Protocol I5B-MC-JGDR(a)

A Phase 1b Study of Olaratumab, Doxorubicin and Ifosfamide in the Treatment of Patients With Advanced or Metastatic Soft Tissue Sarcoma

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Olaratumab (LY3012207)

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Protocol Electronically Signed and Approved by Lilly: 14 March 2017.
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1. Synopsis

Protocol Title:

A Phase 1b Study of Olaratumab, Doxorubicin and Ifosfamide in the Treatment of Patients with Advanced or Metastatic Soft Tissue Sarcoma

Rationale:

Study I5B-MC-JGDG (Study JGDG) was a Phase 1b/randomized Phase 2 study evaluating the efficacy of doxorubicin with or without olaratumab in the treatment of advanced soft tissue sarcoma (STS). The study met its primary endpoint for progression-free survival (PFS) (hazard ratio [HR] = 0.67; p = 0.06 as compared to a prespecified alpha level of 0.2) with an improvement in median PFS and overall survival (OS) of 2.5 months and 11.8 months, respectively, for olaratumab plus doxorubicin over doxorubicin alone, with a manageable safety profile. The OS HR of 0.46 was highly statistically significant (p = 0.0003; Tap et al. 2016). Based on these results, olaratumab has received conditional approval in the United States and European Union in combination with doxorubicin for the treatment of adult patients with STS.

While doxorubicin alone or in combination with other chemotherapeutic agents has been the mainstay of treatment for decades (Linch et al. 2014), in more recent years the combination of doxorubicin, ifosfamide and mesna has demonstrated increased tumor response and PFS compared to doxorubicin alone. However, this regimen is associated with a higher rate of Grade 3 and 4 toxicities and no improvement in OS (Judson et al. 2014), limiting the use of this regimen to distinct clinical settings, such as when shrinkage of the tumor is important and the risk of greater toxicity is felt to represent an acceptable benefit-risk. This regimen has also been evaluated in the neoadjuvant and adjuvant settings for patients with STS (Gortzak et al. 2001; Grobmyer et al. 2004; Pisters et al. 2016).

The positive efficacy results seen with olaratumab in combination with doxorubicin in Study JGDG provide strong rationale for determining whether olaratumab can also be safely added to the doxorubicin, ifosfamide and mesna regimen. It is plausible that the addition of olaratumab to doxorubicin, ifosfamide and mesna may further increase efficacy endpoints such as tumor response rate, PFS and OS, without a clinically significant increase in toxicity. Study I5B-MC-JGDR (Study JGDR) will characterize the safety and tolerability of olaratumab in combination with doxorubicin, ifosfamide and mesna in patients with advanced STS, and if acceptable, determine the dosing regimen of olaratumab in combination with doxorubicin and ifosfamide appropriate for future studies of this combination.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To characterize the safety profile of olaratumab when given in combination with doxorubicin, ifosfamide and mesna and to determine the dosing regimen appropriate for a future Phase 2 study	• DLTs, TEAEs, SAEs and clinical laboratory abnormalities per NCI-CTCAE Version 4.0
Secondary	
• To evaluate the **PK** of olaratumab when combined with doxorubicin, ifosfamide and mesna • To evaluate the **immunogenicity** of olaratumab when combined with doxorubicin, ifosfamide and mesna • To document any **antitumor activity** of olaratumab when combined with doxorubicin, ifosfamide and mesna	• **PK:** C_{max} and AUC from time 0 to the last time point with a measurable concentration, and AUC from time 0 to infinity of olaratumab. Other noncompartmental parameters, such as half-life, clearance and volume of distribution may be reported. Plasma doxorubicin and ifosfamide concentrations will be summarized by descriptive statistics • **Immunogenicity:** Anti-olaratumab antibody levels at baseline, during the study, at the 30-day follow-up visit and in the event of olaratumab IRRs • **Antitumor activity:** Radiographic assessments according to RECIST Version 1.1 criteria every 6 weeks (-7 days) until radiographic documentation of PD. Efficacy endpoints will include objective response rate, PFS, duration of response, disease control rate and OS
Exploratory	
• To explore biomarkers related to, but not limited to tumor microenviroment, immune cells/immune functioning, mechanism of action of study drugs, PDGF, cancer-related pathways and disease state, and their association with demographics, disease state and clinical outcomes	• Biomarker assay results with other trial data

Abbreviations: AUC = area under the concentration curve; C_{max} = maximum observed concentration; DLT = dose-limiting toxicity; IRR = infusion-related reaction; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; OS = overall survival; PD = progressive disease; PDGF = platelet-derived growth factor; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; STS = soft tissue sarcoma; TEAE = treatment-emergent adverse event.

Overall Design:

Study JGDR is a Phase 1b, multicenter, nonrandomized, open-label study of olaratumab combined with doxorubicin, ifosfamide and mesna in the treatment of patients with advanced or metastatic STS.

Dose-Finding Phase:
Olaratumab 15 mg/kg and Loading Dose Cycle Cohorts – Approximately 15 patients will be initially enrolled and treated with a 15-mg/kg dose of olaratumab (on Days 1 and 8 of a 21-day cycle) in combination with doxorubicin, ifosfamide and mesna and assessed for safety after 1 cycle of therapy. If safety of the 15-mg/kg dose of olaratumab is established, 15 additional patients will be enrolled and receive a 20-mg/kg loading dose cycle of olaratumab on Days 1 and 8 of a 21-day cycle in Cycle 1 only, followed by 15 mg/kg on Days 1 and 8 of subsequent cycles in combination with doxorubicin, ifosfamide and mesna.

Should unacceptable toxicity be observed at the olaratumab 15-mg/kg dose, the study will include an option to explore the same regimen using a reduced ifosfamide dose. Provided safety is established at this lower dose of ifosfamide, a loading dose cycle of olaratumab as previously described will also be explored using the reduced ifosfamide dose.

