI will be tabulated for each cohort.

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

5.1. Rationale and Justification for the Study

The study consists of ~~2~~3 parts. Part A will consist of approximately 12 evaluable pediatric patients treated for 1 cycle (21 days) of olaratumab monotherapy at 15 mg/kg on Day 1 and Day 8. If the patient does not experience a DLT in the first cycle of monotherapy, or meet any other criteria for discontinuation, the patient will then receive olaratumab (15 mg/kg) plus one of 3 standard chemotherapy regimens (doxorubicin or vincristine/irinotecan or high-dose ifosfamide per investigator discretion). Part B ~~will consist of at least 12 evaluable pediatric~~ patients~~. These patients~~ will be treated for 1 cycle ~~(21 days)~~ of olaratumab monotherapy at 20 mg/kg on Day 1 and Day 8~~. If the patient does not experience a DLT in the first cycle of monotherapy, or meet any other criteria for discontinuation,~~ then ~~patient will then~~ receive olaratumab (20mg/kg) plus one of 3 standard chemotherapy regimens described in Part A. Part B will be complete when at leat 10 patients (regardless of chemotherapy arm) are evaluable for safety of olaratumab 20 mg/kg from Part B. Part C will be initiated after confirmation of safety of olaratumab 20 mg/kg from Part B. Part C patients will receive olaratumab (20 mg/kg) in combination with any of the 3 chemotherapy regimens (per investigator discretion) from Cycle 1 onward (i.e no olaratumab monotherapy in Cycle 1 of Part C). ~~described in Part A that have successfully passed the DLT criteria described above for Part A (doxorubicin or vincristine/irinotecan or high-dose ifosfamide per investigator discretion).~~ Parts B and C together will enroll up to 45 patients (15 per chemotherapy arm). Treatment will continue until disease progression or other discontinuation criteria are met.

5.3. General Introduction to Olaratumab

Preferred Term	Arm A N = 64 n (%) Median no. of doxorubicin infusions=7		Arm B N = 65 n (%) Median no. of doxorubicin infusions=4	
	Grade 3	Grade ≥ 4	Grade 3	Grade ≥ 4
Patients with any AE	24 (37.5)	27 (42.2)	25 (38.5)	20 (30.8)
Neutropenia[a]	12 (18.8)	23 (35.9)	5 (7.7)	17 (26.2)
Anemia[d]	8 (12.5)	0	6 (9.2)	0
Febrile Neutropenia	7 (10.9)	1 (1.6)	9 (13.8)	0
Fatigue	6 (9.4)	0	2 (3.1)	0
Thrombocytopenia	5 (7.8)	2 (3.1)	3 (4.6)	2 (3.1)
Infections and Infestations[c]	5 (7.8)	0	4 (6.2)	3 (4.6)
Mucositis[b]	2 (3.1)	0	3 (4.6)	0
Hypokalemia	2 (3.1)	0	2 (3.1)	0
Lymphopenia	2 (3.1)	0	1 (1.5)	0
Diarrhea	2 (3.1)	0	0	0
Abdominal Pain[g]	2 (3.1)	0	0	0
Musculoskeletal Pain[f]	5 (7.8)	0	0	0
Infusion-Related Reaction[e]	0	2 (3.1)	0	0
Nausea	1 (1.6)	0	2 (3.1)	0
Decreased Appetite	1 (1.6)	0	0	0
Dry Mouth	1 (1.6)	0	0	0
Dehydration	1 (1.6)	0	0	0
Constipation	0	0	1 (1.5)	0
Dyspnea	0	0	1 (1.5)	0
Cardiac arrhythmias	0	0	1 (1.5)	0
Cardiac dysfunctions	1 (1.6)	0	0	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of randomized patients; n = number of patients with given event.

Data cut-off date: 16 May 2015.

[a] Consolidated term comprising the following preferred terms: leukopenia, neutropenia, neutrophil count decreased, white blood cell count decreased.

[b] Consolidated term comprising the following preferred terms: mucosal inflammation, oropharyngeal pain, stomatitis.

[c] Includes all preferred terms within the MedDRA system organ class of Infections and Infestations.

[d] Consolidated term comprising the following preferred terms: anemia, hemoglobin decreased.

[e] Consolidated term comprising the following preferred terms: hypersensitivity, infusion-related reaction, infusion site erythema, injection site pain.

[f] Consolidated term comprising the following preferred terms: back pain, musculoskeletal chest pain, musculoskeletal pain.

[g] Consolidated term comprising the following preferred terms: abdominal pain upper, abdominal pain.

Note. Arm A = Olaratumab + Doxorubicin; Arm B = Doxorubicin.

Source: JGDG CSR TableJGDG 12.16

5.4 Rationale for Selection of Dose

During clinical development, in Phase 1 dose-escalation trials (JGDC and JGDF) and in Phase 2 monotherapy studies (JGDE and JGDH), olaratumab has been consistently well tolerated, with no DLTs observed in the dose-escalation studies up to a dose of 16 mg/kg weekly times 4 doses in a 6-week cycle, 20 mg/kg administered every 2 weeks, and up to a dose of 15 mg/kg

administered o~~f~~n Day 1 and Day 8 of a 21-day cycle. When used in combination with other therapeutic agents, an increase of toxicities such as neutropenia and infections were observed in combination with liposomal doxorubicin (olaratumab dose of 20 mg/kg every 2 weeks) and with paclitaxel/carboplatin (olaratumab dose of 15 mg/kg on Day 1 and Day 8 every 3 weeks). In Study JGDG (15 mg/kg on Day 1 and Day 8 of a 21-day cycle), an increase in neutropenia and mucositis, but not in neutropenic sepsis or febrile neutropenia, have been observed. These toxicities are acceptable and monitorable and are consistent with the toxicity profile of doxorubicin.

6.1.1. Inclusion Criteria

[1] The patient must have histological or cytological evidence of a diagnosis of solid tumor, excluding lymphomas and melanoma, but including central nervous system (CNS) tumors, that is relapsed or refractory, not be amenable to curative treatment, and for whom chemotherapy with doxorubicin, vincristine/irinotecan, or ifosfamide is deemed appropriate by the investigator. For patients with CNS tumors, neurologic deficits in patients with CNS tumors must have been stable for at least 7 days prior to study enrollment.

[6] The patient has adequate hematologic, organ, and coagulation function ≤2 weeks (14 days) prior to first dose of study drug:

- Absolute neutrophil count (ANC) ≥750/mm^3. Granulocyte colony-stimulating factor (G-CSF) cannot be administered ≤1 week (7 days) prior to first dose of study drug. Pegfilgrast~~in~~m cannot be administered ≤2 weeks (14 days) prior to first dose of study drug.

[8] Both female and male patients of child-bearing potential must agree to use highly effective contraceptive precautions during the trial and up to 3 months following the last dose of ~~study drug~~olaratumab, or longer if~~as~~ appropriate for other study drugs according to their label. A highly effective method of birth control is defined as one that results in a low failure rate (that is, <1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices, sexual abstinence, or a vasectomized partner.