Dose Confirmation Phase:
If a safe and tolerable dosing regimen of olaratumab is identified, approximately15 additional patients will be enrolled in a Dose Confirmation Phase to confirm the safety of this treatment regimen for use in any future studies of this combination.

Patients in both study phases will continue treatment for a maximum of 6 cycles, or until there is documented disease progression, unacceptable toxicity, death, or other discontinuation criteria are met. Patients who discontinue doxorubicin, ifosfamide and mesna treatment without evidence of disease progression will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met. Patients who undergo surgical tumor resection following study treatment are not eligible to receive olaratumab as monotherapy.

Number of Patients: approximately 45-60 total enrolled

Dose-Finding Phase:

Entered: approximately 33-48

Enrolled: approximately 30-45

Dose Confirmation Phase:

Entered: approximately 17

Enrolled: approximately 15

Treatment Arms and Duration:

Phase and Dose Cohort		Drug Name and Dose	Day of 21-day (±3 days) Cycle	Total Dose
Dose-Finding Phase	Olara 15 mg/kg	Olara 15 mg/kg[a]	D1 and D8	
		Dox 25 mg/m^2 per day	D1, D2, D3	75 mg/m^2
		Ifos 2.5 g/m^2 per day[b]	D1, D2, D3, D4[a]	10 g/m^2[a]
		Mesna dose ≥60% of ifos dose[b]	D1, D2, D3, D4	
	Loading Dose Cycle	Olara 20 mg/kg Cycle 1 Olara 15 mg/kg Cycles 2 to 6[a]	D1 and D8 D1 and D8	
		Dox 25 mg/m^2 per day	D1, D2, D3	75 mg/m^2
		Ifos 2.5 g/m^2 per day[b]	D1, D2, D3, D4	10 g/m^2
		Mesna dose ≥60% of ifos dose[b]	D1, D2, D3, D4	
Dose Confirmation Phase	Olara recommended dose	Olara dose determined from Dose-Finding Phase[a]	D1 and D8	
		Dox 25 mg/m^2 per day	D1, D2, D3	75 mg/m^2
		Ifos 2.5 g/m^2 per day[b]	D1, D2, D3, D4	10 g/m^2
		Mesna dose ≥60% of ifos dose[b]	D1, D2, D3, D4	

Abbreviations: D = day; DLT = dose-limiting toxicity; dox = doxorubicin; g = grams; ifos = ifosfamide; IV = intravenous; kg = kilogram; m^2 = square meters; mg = milligrams; olara = olaratumab.

[a] All patients will receive study therapy (olaratumab + doxorubicin/ifosfamide/mesna) for a maximum of 6 cycles, or until a discontinuation criterion is met. Patients who discontinue doxorubicin, ifosfamide and mesna treatment without evidence of disease progression will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met.

[b] If DLT rules are exceeded in the olaratumab 15-mg/kg cohort, a reduced dose of ifosfamide (7.5 g/m^2 total dose) will be explored. This will be accomplished by omitting the Day 4 dose (that is, ifosfamide will be administered at a dose of 2.5 g/m^2 on D1, D2 and D3). The Day 4 dose of mesna will be correspondingly omitted. A Loading Dose Cycle of olaratumab (20 mg/kg on Days 1 and 8 of C1, then 15 mg/kg on Days 1 and 8 of subsequent cycles) may also be explored in combination with the reduced dose of ifosfamide.

2. Schedule of Activities

Table JGDR.1. Pretreatment Schedule of Activities

Day Relative to C1D1	≤28	≤14	≤7	Instructions
Procedure				
Informed consent	X			ICF must be signed before any protocol-specific procedures are performed. Assessments performed prior to the date of consent may be used as study-required assessments, provided they are appropriately documented.
Inclusion/exclusion criteria			X	
Physical examination			X	Including height, weight and vital signs (temperature, blood pressure, pulse rate, respiration rate)
ECOG performance status			X	
Medical history		X		Including assessment of preexisting conditions and historical illnesses.
Prior and current medication	X			
Prior therapies for treatment of underlying disease		X		
AE collection	X			After consent, collect AEs continuously throughout pretreatment period. CTCAE Version 4.0
Radiologic imaging and measurement of palpable or visible lesions	X			RECIST 1.1 Scans performed prior to the date of consent may be used, provided they are within 28 days of enrollment. Imaging requirements include CT scan or MRI of the chest, abdomen and pelvis and other areas, as clinically indicated. It is recommended that CT imaging of the abdomen/pelvis be performed with IV contrast, whenever possible. If this is not feasible/advisable secondary to hypersensitivity or other conditions, then gadolinium-enhanced MRI is preferred. For patients with known serious allergic reactions to CT contrast material, a CT of the chest without contrast and contrast-enhanced MRI of the abdomen/pelvis are encouraged.
ECG	X			
Echocardiogram and/or MUGA scan	X			
Hematology		X		See Appendix 3. To be performed locally for patient management and centrally for analysis purposes.
Coagulation		X		See Appendix 3. To be performed locally.
Clinical chemistry		X		See Appendix 3. To be performed locally for patient management and centrally for analysis purposes.
Urinalysis		X		See Appendix 3. To be performed locally.

Serum pregnancy test			X	Applies only to women of childbearing potential. See Appendix 3. To be performed locally.
Tumor tissue		X		See Section 9.7.2.
Sample collection				See Appendix 4.
Pharmacodynamics				
Pharmacokinetics				
Immunogenicity				
Pharmacogenetics				
Other biomarkers				

Abbreviations: AE = adverse event; C1D1 = Cycle 1 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); ICF = informed consent form; IV = intravenous; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

Table JGDR.2. On-Study Treatment Schedule of Activities

Day within Cycle / Procedure	Cycles 1-6 (olaratumab + doxorubicin + ifosfamide; (Cycle = 21 days)						Cycles 7-N Olaratumab Monotherapy[a] (Cycle = 21 days)		Instructions
	1	**2**	**3**	**4**	**8**	**15**	1	8	
Physical examination	X				X		X		• Perform prior to infusion of study drug(s). • Includes weight and BSA.
Vital signs	X	X	X	X	X	X	X		Vital signs include temperature, blood pressure, pulse rate, respiration rate.
Concomitant medication	X						X		Concomitant medications will be recorded continuously throughout the treatment period.
AE collection	X						X		Collect continuously throughout the treatment period; CTCAE Version 4.0.
ECOG performance status	X						X		
Radiologic imaging and measurement of palpable or visible lesions	X						X		• Perform according to RECIST 1.1, by the same method used at baseline, q 6 weeks (-7 days) from the start of treatment until radiographic disease progression, death, or study completion, whichever occurs first. • Perform as scheduled, even if study treatment is delayed or omitted.
ECG	X						X		• Perform local 12-lead ECG on Day 1 of Cycle 1 through Cycle 6. • Perform local 12-lead ECG on Day 1 of Cycle 7 and approximately 6 months (±14 days) and 12 months (±14 days) after discontinuation of doxorubicin and ifosfamide treatment
Echocardiogram and/or MUGA scan	X C4 and C6						X		• Perform at the end of C4 and C6; perform additional evaluations in the setting of cardiac symptoms and/or at the discretion of the investigator. • For patients receiving olaratumab as monotherapy following discontinuation of combination therapy, perform approximately 6 months (±14 days) and 12 months (±14 days) after discontinuation of doxorubicin and ifosfamide treatment.
Hematology	X				X	X	X	X	≤3 days prior to administration of study treatment on D1 and ≤1 day prior to administration of study treatment on D8, unless more frequent assessment is clinically indicated. Day 15 labs may be drawn within ±1 day of Day 15. See Appendix 3. To be performed locally for patient management and centrally for analysis purposes.

Day within Cycle Procedure	Cycles 1-6 (olaratumab + doxorubicin + ifosfamide; (Cycle = 21 days)						Cycles 7-N Olaratumab Monotherapy[a] (Cycle = 21 days)		Instructions
	1	2	3	4	8	15	1	8	
Coagulation	X						X		≤3 days prior to administration of study treatment on D1, unless more frequent assessment is clinically indicated. For patients receiving olaratumab as monotherapy following combination therapy discontinuation, perform on D1 of every other cycle. See Appendix 3. To be performed locally.
Clinical chemistry	X				X	X	X		≤3 days prior to administration of study treatment on D1 and ≤1 day prior to administration of study treatment on D8, unless more frequent assessment is clinically indicated. Day 15 labs may be drawn within ±1 day of Day 15. See Appendix 3. To be performed locally for patient management and centrally for analysis purposes.
Urinalysis	X	X	X	X					Monitor patients for evidence of micro- and/or macroscopic hematuria and treat according to institutional standards.
Pregnancy test	X						X		• Applies only to women of childbearing potential • Where required by local law or regulation, perform once every 21 days (-7 days) prior to administration of study treatment. • To be performed locally
Administer olaratumab	X				X		X	X	Administer IV over 60 (±5) min. Administer until a maximum of 6 cycles is complete, or until PD, unacceptable toxicity, death, or other withdrawal criteria are met. Patients who discontinue doxorubicin, ifosfamide and mesna treatment without evidence of disease progression will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met. Patients who undergo surgical tumor resection following study treatment are not eligible to receive olaratumab as monotherapy. See section 7.1.1 for olaratumab premedication requirements. See section 7.8.1 for olaratumab IRR monitoring period requirements.
Administer doxorubicin	X	X	X						Administer IV over less than 60 (±5) min or as a continuous IV infusion (according to institutional guidelines) after completion of olaratumab infusion and any required observation period. Administer until a maximum of 6 cycles is complete, or until PD, unacceptable toxicity, death, or other withdrawal criteria are met. See Section 7.1.2 for details of dexrazoxane administration.

Day within Cycle Procedure	Cycles 1-6 (olaratumab + doxorubicin + ifosfamide; (Cycle = 21 days)						Cycles 7-N Olaratumab Monotherapy[a] (Cycle = 21 days)		Instructions
	1	2	3	4	8	15	1	8	
Administer ifosfamide	X	X	X	X *					Administer IV over 3 hours (±15 min). Administer until a maximum of 6 cycles is complete, or until PD, unacceptable toxicity, death, or other withdrawal criteria are met. *Patients treated in cohorts with ifosfamide dose reduction will have the Day 4 dose omitted (that is, ifosfamide will be administered at a dose of 2.5 g/m^2 on D1, D2 and D3).
Administer mesna	X	X	X	X					See Section 7.1.3 for details of mesna administration.
G-CSF	X								The use of G-CSFs is required. Administer according to ASCO and NCCN guidelines. In general, G-CSF products like filgrastim or pegfilgrastim should be administered approximately 24 hours after the completion of cytotoxic chemotherapy (for example, on Day 5 for patients in full-dose ifosfamide cohorts or Day 4 for patients in reduced-dose ifosfamide cohorts).
Sample collection									For all sample collection, see Appendix 4.
Pharmacodynamics									
Pharmacokinetics									
Immunogenicity									
Pharmacogenetics									
Other biomarkers									

Abbreviations: AE = adverse event; ASCO = American Society of Clinical Oncology; BSA = body surface area; C = cycle; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); G-CSF = granulocyte-colony stimulating factor; IRR = infusion-related reaction; IV = intravenously; LVEF = left ventricular ejection fraction; min = minutes; MUGA = multiple-gated acquisition; NCCN = National Comprehensive Cancer Network; PD = progressive disease; q = every; RBC = red blood cell; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

[a] Olaratumab monotherapy schedule applies to patients who have completed 6 cycles of olaratumab plus doxorubicin and ifosfamide and are continuing treatment with olaratumab monotherapy or have discontinued doxorubicin plus ifosfamide and are continuing with olaratumab monotherapy. Note: if a patient discontinues doxorubicin plus ifosfamide treatment prior to completing 6 cycles and is continuing treatment with olaratumab monotherapy, perform procedures according to the olaratumab monotherapy schedule beginning the next cycle after the patient discontinues doxorubicin/ifosfamide.