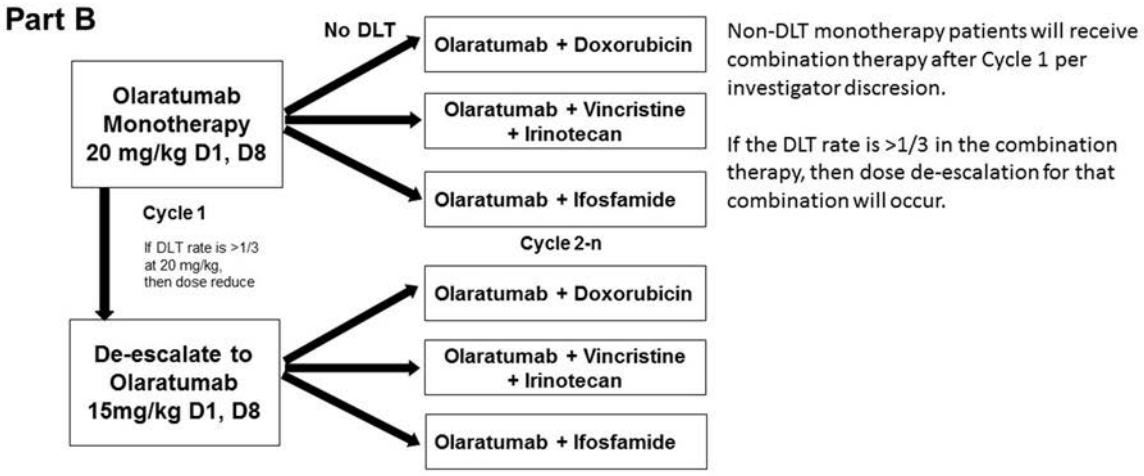
6.2 Summary of Study Design

Study JGDN is a multicenter, dose-escalation, open-label Phase 1 pediatric safety clinical trial with ~~2~~3 distinct components, Part A, Part B, and Part ~~B~~C.

Part B ~~will consist of at least 12 evaluable pediatric patients. These~~ patients will be treated for 1 cycle (21 days) of olaratumab monotherapy at 20 mg/kg on Day 1 and Day 8~~. If the patient does not experience a DLT in the first cycle of monotherapy, or meet any other criteria for discontinuation,~~ then ~~patient will then~~ receive olaratumab (20mg/kg) plus one of 3 standard chemotherapy regimens described in Part A ~~that have successfully passed the DLT criteria~~

~~described above for Part A (doxorubicin or vincristine/irinotecan or high-dose ifosfamide per investigator discretion)~~. Part B will be complete when at least 10 patients (regardless of assigned chemotherapy arm) are evaluable for safety of olaratumab 20mg/kg monotherapy. Treatment will continue until disease progression or other discontinuation criteria are met.

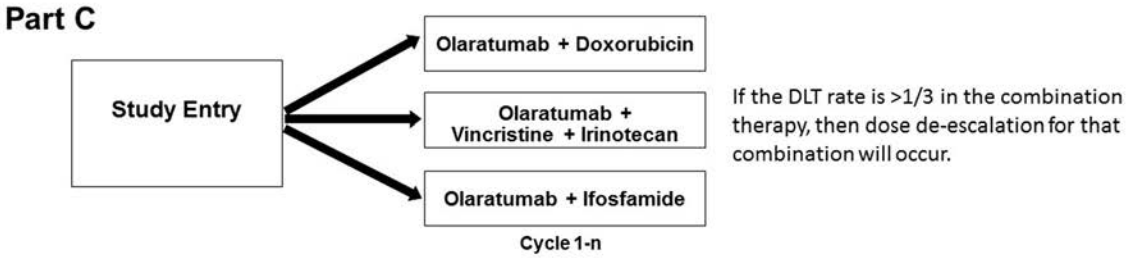
Figure JGDN.6.2 was deleted and replaced with the following:



Abbreviations: D = day; DLT = dose-limiting toxicity; n = number of cycles.

Part C will receive olaratumab (20 mg/kg) in combination with any of the 3 chemotherapy regimens from Cycle 1 onwards (ie. no olaratumab monotherapy in Cycle 1). Treatment will continue until disease progression or other discontinuation criteria are met.

Part C is illustrated in Figure JGDN.6.3



Abbreviations: DLT = dose-limiting toxicity; n = number of cycles.

Figure JGDN.6.3. Illustration of Part C of the study design.

Parts B and C together will enroll up to 45 patients (15 per chemotherapy arm).

The planned duration of treatment is not fixed; patients will remain on study until they fulfill one of the criteria for study discontinuation (Section 6.3). Patients on study treatment who continue to experience clinical benefit and no undue risks may continue olaratumab monotherapy after completion of chemotherapy until one of the criteria for discontinuation is met if deemed

medically appropriate in the opinion of the investigator and following discussion and agreement by the medical monitor.

This study will enroll a minimum of 24 (maximum of 7~~0~~9) pediatric patients, including a minimum of 10 osteosarcoma patients and 10 rhabdomyosarcoma patients across all treatment arms, if possible. The goal will be to enroll approximately 20 evaluable patients in each combination arm (across Parts A, B, and ~~B~~C) to characterize the safety and PK profile of olaratumab and the respective chemotherapeutic agents, and to inform dose choice for potential later-phase studies.

6.2.1. Primary Endpoint

Primary endpoint is defined as DLT and PK data exposure matching. The primary endpoint analysis will occur after the final patient enrolled has been evaluated for at least 2 cycles ~~(Cycle 1 is monotherapy; Cycle 2 is combination therapy)~~.

6.2.2. Study Completion and End of Trial

Any patient enrolled in Part A or Part B that has completed at least 1 cycle of treatment or discontinued due to an AE (during Cycle 1), and completed the required post-treatment safety assessment, will be considered to have completed the monotherapy portion of the study. Patients in Part A or Part B completing Cycle 1 who do not continue to Cycle 2 will be considered evaluable for monotherapy DLTs and PK. Any patient enrolled in Part A or Part B that has completed at least 2 cycles of treatment or discontinued due to an AE (during Cycle 2), and completed the required post-treatment safety assessment, will be considered to have completed the study. Any patient enrolled in Part C that has completed 1 cycle of treatment or discontinued due to an AE (during Cycle 1), and completed the required post-treatment safety assessment, will be considered to have completed the study. However, in all parts of the study, additional cycles of therapy may continue as long as the patient is receiving benefit and no criteria for discontinuation have been met. All secondary and exploratory endpoint analyses will be updated at study completion.

7.1 Materials and Supplies

Olaratumab will be provided to the sites by Lilly.

Olaratumab for injection is supplied in single-use 500 mg/50 mL vials containing 10 mg/mL of olaratumab in histidine buffer, administered to patients as an IV infusion at 10, 15, or 20 mg/kg.

~~Doxorubicin hydrochloride, dexrazoxane, vincristine sulfate, irinotecan hydrochloride, and ifosfamide will be supplied by Lilly~~

Other drug products (i.e. doxorubicin hydrochloride, dexrazoxane, vincristine sulfate, irinotecan hydrochloride, and ifosfamide) to be used in Study JGDN will be supplied by Lilly, but commercially available supply may be used as directed by Lilly for cases of regional restrictions or supply limitations.

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

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

7.2.1. Premedication

Doxorubicin

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

Dexrazoxane may be administered at a 10:1 ratio (dexrazoxane:doxorubicin) at the investigator's discretion via IV injection, beginning within 30 minutes prior to each doxorubicin infusion for the prevention of cardiotoxicity. It is recommended that all patients receiving doxorubicin also receive dexrazoxane.

Vincristine

Laxatives and/or stool softeners ~~should~~may be used preemptively during vincristine-containing cycles.

Ifosfamide

When the treatment includes ifosfamide, mesna should be administered at a minimum dose equal to 60% of the ifosfamide dose according to institutional guidelines, including divided dose or continuous infusion. ~~The mesna dose maybe divided equally between 3 infusions:~~

~~1. together with the ifosfamide infusion,~~
~~2. 4 hours after the ifosfamide infusion, and~~
3. ~~8 hours after the infusion.~~

7.2.2. Dosing Schedule

The following treatments will be administered in this study every 3-week (21-day) ± 3 day cycle (Table JGDN.7.1 and Table JGDN.7.2)

Part C:

All Cycles

Olaratumab as IV infusion on Day 1 and Day 8 (at 20 mg/kg),

AND

Doxorubicin as IV infusion on Day 1 and Day 2 (at 37.5 mg/m^2; up to 6 cycles or a cumulative dose of 450 mg/m^2)

OR

Vincristine as IV on Day 1 and Day 8 (patients ≥ 10 kg: 1.5 mg/m^2, patients <10 kg: 0.05 mg/kg. Dose is capped at 2 mg) plus irinotecan as IV on Days 1, 2, 3, 4, and 5 (at 50 mg/m^2),

OR

Ifosfamide as IV on Days 1, 2, 3, 4, and 5 (at 2.8 g/m^2; up to 6 cycles or a cumulative dose of 84 g/m^2). Treatment beyond 84 g/m^2 requires consultation with the Lilly CRP/CRS.

Table JGDN.7.1. Treatment Regimens/Dosing Schedule (Part A and Part B)

	Study Drug		Dose	Route	Timing
Cycle 1	Olaratumab[a]	Part A	15 mg/kg	IV	approximately 1 hour infusion on Day 1 and Day 8 of each 21-day cycle
		Part B	20 mg/kg		
Cycle 2-n	Olaratumab[a]	Part A	15 mg/kg	IV	approximately 1 hour infusion Day 1 and Day 8 of each 21-day cycle
		Part B	20 mg/kg		
	1-hour observation period[b] followed by				
	Doxorubicin[c,dg]	Parts A and B	37.5 mg/m^2	IV	Day 1 and Day 2 of each 21-day cycle
			OR		
	Vincristine[e]	Parts A and B	1.5 mg/m^2	IV	Day 1 and Day 8 of each 21-day cycle
	Irinotecan[g]	Parts A and B	50 mg/m^2	IV	Days 1, 2, 3, 4, and 5 of each 21-day cycle
			OR		
	Ifosfamide[fg]	Parts A and B	2.8 g/m^2	IV	approximately 2 to 3 hour infusion on Days 1, 2, 3, 4, and 5 of each 21-day cycle

Abbreviations: eCRF = electronic case report form; IV = intravenous.

a Administer ~~P~~premedication ~~is recommended~~ prior to infusion of olaratumab. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at the investigator's discretion. Premedication must be provided in the setting of a prior Grade 1-2 infusion-related reaction, as detailed in Section 7.2.4.1. All premedication administered must be adequately documented in the eCRF.

b A 1-hour observation period is required after the administration of the first and second doses of olaratumab. If there is no evidence of an infusion-related reaction during the initial 2 cycles of olaratumab, then no observation period is required for subsequent treatment cycles. In the event an infusion-related reaction occurs thereafter, then the 1-hour observation period should be reinstituted; see Section 7.2.4.1.

c Administer doxorubicin for up to 6 cycles only ~~(Cycles 2-7)~~ or cumulative dose of 450 mg/m^2.

d Administer doxorubicin according to institutional guidelines and/or clinical practice as an IV injection or as an infusion in less than 60 minutes (+10 minutes). Decrease the rate of doxorubicin administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occurs.

e For patients weighing less than 10 kg, the dose of vincristine should be 0.05 mg/kg. The dose is capped at 2 mg for all patients.

f Administer ifosfamide for up to 6 cycles only ~~(Cycles 2-7)~~ or a cumulative dose of 84 g/m^2. Treatment beyond 84 g/m^2 requires consultation with the Lilly clinical research physician/clinical research scientist.

g For sequential day chemotherapy, it is recommended to allow a minimum of 20 hours between dosing, unless institutional standard varies.

Table 7.2 Treatment Regimens/Dosing Schedule (Part C)

	Study Drug	Dose	Route	Timing
Cycle 1-n	Olaratumab[a]	20 mg/kg	IV	approximately 1 hour infusion on Day 1 and Day 8 of each 21-day cycle
				1-hour observation period[b] followed by
	Doxorubicin[c,d,g]	37.5 mg/m^2	IV	Day 1 and Day 2 of each 21-day cycle
				OR
	Vincristine[e]	1.5 mg/m^2	IV	Day 1 and Day 8 of each 21-day cycle
	Irinotecan[g]	50 mg/m^2	IV	Days 1, 2, 3, 4, and 5 of each 21-day cycle
				OR
	Ifosfamide[f,g]	2.8 g/m^2	IV	approximately 2 to 3 hour infusion on Days 1, 2, 3, 4, and 5 of each 21-day cycle

Abbreviations: eCRF = electronic case report form; IV = intravenous.

a Administer premedication prior to infusion of olaratumab. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at the investigator's discretion. Premedication must be provided in the setting of a prior Grade 1-2 infusion-related reaction, as detailed in Section 7.2.4.1. All premedication administered must be adequately documented in the eCRF.

b A 1-hour observation period is required after the administration of the first and second doses of olaratumab. If there is no evidence of an infusion-related reaction during the initial 2 cycles of olaratumab, then no observation period is required for subsequent treatment cycles. In the event an infusion-related reaction occurs thereafter, then the 1-hour observation period should be reinstituted; see Section 7.2.4.1.

c Administer doxorubicin for up to 6 cycles only or cumulative dose of 450 mg/m^2.

d Administer doxorubicin according to institutional guidelines and/or clinical practice as an IV injection or as an infusion in less than 60 minutes (+10 minutes). Decrease the rate of doxorubicin administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occurs.

e For patients weighing less than 10 kg, the dose of vincristine should be 0.05 mg/kg. The dose is capped at 2 mg for all patients.

f Administer ifosfamide for up to 6 cycles only or a cumulative dose of 84 g/m^2. Treatment beyond 84 g/m^2 requires consultation with the Lilly clinical research physician/clinical research scientist.

g For sequential day chemotherapy, it is recommended to allow a minimum of 20 hours between dosing, unless institutional standard varies.