Table JGDR.3. Post-Treatment Follow-Up Schedule of Activities

Procedure	Short-Term Follow-Up[a]	Long-Term Follow-Up	Instructions
Visit	**801**	**802–8XX**	
Physical examination	X		Including weight and vital signs (temperature, blood pressure, pulse rate, respiration rate)
Concomitant medication	X		
AE collection	X		CTCAE Version 4.0.
ECOG performance status	X		
Radiologic imaging and measurement of palpable or visible lesions	X	X*	*__**For patients whose disease has not progressed:**__ Perform q 6 weeks × 2, then q 3 mo until: • the patient has objective disease progression according to RECIST 1.1 or • the study's primary/final analysis Perform using the same method used at baseline and throughout the study. __**For patients who have had objective disease progression:**__ Radiologic tests and measurement of palpable or visible lesions are no longer required; these patients should be followed up for OS and collection of post-study treatment anticancer therapy information collection as indicated below.
Collection of survival information		X	Perform q 2 mo (±7 days) for the first 2 years after discontinuation from study treatment and q 6 mo (±14 days) thereafter until death or study completion. If an in-person visit is not possible, confirm survival by contacting the patient directly via phone.
Collection of post-study treatment anticancer therapy information	X	X	Perform q 2 mo (±7 days) for the first 2 years after discontinuation from study treatment and q 6 mo (±14 days) thereafter until death or study completion.
ECG	X	X	• All patients should have a 12-lead ECG performed at short-term follow-up. • Patients should also have a 12-lead ECG performed approximately 6 months (±7 days) and 12 months (±7 days) after the end of treatment with doxorubicin and ifosfamide.

Procedure	Short-Term Follow-Up[a]	Long-Term Follow-Up	Instructions
Visit	**801**	**802–8XX**	
Echocardiogram and/or MUGA scan		X	Perform at 6 months (±7 days) and 12 months (±7 days) after the end of treatment with doxorubicin and ifosfamide. Echocardiograms/MUGA scans may be discontinued if the patient begins another anticancer therapy. Perform additional evaluations in the setting of cardiac symptoms and/or at the discretion of the investigator.
Hematology	X		See Appendix 3. To be performed locally for patient management and centrally for analysis purposes.
Coagulation	X		See Appendix 3. To be performed locally.
Clinical chemistry	X		See Appendix 3. To be performed locally for patient management and centrally for analysis purposes.
Urinalysis	X		See Appendix 3. To be performed locally.
Sample collection			For all sample collection, see Appendix 4.
Pharmacodynamics			
Pharmacokinetics			
Immunogenicity			
Pharmacogenetics			
Other biomarkers			

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); mo = month; MUGA = multiple-gated acquisition; OS = overall survival; q = every; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

[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). No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

Table JGDR.4. Continued Access Schedule of Activities

Visit	Study Treatment 501-5XX	Follow-Up[a] 901	
Procedure[b]			**Instructions**
AE collection	X	X	CTCAE Version 4.0 See Section 9.2.
Pharmacokinetics and immunogenicity		X	If a patient experiences an IRR, collect blood samples for pharmacokinetics and immunogenicity analysis 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.
Administer olaratumab	X		21-day cycles Administer until PD, unacceptable toxicity, death, or other withdrawal criteria are met.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reaction.

[a] Continued access follow-up begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

[b] Efficacy assessments will be done at the investigator's discretion based on the standard of care.

3. Introduction

3.1. Background

3.1.1. Soft Tissue Sarcoma

Soft tissue sarcoma (STS) is a heterogeneous group of malignant tumors that arise from tissue of mesenchymal origin. Soft tissue sarcoma arises primarily from the embryonic mesoderm, with some neuroectodermal contribution and differentiation to non-epithelial extraskeletal tissue, including striated skeletal and smooth muscle, adipose and fibrous tissue (Sharma et al. 2013; D'Angelo et al. 2014; Linch et al. 2014). There are approximately 50 different types of STS that can be found in almost any anatomic location (American Cancer Society 2014; Linch et al. 2014). STS is rare, comprising approximately 1% of adult cancers. The annual incidence of STS in the United Kingdom and United States (US) is 3300 and 10,000, respectively (Jemal et al. 2009; Soft tissue sarcoma statistics page [WWW] 2010). A multidisciplinary setting with teams specializing in the treatment of STS is the best treatment approach for these tumors. Management of localized disease is usually with curative intent, using surgical resection with or without radiotherapy and chemotherapy. In spite of initial aggressive management, there is frequent recurrence of local inoperable or metastatic disease, and at this point systemic therapy plays a prominent role in the multidisciplinary management of STS (Linch et al. 2014).

The mainstay therapy for treating advanced-stage STS has been chemotherapy, which in the first-line setting has provided overall response rates of approximately 25% (Linch et al. 2014). Even with the use of chemotherapy, advanced-stage STS is usually fatal and there remains a need for novel and effective therapies. Doxorubicin either alone or in combination has served as the initial treatment for metastatic sarcoma for many years. Various other drug combinations have also been explored (Linch et al. 2014). In more recent years, the addition of ifosfamide to doxorubicin has demonstrated increased tumor response and progression-free survival (PFS) compared to doxorubicin alone, with a similar overall survival (OS) and a higher incidence of Grade 3 and 4 toxicities (Judson et al. 2014). This regimen is used in the clinical setting where shrinking of the tumor is important and where the patient can tolerate the risk of greater toxicities compared to doxorubicin alone; this regimen has also been evaluated in the neoadjuvant and adjuvant settings for patients with STS (Gortzak et al. 2001; Grobmyer et al. 2004; Pisters et al. 2016).