7.2.3. Dose Progression through Study Parts ~~Escalation from Part A to Part B~~

Safety will be the primary criteria for the dose escalation or de-escalation of both olaratumab monotherapy and the combination regimens. No dose escalation can occur without prior discussion and agreement between the investigators and the Lilly CRP/CRS/Lilly study team; the decision will be documented in writing. Sites will be notified of this decision in writing.

Based on the ongoing safety reviews, modifications to the dose-escalation strategy or other design elements may be made via protocol amendment to ensure patient safety.

Part B will be initiated after acceptable safety results from Part A, including a minimum of 6 evaluable patients, and the PK profile from Part A monotherapy. Part B will be complete when

at least 10 patients (regardless of assigned chemotherapy arm) are evaluable for safety of olaratumab 20mg/kg monotherapy .

Part C will open for enrollment after a complete safety review of the first 10 patients (regardless of chemotherapy arm) to complete Part B monotherapy (olaratumab 20 mg/kg). Once safety of olaratumab 20/mg/kg is determined, Part C will open for enrollment. This safety review will be performed by the Lilly CRP/CRS/Lilly study team and investigators and documented in writing. Sites will be notified of this decision in writing.

7.2.3.2. Dose-Escalation Method

Part B will be initiated after the following criteria have been met:

- Acceptable safety results, which must include a minimum of 6 evaluable patients, and the PK profile from Part A monotherapy
- At least one of the 15 mg/kg combination arms has met the following DLT criteria: less than one third (that is, approximately 33.3% [minimum of 3 patients]) DLT rate. Only the combination arms in Part A that have met these criteria may be studied in Parts B and C.

In Part A, if the DLT rate is >1/3 (that is, greater than 4 out of 12 patients) during Cycle 1 monotherapy, then the dose of olaratumab will be reduced to 10 mg/kg. In Part B, if the DLT rate is >1/3 during Cycle 1 monotherapy, then the dose of olaratumab will be reduced to 15 mg/kg. In Part C, if the DLT rate is >1/3 during Cycle 1 combination therapy, then the dose of olaratumab will be reduced to 15 mg/kg.

If the DLT rate is >1/3 in the first cycle (Parts A and B Cycle 2, or Part C Cycle 1) of any of the chemotherapy arms, then appropriate dose de-escalation of olaratumab for that combination will occur.

7.2.4. Dose Adjustments and Delays

In the event that a patient experiences a DLT or a DLT-equivalent (a DLT occurring in Cycle 3 of later of Parts A and B or Cycle 2 or later of Part C), treatment will be interrupted. Dosing can be resumed after resolution of the toxicity to baseline levels at the next lower dose level (Table JGDN.7.~~2~~3) already deemed safe upon discussion with the Lilly CRP/CRS. For Grade 3/4 toxicities that are not dose-limiting, see Section 7.2.4.1.2. for hematologic toxicities and Section 7.2.4.1.3 for nonhematologic toxicities.

7.2.4.1.1. Infusion-Related Reactions

In general ~~(may vary if patient recently received premedication)~~, if a patient experiences a Grade 1 or 2 IRR, the infusion should stop and the patient should be treated with an antihistamine (for example, diphenhydramine hydrochloride), glucocorticoid (for example, dexamethasone), acetaminophen (or equivalent), and oxygen (as indicated), according to standard medical practices. After recovery, the infusion rate should be decreased 50% for the duration of the infusion. If subsequent infusions are then tolerated with the use of

premedications as above and a 50% decrease in infusion rate, the infusion rate may be increased to a rate deemed appropriate by the investigator, as long as it does not exceed 25 mg/min.

A Grade 3 or 4 IRR will require immediate treatment, including, but not limited to, 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.

7.2.4.1.2. Hematologic Toxicity

Table JGDN.7.~~3~~4 summarizes the olaratumab dose modifications required in case of olaratumab-related hematologic toxicities during any cycle.

Table JGDN.7.~~3~~4. General Guidelines for Olaratumab Dose Modification Due to Hematologic Toxicity Deemed Related to Olaratumab

Toxicity	Required Dose Modification
Neutropenia	
ANC Grade 1-3	No dose modification required
ANC <500/mm^3 (Grade ≥4)	No treatment administered; treatment cycle delayed
At retreatment:	
If Grade ≥3 neutropenic fever/infection has occurred	Withhold dose until ANC is ≥ 750/mm^3; for the 15-mg/kg cohort (Part A), reduce dose to 10 mg/kg; for the 20-mg/kg cohort (Part B and Part C), reduce dose to 15 mg/kg.
If Grade 4 neutropenia lasting >1 week has occurred	Withhold dose until ANC is ≥ 750/mm^3; for the 15-mg/kg cohort (Part A), reduce dose to 10 mg/kg; for the 20-mg/kg cohort (Part B and Part C), reduce dose to 15 mg/kg.
Grade 4 ANC without fever/infection lasting ≤ 1 week	Administer the next olaratumab at full dose at investigator's discretion with recommended use of prophylactic G-CSFs
Second incidence of either: 1) Grade ≥3 neutropenic fever/infection 2) Grade 4 neutropenia lasting > 1 week	For the 15-mg/kg cohort (Part A) that have been reduced to 10-mg/kg, discontinue olaratumab; for the 20-mg/kg cohort (Part B and Part C) that have been reduced to 15-mg/kg, a second dose level reduction to 10 mg/kg
Thrombocytopenia	
Platelets <75,000/mm^3	No treatment administered; treatment delayed until resolved to ≥75,000/mm^3
Anemia	
Hemoglobin <8 g/dL	No treatment administered; treatment delayed until resolved to ≥8 g/dL, transfusion with packed red blood cells allowed

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

7.2.4.1.3. Nonhematologic Toxicity

General guidelines for dose modification for other nonhematologic toxicities related to olaratumab are shown in Table JGDN.7.45.

Table JGDN.7.45. 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.
Grade 3	For a Grade 3 toxicity not adequately controlled with appropriate supportive care, the dose must be withheld until toxicity is ≤ Grade 1 or has returned to pretreatment baseline; then treatment may resume at a reduced dose of 10 mg/kg for the 15-mg/kg cohort (Part A) and reduced dose of 15 mg/kg for the 20-mg/kg cohort (Part B and Part C). If toxicity recurs after therapy resumes, then treatment should be discontinued for the 15-mg/kg cohort (Part A) or the dose reduced to 10 mg/kg for the 20-mg/kg cohort (Part B and Part C).
Grade 4	The dose must be withheld until dose toxicity is ≤ Grade 1 or has returned to baseline. Permanent discontinuation should be considered for any patient experiencing Grade 4 non-hematologic toxicity assessed as related to olaratumab. However, if resumption of dosing is deemed appropriate by the investigator, treatment may resume only after consultation with the Lilly study physician, with the dose reduced to 10 mg/kg for the 15-mg/kg cohort (Part A); dose reduced to 15 mg/kg for the 20-mg/kg cohort (Part B and Part C). If Grade 4 toxicity recurs after therapy resumes, treatment with olaratumab will be discontinued.

7.2.4.2. Doxorubicin Dose Adjustments

The dose adjustments and delays for doxorubicin apply to patients treated with olaratumab plus doxorubicin.

7.2.4.3.2.1. Neurologic Toxicity

Autonomic neuropathy is manifested as constipation (which can be severe), abdominal pain, urinary retention, and paralytic ileus. Laxatives or stool softeners should be ~~given~~considered routinely to prevent constipation. These symptoms resolve with time and may not occur with subsequent treatment. If bladder atony occurs, vincristine should be held until symptoms resolve. Worsening neuropathy requires dose delay, reduction, or discontinuation.

Table JGDN.7.~~7~~8. General Guidelines for Dose Modification of Vincirstine due to Toxicity

Toxicity/Worst Counts in Cycle	Vincristine Dose Reduction
Neurotoxicity	
Grade 1 or 2	Full dose
Grade 3 or 4	Hold until Grade ≤1 then 50% of initial dose [a]
Severe paralytic ileus	Hold until normal bowel movement then 50% of initial dose
~~Respiratory symtoms (for example, bronchospasm)pneumonitis)~~	~~Discontinue~~

Grade 3 other related nonhematologic/organ toxicity	Hold
Grade 4 other related nonhematologic/organ toxicity	Discontinue

[a] Reescalation to 75% or full dose should be considered at the start of each vincristine containing cycle based on patient's symptoms.

7.2.4.5.1. Urotoxic Effects

The incidence of ~~**urotoxic effects**~~urotoxic effects without an uroprotector can be up to 40% and is dose dependent; coadministration with mesna and adequate hydration are mandatory. Patients may present with hematuria, symptomatic cystitis, or bladder fibrosis. Past or concomitant radiation of the bladder or busulfan treatment may increase the risk of hemorrhagic cystitis. Several methods of treatment for established hematuria have been described: bladder irrigation with water or normal saline, intravesical instillation of astringents (alum, silver nitrate), systemic administration of antifibrinolytics (aminocaproic acid, tranexamic acid), cystoscopy to evacuate the bladder of clots, continuous bladder irrigation, and intravesical prostaglandins. For severe or refractory hematuria**,** intravesical formalin, phenol, or prostaglandin has been used ± surgical intervention (electrocautery, cryosurgery, diversion of urine flow, hypogastric artery ligation, or cystectomy). Ifosfamide should be discontinued or dose reduced for macroscopic hematuria.

7.3 Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive olaratumab in this study. Before each patient's enrollment into the study, an eligibility check must be conducted between the investigational site and the Lilly clinical research personnel to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the site will register the patient by assigning the patient a unique study identification number via the Interactive Web Response System (IWRS), which is accessible 24 hours a day. Study drug will be allocated to patients using the IWRS. No dose escalations (that is, initiating Parts B and C for a chemotherapy combination) can occur without prior discussion and agreement with the responsible Lilly CRP or CRS.

7.5 Concomitant Therapy

With the exceptions listed in the sections below, no other chemotherapy, investigational medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, or surgery for cancer will be permitted while patients are on study treatment. Palliative radiotherapy (of ≤14 calendar days, e.g., for a solitary skeletal metastasis) after Cycle 7 may be allowed as long as the patient has not developed another reason for study discontinuation and other sites of disease are available for response assessment. Palliative radiation may not occur prior to discussion with the study medical monitor and written approval.

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

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

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

7.5.1.2. Mesna

For patients in the ifosfamide arm, mesna should be administered at a minimum dose equal to 60% of the ifosfamide dose according to institutional guidelines, including divided dose or continuous infusion. ~~The mesna dose should be divided equally between 3 infusions given together with the ifosfamide infusion, 4 hours after the ifosfamide infusion, and 8 hours after the infusion.~~

7.5.2. Prohibited Therapies

Additional concurrent chemotherapy, radiation therapy, biologic response modifiers, or other investigational or approved anticancer agents may not be administered to patients on this study. Palliative radiotherapy (of ≤14 calendar days, e.g., for a solitary skeletal metastasis) after Cycle 7 may be allowed as long as the patient has not developed another reason for study discontinuation and other sites of disease are available for response assessment. Palliative radiation may not occur prior to discussion with the study medical monitor and written approval. ~~Palliative radiation or surgery to symptomatic sites of disease will not be permitted while on study.~~

7.6.1. Evaluable Patients

Any patient from Parts A or B who is discontinued from the study before completing 1 cycle of olaratumab treatment will be deemed non-evaluable for assessment of olaratumab monotherapy, unless the patient experiences a DLT prior to withdrawal. Any patient who is discontinued from the study before completing 1 cycle of combination chemotherapy treatment (Cycle 2 for Parts A or B or Cycle 1 for Part C) will be deemed non-evaluable for assessment of a combination chemotherapy, unless the patient experiences a DLT or DLE-equivalent prior to withdrawal.

If a~~the~~ patient from Parts A or B is noncompliant during Cycle 1 due to reasons other than drug-related toxicity, he or she will be considered non-evaluable for olaratumab monotherapy and may be replaced. If a~~the~~ patient from Parts A or B is noncompliant during Cycle 2 or a patient from Part C is noncompliant during Cycle 1 due to reasons other than drug-related toxicity, he or she will be considered non-evaluable for combination chemotherapy and may be replaced.

Nonevaluable patients may be replaced to ensure that enough patients complete 1 cycle of olaratumab monotherapy or combination chemotherapy, unless accrual to that cohort has stopped due to a DLT.

Patients who are not evaluable for pharmacokinetics, but who complete 1 cycle of olaratumab monotherapy or 1 cycle of combination chemotherapy ~~(Cycle 2)~~, may be replaced to ensure adequate PK data, unless accrual to that cohort has stopped due to a DLT.