3.1.2. Olaratumab

Olaratumab is a recombinant human immunoglobulin G subclass 1-type monoclonal antibody that binds to platelet-derived growth factor receptor alpha (PDGFRα). This antibody possesses high-affinity binding for PDGFRα and blocks platelet-derived growth factor (PDGF)-AA, -BB and -CC from binding to the receptor. In addition to blocking ligand-induced cell mitogenesis and receptor autophosphorylation, olaratumab inhibits ligand-induced phosphorylation of the downstream signaling molecules Akt and mitogen-activated protein kinase (Loizos et al. 2005; Study Report IMC-3G3-01).

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

3.2. Study Rationale

Study I5B-MC-JGDG (Study JGDG) was a Phase 1b/randomized Phase 2 study evaluating the efficacy of doxorubicin with or without olaratumab in the treatment of advanced STS. The study met its primary endpoint for PFS (hazard ratio [HR] = 0.67; p = 0.06 as compared to a prespecified alpha level of 0.2) with an improvement in median PFS and OS of 2.5 months and 11.8 months, respectively, for olaratumab plus doxorubicin over doxorubicin alone, with a manageable safety profile. The OS HR of 0.46 was highly statistically significant (p = 0.0003; Tap et al. 2016). Based on these results, olaratumab has received conditional approval in the US and European Union in combination with doxorubicin for the treatment of adult patients with STS.

While doxorubicin alone or in combination with other chemotherapeutic agents has been the mainstay of treatment for decades (Linch et al. 2014), in more recent years the combination of doxorubicin, ifosfamide and mesna has demonstrated increased tumor response and PFS compared to doxorubicin alone. However, this regimen is associated with a higher rate of Grade 3 and 4 toxicities and no improvement in OS (Judson et al. 2014), limiting the use of this regimen to distinct clinical settings, such as when shrinkage of the tumor is important and the risk of greater toxicity is felt to represent an acceptable benefit-risk. This regimen has been evaluated in the neoadjuvant and adjuvant settings for patients with STS (Gortzak et al. 2001; Grobmyer et al. 2004; Pisters et al. 2016).

The positive efficacy results seen with olaratumab in combination with doxorubicin in Study JGDG provide strong rationale for determining whether olaratumab can also be safely added to the doxorubicin, ifosfamide and mesna regimen. It is plausible that the addition of olaratumab to doxorubicin, ifosfamide and mesna may further increase efficacy endpoints such as tumor response rate, PFS and OS, without a clinically significant increase in toxicity. Study I5B-MC-JGDR (Study JGDR) will characterize the safety and tolerability of olaratumab in combination with doxorubicin, ifosfamide and mesna in patients with advanced STS, and if acceptable, determine the dosing regimen of olaratumab in combination with doxorubicin and ifosfamide appropriate for future studies of this combination.

3.2.1. Rationale for Amendment (a)

The original Study JGDR protocol, version dated 14 March 2017, was amended to remove visits and/or procedures not intended for patients receiving olaratumab monotherapy only after completing 6 cycles of olaratumab plus doxorubicin and ifosfamide (or discontinued doxorubicin and ifosfamide before). In particular, visits and procedures specifically used to administer and monitor for toxicity from the doxorubicin and ifosfamide combination have been removed for patients receiving olaratumab monotherapy.

The timing of ECHO/MUGA scans after discontinuation of doxorubicin plus ifosfamide treatment was clarified and ECG evaluations were added at the same frequency to ensure complete evaluation of any potential cardiotoxic effects following treatment with doxorubicin plus ifosfamide.

The wording pertaining to required contraceptive use following study treatment has been clarified to align with label requirement for doxorubicin.

In addition, some minor editorial changes have been made throughout the protocol to improve clarity and practicality of the protocol and secure alignment with the intended study design.

3.3. Benefit-Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of olaratumab are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

Table JGDR.5 shows the objectives and endpoints of the study.

Table JGDR.5. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the safety profile of olaratumab when given in combination with doxorubicin, ifosfamide and mesna and to determine the dosing regimen appropriate for a future Phase 2 study	• DLTs, TEAEs, SAEs and clinical laboratory abnormalities per NCI-CTCAE Version 4.0
Secondary	
• To evaluate the **PK** of olaratumab when combined with doxorubicin, ifosfamide and mesna • To evaluate the **immunogenicity** of olaratumab when combined with doxorubicin, ifosfamide and mesna • To document any **antitumor activity** of olaratumab when combined with doxorubicin, ifosfamide and mesna	• **PK:** C_{max} and AUC from time 0 to the last time point with a measurable concentration, and AUC from time 0 to infinity of olaratumab. Other noncompartmental parameters, such as half-life, clearance and volume of distribution may be reported. Plasma doxorubicin and ifosfamide concentrations will be summarized by descriptive statistics • **Immunogenicity:** Anti-olaratumab antibody levels at baseline, during the study, at the 30-day follow-up visit and in the event of olaratumab IRRs • **Antitumor activity:** Radiographic assessments according to RECIST Version 1.1 criteria every 6 weeks (-7 days) until radiographic documentation of PD. Efficacy endpoints will include objective response rate, PFS, duration of response, disease control rate and OS
Exploratory	
• To explore biomarkers related to, but not limited to tumor microenvironment, immune cells/immune functioning, mechanism of action of study drugs, PDGF, cancer-related pathways and disease state, and their association with demographics, disease state and clinical outcomes	• Biomarker assay results with other trial data

Abbreviations: AUC = area under the concentration curve; C_{max} = maximum observed concentration; DLT = dose-limiting toxicity; IRR = infusion-related reaction; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

5. Study Design

5.1. Overall Design

Study JGDR is a multicenter, nonrandomized, open-label, Phase 1b study of intravenous (IV) olaratumab in combination with doxorubicin, ifosfamide and mesna in patients with advanced or metastatic STS.