Attachment 1. Protocol JGDN Study Schedule

JGDN Study Schedule, Screening and Baseline Assessments (All Parts)

Relative Day Prior to Cycle 1 Day 1	≤28	≤14	≤7	Comments
Eligibility Assessments				
Lansky/Karnofsky performance status		X		To be assessed by the investigator.
Efficacy Assessments				
Imaging Studies (CT/MRI/chest x-ray)	X			For rapidly growing tumors, scans should be performed ≤14 days prior to C1D1. Scans performed prior to the date of consent may be used provided they are within 2~~1~~8 days of C1D1. RECIST v1.1 should be used for all tumors with the exception of CNS tumors; RANO or Macdonald criteria should be used for CNS tumors.
RECIST v1.1, RANO, or Macdonald Tumor Assessments	X			

JGDN Study Schedule, Treatment Period for Olaratumab in Combination with Doxorubicin (Parts A and B)

All evaluations must be done on the day of study drug administration. In case of dose interruption, these evaluations will also be done at minimum frequency every 21 days (±3 days).

JGDN Study Schedule, Treatment Period for Olaratumab in Combination with Doxorubicin (Part C)

Day	Treatment Period 21-Day Cycles Cycle 1-n				Comments
	Day 1[a]	Day 2[a]	Day 8[a]	Day 15[a]	
Eligibility Assessments					
Lansky/Karnofsky performance status	X				
ECG	X				Baseline ECG can be used for C1D1 if completed within 7 days. Consecutive replicate ECGs will be obtained (3 readings), whenever feasible for the patient, at approximately 1-minute intervals.
ECHO or MUGA	X				ECHO or MUGA scans must be performed PRIOR to Cycles 1, 3, and 5 and results must be available prior to doxorubicin administration for those cycles. Additional ECHO/MUGA may be performed at the investigator's discretion as clinically indicated.
Safety Assessments					

Day	Treatment Period 21-Day Cycles Cycle 1-n				Comments
	Day 1[a]	Day 2[a]	Day 8[a]	Day 15[a]	
Physical Exam	X		X		Physical exam includes weight and BSA measurement.
Vital Signs	X	X	X		Vital sign measurements include temperature, pulse rate, and blood pressure. On Day 1, obtain vital signs prior to and after the completion of the olaratumab infusion (prior to dexrazoxane, if used; or if not used, then prior to doxorubicin) and within 1 hour after completion of the doxorubicin infusion. On Day 2, obtain vital signs prior to dexrazoxane infusion (patients receiving dexrazoxane and doxorubicin) or prior to doxorubicin infusion (patients receiving doxorubicin only) and within 1 hour after completion of the doxorubicin infusion. On Day 8, obtain vital signs prior to and after the completion of the olaratumab infusion.
Adverse Event Assessment	X	X	X		All AEs considered at least possibly-related to study treatment will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.
Concomitant Medication Assessment	X	X	X		
Laboratory Assessments (See Attachment 2 for details)					
Hematology Profile	X		X	X	Hematology measurements must be collected on Day 15 only during Cycle 1 and Cycle 2.
Coagulation Profile	X				Perform every other cycle beginning at Cycle 1 Day 1. Baseline value can be used for C1D1 if completed within 7 days.
Chemistry Profile	X				
Urinalysis	X				Includes a routine urinalysis, and if clinically indicated, a microscopic analysis. If routine analysis indicates > 2+ proteinuria, then a 24-hour urine must be collected and must demonstrate ≤ 1000 mg of protein in 24 hours or urine protein/creatinine ratio < 1, prior to proceeding to the next cycle
Pregnancy Test	X				Urine pregnancy test on Day 1 of every cycle or per local practice (whichever is of shorter duration) and at short-term follow-up visit. If the urine pregnancy test performed on Day 1 of the cycle is positive, confirm with a serum pregnancy test.
Immunogenicity	See Attachment 4 for specific time points.				When possible, an immunogenicity sample will be collected at the same time as the PK sample. If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
Efficacy Assessments					

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 8[a]	Day 15[a]	Comments
Imaging Studies (CT/MRI)	X				Imaging studies and tumor assessments are to be obtained every 2 cycles (-7 days) until documented progression for patients with CR, PR, or SD. RECIST v1.1 should be used for all tumors with the exception of CNS tumors; RANO or Macdonald criteria should be used for CNS tumors.
RECIST v1.1, RANO, or Macdonald Tumor Assessments	X				
Other Assessments					
PK Sampling	See Attachment 4 for specific time points				
Biomarker Sampling	X				During treatment, a single sample will be collected prior to dosing at Cycle 3 Day 1.
Biopsy/Tumor Tissue Submission	X				Optional tumor tissue from biopsy for biomarkers and tumor type. May be collected any time during or after Cycle 1 Day 1.
Premedication					
Premedication prior to olaratumab administration	X		X		In Cycle 1 (both Day 1 and Day 8 doses), all patients should receive premedication with dexamethasone (or equivalent medication) and an H1 antagonist intravenously 30–60 minutes prior to olaratumab infusion. Additional premedication may be provided at investigator discretion. For all subsequent cycles, all patients should receive premedication with an H1 antagonist (for example, diphenhydramine) intravenously 30–60 minutes prior to each dose of olaratumab. Additional premedication may be provided at investigator discretion. For a patient who has had a Grade 1 or 2 olaratumab infusion reaction in a previous cycle, patients should be premedicated with antihistamine and glucocorticoid (for example, dexamethasone) intravenously 30–60 minutes prior to olaratumab infusion, and acetaminophen (or equivalent) for all subsequent infusions. Additional premedication may be provided at investigator discretion.
Administer dexrazoxane	X	X			Dexrazoxane may be given at 10:1 ratio (dexrazoxane to doxorubicin) prior to doxorubicin on Day 1 and Day 2 at the investigator' discretion. Dexrazoxane is recommended for all patients receiving doxorubicin.
Clinical Drug Supplies					
Administer olaratumab	X		X		

Day	Treatment Period 21-Day Cycles Cycle 1-n				Comments
	Day 1[a]	Day 2[a]	Day 8[a]	Day 15[a]	
Administer doxorubicin	X	X			Doxorubicin to be administered at 37.5 mg/m^2 on Day 1 and Day 2 to be continued for 6 Cycles or a cumulative dose of 450 mg/m^2

Abbreviations: AE = adverse event; BSA = body surface area; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; IRR = infusion-related reaction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PK = pharmacokinetics; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors Version 1.1; SD = stable disease.

[a] A delay of up to 3 days will be permitted due to holidays, weekends, inclement weather or other unforeseen circumstances, including unexpected changes in patient schedules, and will not count as a protocol deviation. However, assessments must be done prior to treatments and the interval between cycles may not be less than 21 days. In later cycles, longer delays may be allowed in consultation with Lilly medical representative.

JGDN Study Schedule, Treatment Period for Olaratumab in Combination with Vincristine and Irinotecan (Part A and B)

All evaluations must be done on the day of study drug administration. In case of dose interruption, these evaluations will also be done at minimum frequency every 21 days (±3 days).

JGDN Study Schedule, Treatment Period for Olaratumab in Combination with Vincristine and Irinotecan (Part C)

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 3[a]	Day 4[a]	Day 5[a]	Day 8[a]	Day 15[a]	Comments
Eligibility Assessments								
Lansky/Karnofsky performance status	X							
ECG	X							Consecutive replicate ECGs will be obtained (3 readings), whenever feasible for the patient, at approximately 1-minute intervals.
Safety Assessments								
Physical Exam	X					X		Physical exam includes weight and BSA measurement.
Vital Signs	X	X	X	X	X	X		Vital sign measurements include temperature, pulse rate, and blood pressure. On Day 1, obtain vital signs prior to and after the completion of the olaratumab infusion (prior to vincristine) and within 1 hour after completion of the irinotecan infusion. On Days 2-5, obtain vital signs prior to irinotecan infusion and within 1 hour after completion of the infusion. On Day 8, obtain vital signs prior to and after the completion of the olaratumab infusion (prior to vincristine) and within 1 hour after completion of the vincristine infusion.
Adverse Event Assessment	X	X	X	X	X	X		All AEs considered at least possibly-related to study treatment will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.
Concomitant Medication	X	X	X	X	X	X		

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 3[a]	Day 4[a]	Day 5[a]	Day 8[a]	Day 15[a]	Comments
Assessment								
Laboratory Assessments (See Attachment 2 for details)								
Hematology Profile	X					X	X	Hematology measurements must be collected on Day 15 only during Cycle 1 and Cycle 2.
Coagulation Profile	X							Perform every other cycle beginning at Cycle 1 Day 1. Baseline value can be used for C1D1 if completed within 7 days.
Chemistry Profile	X							
Urinalysis	X							Includes a routine urinalysis, and if clinically indicated, a microscopic analysis. If routine analysis indicates > 2+ proteinuria, then a 24-hour urine must be collected and must demonstrate ≤ 1000 mg of protein in 24 hours, or urine protein/creatinine ratio < 1, prior to proceeding to the next cycle.
Pregnancy Test	X							Urine pregnancy test on Day 1 of every cycle or per local practice (whichever is of shorter duration) and at short-term follow-up visit. If the urine pregnancy test performed on Day 1 of the cycle is positive, confirm with a serum pregnancy test.
Immunogenicity	See Attachment 4 for specific time points.							When possible, an immunogenicity sample will be collected at the same time as the PK sample. If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
Efficacy Assessments								
Imaging Studies (CT/MRI)	X							Imaging studies and tumor assessments are to be obtained every 2 cycles (±7 days) until documented progression for patients with CR, PR, or SD. RECIST v1.1 should be used for all tumors with the exception of CNS tumors; RANO or
RECIST v1.1, RANO, or Macdonald Tumor Assessments	X							

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 3[a]	Day 4[a]	Day 5[a]	Day 8[a]	Day 15[a]	Comments
								Macdonald criteria should be used for CNS tumors.
Other Assessments								
PK Sampling	See Attachment 4 for specific time points.							
Biomarker Sampling	X							During treatment, a single sample will be collected prior to dosing at Cycle 3 Day 1.
Biopsy/Tumor Tissue Submission	X							Optional tumor tissue from biopsy for biomarkers and tumor type. May be collected any time during or after Cycle 1 Day 1.
Premedication								
Premedication prior to olaratumab administration	X					X		In Cycle 1 (both Day 1 and Day 8 doses), all patients should receive premedication with dexamethasone (or equivalent medication) and an H1 antagonist intravenously 30–60 minutes prior to olaratumab infusion. Additional premedication may be provided at investigator discretion. For all subsequent cycles, all patients should receive premedication with an H1 antagonist (for example, diphenhydramine) intravenously 30–60 minutes prior to each dose of olaratumab. Additional premedication may be provided at investigator discretion. For a patient who has had a Grade 1 or 2 olaratumab infusion reaction in a previous cycle, patients should be premedicated with antihistamine and glucocorticoid (for example dexamethasone) intravenously 30–60 minutes prior to olaratumab infusion, and acetaminophen (or equivalent) for all subsequent infusions. Additional premedication may be provided at investigator discretion.
Clinical Drug Supplies								
Administer olaratumab	X					X		
Administer vincristine	X					X		
Administer irinotecan	X	X	X	X	X			

Abbreviations: AE = adverse event; BSA = body surface area; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; IRR = infusion-related reaction; MRI = magnetic resonance imaging; PK = pharmacokinetics; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors Version 1.1; SD = stable disease.

[a] A delay of up to 3 days will be permitted due to holidays, weekends, inclement weather or other unforeseen circumstances, including unexpected changes in patient schedules, and will not count as a protocol deviation. However, assessments must be done prior to treatments and the interval between cycles may not be less than 21 days. In later cycles, longer delays may be allowed in consultation with Lilly medical representative.

JGDN Study Schedule, Treatment Period for Olaratumab in Combination with Ifosfamide (Part A and B)

All evaluations must be done on the day of study drug administration. In case of dose interruption, these evaluations will also be done at minimum frequency every 21 days (±3 days).

	Treatment Period 21-Day Cycles									
	Cycle 1		**Cycle 2-n**							
Day	**Day 1 (±3)**	**Day 8 (±3)**	**Day 1 (±3)**	**Day 2 (±3)**	**Day 3 (±3)**	**Day 4 (±3)**	**Day 5 (±3)**	**Day 8 (±3)**	**Day 15 (±3)**	**Comments**
Premedication										
Mesna Administration			X	X	X	X	X			Administer at a minimum 60% of the ifosfamide dose according to institutional guidelines. ~~The mesna dose should be divided equally between 3 infusions given together with the ifosfamide infusion, 4 hours after the ifosfamide infusion, and 8 hours after the infusion.~~

JGDN Study Schedule, Treatment Period for Olaratumab in Combination with Ifosfamide (Part C)

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 3[a]	Day 4[a]	Day 5[a]	Day 8[a]	Day 15[a]	Comments
Eligibility Assessments								
Lansky/Karnofsky performance status	X							
ECG	X							Consecutive replicate ECGs will be obtained (3 readings), whenever feasible for the patient, at approximately 1-minute intervals.
Safety Assessments								
Physical Exam	X					X		Physical exam includes weight and BSA measurement.
Vital Signs	X	X	X	X	X	X		Vital sign measurements include temperature, pulse rate, and blood pressure. On Day 1, obtain vital signs prior to and after the completion of the olaratumab infusion (prior to ifosfamide) and within 1 hour after completion of the ifosfamide infusion. On Days 2-5, obtain vital signs prior to ifosfamide infusion and within 1 hour after completion of the infusion. On Day 8, obtain vital signs prior to and after the completion of the olaratumab infusion.
Adverse Event Assessment	X	X	X	X	X	X		All AEs considered at least possibly-related to study treatment will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.
Concomitant Medication Assessment	X	X	X	X	X	X		
Laboratory Assessments (See Attachment 2 for details)								
Hematology Profile	X					X	X	Hematology measurements must be collected on Day 15 only during Cycle 1 and Cycle 2.
Coagulation Profile	X							Perform every other cycle beginning at Cycle 1 Day 1.
Chemistry Profile	X							
Urinalysis	X							Includes a routine urinalysis, and if clinically indicated, a microscopic analysis. If routine analysis indicates > 2+ proteinuria, then a 24-hour urine must be collected and must