Dose-Finding Phase

Bone marrow suppression occurs relatively frequently with the doxorubicin, ifosfamide and mesna regimen and can lead to complications such as fever and neutropenia, infection, or bleeding, which are generally considered DLT-level toxicities and thus can confound determination of DLT in the setting of combination with olaratumab. The EORTC Phase 3 study (Judson et al. 2014) demonstrated a 46% rate of febrile neutropenia in patients with STS who were treated with doxorubicin, ifosfamide and mesna. Because of this relatively high rate of DLT-level toxicity with the backbone doxorubicin, ifosfamide and mesna regimen and the generally acceptable toxicity profile of the 15-mg/kg dose of olaratumab (Days 1 and 8 every 21 days) in combination with other chemotherapeutic agents including doxorubicin, approximately 15 patients will be enrolled at the first dose level of olaratumab (and evaluated after 6, 9 and 15 patients have received 1 cycle of therapy) to allow sufficient patient numbers to judge initial tolerability of olaratumab in combination with doxorubicin, ifosfamide and mesna. See Table JGDR.7 for a detailed explanation of the dose-limiting toxicity (DLT) thresholds that will be used to govern enrollment in the Dose-Finding Phase and Section 10.1 for the statistical justification of the study design.

Olaratumab 15-mg/kg Dose Level: The first phase of the study (Dose-Finding Phase) will evaluate the safety and tolerability of adding olaratumab to the regimen of doxorubicin (75 mg/m^2 plus given as IV infusions of 25 mg/m^2 on Days 1 to 3), ifosfamide (10 g/m^2 given as IV infusions of 2.5 g/m^2 on Days 1 to 4) and mesna according to a 21-day cycle. Fifteen patients will be initially enrolled and treated with a 15-mg/kg dose of olaratumab (on Days 1 and 8 of a 21-day cycle) in combination with doxorubicin, ifosfamide and mesna and assessed for safety after 1 cycle of therapy. The full cohort of 15 patients will be enrolled if 5 or fewer patients with DLTs are observed in the first 6 and 9 patients, respectively.

Olaratumab 20-mg/kg Loading Dose Cycle Dose Level: Following an evaluation of safety in the full cohort of 15 patients (and provided 8 or fewer of these patients have experienced DLTs), the study will progress to evaluate a loading dose cycle of olaratumab (20 mg/kg IV on Days 1 and 8 of Cycle 1 only, then 15 mg/kg on Days 1 and 8 of subsequent cycles) in combination with doxorubicin, ifosfamide and mesna in a new cohort of 15 patients. Section 5.5.1 details the rationale for the loading dose. The full cohort of 15 patients will be enrolled if 5 or fewer patients with DLTs are observed in the first 6 and 9 patients, respectively.

Olaratumab 15-mg/kg Dose Level: Ifosfamide Dose Reduction Option

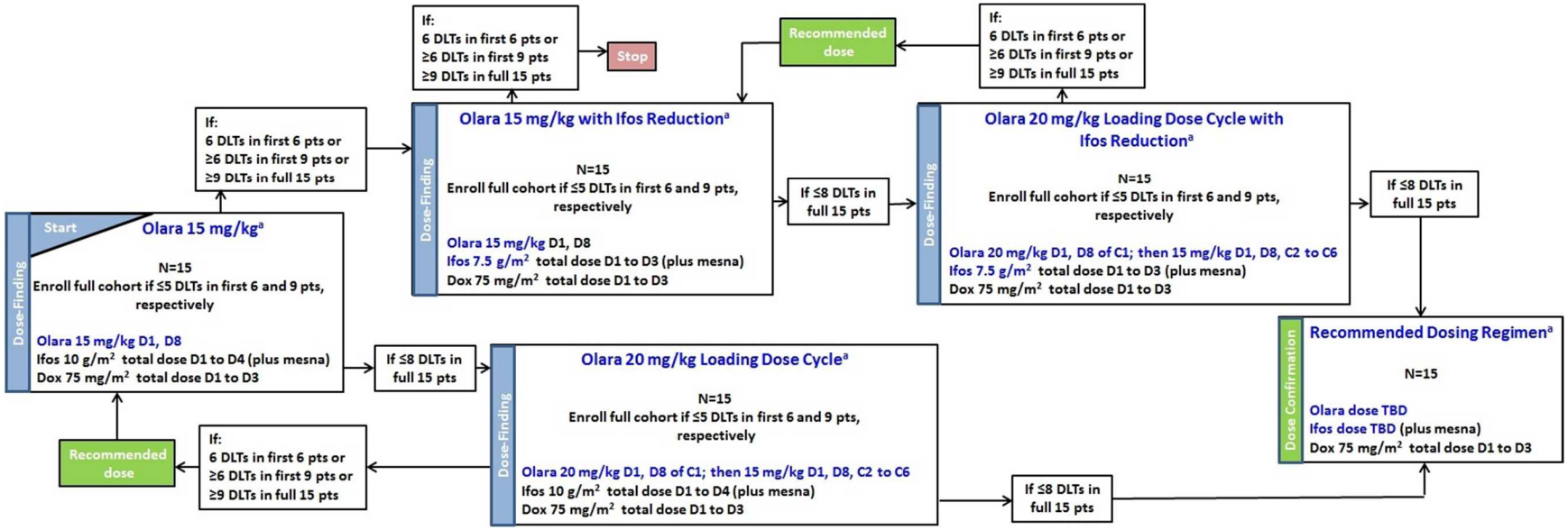
If during enrollment into the olaratumab 15-mg/kg dose level, DLTs are observed in 6 of the first 6 patients, in ≥6 of the first 9 patients, or in ≥9 of the full cohort of 15 patients, the study will

proceed to explore a reduced ifosfamide dose (7.5 g/m^2 total dose) in combination with olaratumab 15 mg/kg and the same doxorubicin dose in a new cohort of 15 patients. If DLTs are observed in 6 of the first 6 patients, in ≥6 of the first 9 patients, or in ≥9 of the full cohort of 15 patients at this reduced ifosfamide dose, the study will halt and no further patients will be enrolled. If 8 or fewer patients with DLTs are observed in this full cohort of 15 patients, the study will progress to explore the olaratumab Loading Dose Cycle as previously described in combination with the reduced ifosfamide dose (and same doxorubicin dose) as previously described.

Olaratumab 20-mg/kg Loading Dose Cycle Dose Level: Ifosfamide Dose Reduction Option
If during enrollment into the olaratumab 20-mg/kg Loading Dose Cycle dose level, DLTs are observed in 6 of the first 6 patients, in ≥6 of the first 9 patients, or in ≥9 of the full cohort of 15 patients, no further patients will be enrolled at this dose level and olaratumab 15 mg/kg will be declared the recommended dose for combination with reduced-dose ifosfamide/mesna and doxorubicin. If 8 or fewer patients with DLTs are observed in this full cohort, the olaratumab 20-mg/kg loading dose cycle together with a reduced ifosfamide/mesna dose will be declared the recommended doses for combination with doxorubicin.

Dose Confirmation Phase: If a safe and tolerable regimen of olaratumab in combination with doxorubicin, ifosfamide and mesna is established in the Dose-Finding Phase, the second phase of the study (Dose Confirmation Phase) will open to further evaluate the regimen at the recommended doses of olaratumab and ifosfamide/mesna in combination with doxorubicin in an additional 15 patients, with the goal of treating a total of 30 patients with the recommended regimen. Patients will continue combination treatment for up to a maximum of 6 cycles, unless there is documented disease progression, unacceptable toxicity, death, or other discontinuation criteria are met (Section 8). Patients who discontinue doxorubicin, ifosfamide and mesna treatment without evidence of disease progression will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met (Section 8). Patients who undergo surgical tumor resection following study treatment are not eligible to receive olaratumab as monotherapy.

Figure JGDR.1 illustrates the study design.



Abbreviations: D = day; DLT = patients experiencing a dose-limiting toxicity; Dox = doxorubicin; g = grams; Ifos = ifosfamide; kg = kilogram; m^2 = square meters; mg = milligrams; Olara = olaratumab; N = number; TBD = to be determined.

[a] Patients who discontinue combination study therapy without evidence of disease progression will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met.

Figure JGDR.1. Illustration of study design.

5.1.1. Dose-Finding Phase: Olaratumab 15-mg/kg Dose Level

The purpose of this single-arm cohort is to determine whether a 15-mg/kg dose of olaratumab (on Days 1 and 8) may be safely added to the doxorubicin, ifosfamide and mesna regimen in patients with advanced or metastatic STS. No intrapatient dose escalation is permitted in this cohort. Patients who do not complete Cycle 1 treatment for reasons other than a DLT will be replaced. Safety data for this patient cohort will be reviewed prior to dose escalation. The total number of patients with DLTs and the type of DLTs will be considered prior to making a decision to escalate the olaratumab dose.

5.1.2. Dose-Finding Phase: Olaratumab 20 mg/kg Loading Dose Cycle Level

The purpose of this single arm cohort is to determine whether a 20 mg/kg loading dose cycle of olaratumab (given on Days 1 and 8 of Cycle 1 only, followed by 15 mg/kg on Days 1 and 8 of subsequent cycles) may be safely added to the doxorubicin, ifosfamide and mesna regimen in patients with advanced or metastatic STS. Patients who do not complete Cycle 1 treatment for reasons other than a DLT will be replaced. Safety data for this will be reviewed prior to dose determination for the Dose Confirmation Phase. The total number of patients with DLTs and the type of DLTs will be considered prior to making a dose determination.

5.1.3. Dose-Finding Phase: Ifosfamide Dose Reduction Options

If DLT rules (see Section 7.2.2.1) are exceeded at the olaratumab 15-mg/kg dose, the study includes the option to explore a reduced ifosfamide dose (7.5 g/m^2 given as daily IV infusions of 2.5 g/m^2 on Days 1 to 3) in combination with olaratumab 15 mg/kg (and doxorubicin). See Section 5.5.2 for the rationale for this reduced dose. If the 15-mg/kg dose of olaratumab is determined to be safe and tolerable in combination with the reduced ifosfamide dose (see Section 7.2.2 for DLT criteria to advance to next phase), a second cohort exploring a 20-mg/kg loading dose cycle of olaratumab in combination with ifosfamide at the reduced dose will be enrolled. These cohorts will be evaluated in the same manner as described in Sections 5.1.1 and 5.1.2.

5.1.4. Dose Confirmation Phase

Provided a safe and tolerable dose of olaratumab in combination with doxorubicin, ifosfamide and mesna (ifosfamide/mesna at full dose or reduced dose) is identified, this dose will be explored in a Dose Confirmation Phase of the study.

5.2. Number of Patients

Study JGDR aims to enroll approximately 45 to 60 patients in total, with the goal of treating a total of approximately 30 patients with the recommended regimen.

5.3. Study Completion Definition

The study will be considered complete 30 days after all patients in the Dose Confirmation Phase complete or discontinue olaratumab and doxorubicin, ifosfamide and mesna combination therapy. See Section 7.9 for details on treatment after the completion of the study.

5.4. Scientific Rationale for Study Design

See Section 3.2.