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 3[a]	Day 4[a]	Day 5[a]	Day 8[a]	Day 15[a]	Comments
								demonstrate ≤ 1000 mg of protein in 24 hours, or urine protein/creatinine ratio < 1, prior to proceeding to the next cycle.
Pregnancy Test	X							Urine pregnancy test on Day 1 of every cycle or per local practice (whichever is of shorter duration) and at short-term follow-up visit. If the urine pregnancy test performed on Day 1 of the cycle is positive, confirm with a serum pregnancy test.
Immunogenicity	See Attachment 4 for specific time points.							When possible, an immunogenicity sample will be collected at the same time as the PK sample. If a patient experiences an IRR to olaratumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
Efficacy Assessments								
Imaging Studies (CT/MRI)	X							Imaging studies and tumor assessments are to be obtained every 2 cycles (±7 days) until documented progression for patients with CR, PR, or SD. RECIST v1.1 should be used for all tumors with the exception of CNS tumors; RANO or Macdonald criteria should be used for CNS tumors.
RECIST v1.1, RANO, or Macdonald Tumor Assessments	X							
Other Assessments								
PK Sampling	See Attachment 4 for specific time points							
Biomarker Sampling	X							During treatment, a single sample will be collected prior to dosing at Cycle 3 Day 1.
Biopsy/Tumor Tissue Submission	X							Optional tumor tissue from biopsy for biomarkers and tumor type. May be collected any time during or after Cycle 1 Day 1.
Premedication								
Premedication prior to olaratumab administration	X					X		In Cycle 1 (both Day 1 and Day 8 doses), all patients should receive premedication with dexamethasone (or equivalent medication) and an H1 antagonist intravenously 30–60 minutes prior to olaratumab infusion. Additional premedication may be

Day	Treatment Period 21-Day Cycles Cycle 1-n Day 1[a]	Day 2[a]	Day 3[a]	Day 4[a]	Day 5[a]	Day 8[a]	Day 15[a]	Comments
								provided at investigator discretion. For all subsequent cycles, all patients should receive premedication with an H1 antagonist (for example, diphenhydramine) intravenously 30–60 minutes prior to each dose of olaratumab. Additional premedication may be provided at investigator discretion. For a patient who has had a Grade 1 or 2 olaratumab infusion reaction in a previous cycle, patients should be premedicated with antihistamine and glucocorticoid (for example, dexamethasone) intravenously 30–60 minutes prior to olaratumab infusion, and acetaminophen (or equivalent) for all subsequent infusions. Additional premedication may be provided at investigator discretion.
Mesna Administration	X	X	X	X	X			Administer at a minimum 60% of the ifosfamide dose according to institutional guidelines.
Clinical Drug Supplies								
Administer olaratumab	X					X		
Administer ifosfamide	X	X	X	X	X			Administer ifosfamide for up to 6 cycles or a cumulative dose of 84 g/m^2. Treatment beyond 84 g/m^2 requires consultation with the Lilly CRP/CRS.

Abbreviations: AE = adverse event; BSA = body surface area; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; IRR = infusion-related reaction; MRI = magnetic resonance imaging; PK = pharmacokinetics; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria In Solid Tumors; SD = stable disease.

[a] A delay of up to 3 days will be permitted due to holidays, weekends, inclement weather or other unforeseen circumstances, including unexpected changes in patient schedules, and will not count as a protocol deviation. However, assessments must be done prior to treatments and the interval between cycles may not be less than 21 days. In later cycles, longer delays may be allowed in consultation with Lilly medical representative.

JGDN Study Schedule, Follow-up Assessments (All Parts)

Day	Follow-up	Comments

	Short-Term[a]	Long-Term[b]	
	30 days (±7) after discontinuation date	~~Patients who discontinued for reasons other than progressive disease~~	
Efficacy Assessments			
Imaging Studies (CT/MRI)	X (if applicable)	X	For patients who have discontinued study treatment due to toxicity or reasons other than progressive disease, imaging studies and tumor assessments are to be obtained every 6 weeks (±7 days) until progression or initiation of other anti-cancer therapy. RECIST v1.1 should be used for all tumors with the exception of CNS tumors; RANO or Macdonald criteria should be used for CNS tumors.
RECIST v1.1, RANO, or Macdonald Tumor Assessments	X (if applicable)	X	
Subsequent Anti-Cancer Treatments, and Associated Disease Progression Date		X	For all patients ~~who have discontinued study treatment due to toxicity or reasons other than progressive disease~~, details on subsequent anticancer treatment (start/stop dates and treatments administered) and first post-study treatment disease progression date should be recorded.

Attachment 4. Protocol JGDN Pharmacokinetic and Immunogenicity Sampling Schedule

Pharmacokinetic and Immunogenicity Sampling (Part A and Part B)

Sample Number	Cycle	Day	Sampling Time	Olaratumab PK[a]	Combination agents PK[b]	Immunogenicity[c]
1	1	1	Prior to olaratumab infusion	X		X
2		8	Within 5 min post olaratumab infusion	X		
3	2	1	Within 15 min prior to olaratumab infusion	X		X
4		1	Within 5 min post chemotherapy infusion	X	X	
5		8	Within 5 min post olaratumab infusion	X		
6	3 and then every other cycle	1	Within 15 min prior to olaratumab infusion	X		X
7	30-day follow-up (Visit 801)		Any time	X		X

Abbreviation: PK = pharmacokinetics.
a A 2.5-mL (~1 mL if patient has <19kg) blood sample will be collected (to generate serum for bioanalysis).
b A 2-mL (~1 mL if patient has <19kg) blood sample will be collected (to generate plasma for bioanalysis).
c A 3.5-mL blood sample will be collected (to generate serum for anti-olaratumab antibody analysis).

Pharmacokinetic and Immunogenicity Sampling (Part C)

Sample Number	Cycle	Day	Sampling Time	Olaratumab PK[a]	Combination agents PK[b]	Immunogenicity[c]
1	1	1	Prior to olaratumab infusion	X		X
2		1	Within 5 min post chemotherapy infusion	X	X	
3		8	Within 5 min post olaratumab infusion	X		
4	2	1	Within 15 min prior to olaratumab infusion	X		X
5		8	Within 5 min post olaratumab infusion	X		
6	3 and then every other cycle	1	Within 15 min prior to olaratumab infusion	X		X
7	30-day follow-up (Visit 801)		Any time	X		X

Abbreviation: PK = pharmacokinetics.
a A 2.5-mL (~1 mL if patient has <19kg) blood sample will be collected (to generate serum for bioanalysis).
b A 2-mL (~1 mL if patient has <19kg) blood sample will be collected (to generate plasma for bioanalysis).
c A 3.5-mL blood sample will be collected (to generate serum for anti-olaratumab antibody analysis).