5.5. Justification for Dose

5.5.1. Olaratumab

In combination with doxorubicin, ifosfamide and mesna, this study will start at an olaratumab dose of 15 mg/kg on Days 1 and 8 of a 21-day cycle. This dosing regimen has been demonstrated to have an acceptable safety profile in combination with doxorubicin (Study JGDG) and was associated with improvement in PFS and OS. If this dose of olaratumab is found to be safe and tolerable with the doxorubicin and ifosfamide combination, then an olaratumab Loading Dose Cycle of 20 mg/kg on Days 1 and 8 of a 21-day cycle in Cycle 1 only, followed by 15 mg/kg on Days 1 and 8 of subsequent cycles will be explored.

In Study JGDG, PK model simulations indicated that olaratumab loading doses of 20 mg/kg administered on Day 1 and Day 8 of Cycle 1 would allow steady-state olaratumab serum levels to be achieved with the first administration and would minimize the number of patients whose serum trough level at the end of the first cycle of treatment (C_{min1}) falls below 61 µg/mL during the first 2 cycles. Additionally, a dose of 20 mg/kg olaratumab administered on Day 1 and Day 8 during the first cycle, followed by 15 mg/kg administered on Day 1 and Day 8 of all subsequent cycles is predicted to yield maximum serum concentrations within the overall range observed in Study JGDG. Therefore, olaratumab-related safety risks related to high serum concentrations or exposure using this loading dose approach are expected to be similar to those in Study JGDG. This dosing strategy is expected to minimize the number of patients exposed to subtherapeutic olaratumab serum levels without an increased risk of toxicity, thereby optimizing the benefit-risk ratio. This loading dose cycle strategy is analogous to that used in Study JGDK and under study in the ongoing Phase 3 Study JGDJ.

5.5.2. Doxorubicin, Ifosfamide and Mesna

The doxorubicin, ifosfamide and mesna regimen is an effective option for patients with sarcoma and has been studied using a diverse range of doses and across subtypes (Worden et al. 2005; Maurel et al. 2009; Judson et al. 2014). The doses of doxorubicin, ifosfamide and mesna chosen for Study JGDR are based on the EORTC study reported by Judson et al, the largest randomized study to date using the doxorubicin, ifosfamide and mesna regimen in patients with STS. In that study, patients received doxorubicin 25 mg/m^2 per day on Days 1 to 3 and ifosfamide 2.5 g/m^2 per day on Days 1 to 4 (plus mesna), followed by pegfilgrastim. Treatment was repeated every 3 weeks until disease progression or unacceptable toxic effects, up to a maximum of 6 cycles.

In the event the 15-mg/kg dose of olaratumab in combination with doxorubicin, ifosfamide and mesna is not tolerated, the study includes an option to explore a reduced dose of ifosfamide (7.5 g/m^2 given as daily IV infusions of 2.5 g/m^2 on Days 1 to 3, a dose of ifosfamide used in clinical practice [Grobmyer et al. 2004]) during the Dose-Finding phase.

6. Study Population

All patients meeting the eligibility requirements will be considered for enrollment regardless of race, religion, or gender. The investigator or the sponsor will not grant exceptions to eligibility criteria. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria:

[1] Have a histological diagnosis of advanced STS (by local pathology review), for which treatment with doxorubicin, ifosfamide and mesna is deemed appropriate by the investigator. Patients with a diagnosis of Grade 1 liposarcoma (atypical lipomatous neoplasms) are eligible if there is histological or radiographic evidence of evolution to more aggressive disease.

[2] Have measurable or nonmeasurable but evaluable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (Eisenhauer et al. 2009). Tumors within a previously irradiated field will be designated as "nontarget" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiotherapy.

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

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

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

- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L. Granulocyte-colony-stimulating factor (G-CSF) cannot be administered within 2 weeks (14 days) prior to enrollment.
- Platelet count $\geq 100 \times 10^9$/L
- Hemoglobin ≥9.0 g/dL. No transfusions are allowed within 2 weeks (14 days) prior to enrollment.
- Serum creatinine ≤1.5 times upper limit of normal (ULN). If creatinine is above the ULN, the patient's creatinine clearance must be ≥65 mL/min (refer to Appendix 6 for the Cockcroft-Gault formula for creatinine clearance).
- Total bilirubin within ULN (except for patients with Gilbert's syndrome, who must have a total bilirubin <3 mg/dL)
- Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤3.0 × ULN; if the liver has tumor involvement, AST and ALT ≤5.0 × ULN are acceptable

- An adequate coagulation function as defined by international normalized ratio (INR) ≤1.5 × ULN or prothrombin time ≤1.5 × ULN, and partial thromboplastin time ≤1.5 × ULN (unless receiving anticoagulant therapy). Patients receiving warfarin are recommended to switch to low molecular weight heparin and should have achieved stable coagulation status prior to the first dose of study treatment.

[6] Have a performance status of 0 to 1 on the Eastern Cooperative Oncology Group scale.

[7] Have received no prior lines of systemic therapy (adjuvant or neo-adjuvant treatment will not be counted as a prior line) and are suitable to receive doxorubicin, ifosfamide and mesna. All previous anticancer treatments must have completed ≥3 weeks (21 days) prior to the first dose of study treatment.

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

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

[10] Have sufficient available material from archived formalin-fixed paraffin-embedded tumor tissue for biomarker-related studies. If such tissue is not available, a newly obtained core or excisional biopsy of a tumor lesion must be performed. Patients for whom it is inadvisable to undergo a new biopsy in the opinion of the investigator (for example, due to technically challenging tumor location) may be enrolled, after prior discussion with the Lilly clinical research physician (CRP). Refer to Section 9.7.2 regarding tissue collection requirements.

[11] Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

[12] If male, must be sterile or agree to use an *effective method of contraception* or a *highly effective method of contraception* during the study and for at least:

- 3 months following the last dose of olaratumab
- 6 months following the last dose of doxorubicin or ifosfamide

Refer to Appendix 1 for definitions of *effective method of contraception* and *highly effective method of contraception*.

[13] If female and of child-bearing potential, must:

a. have a negative serum pregnancy test within 7 days prior to the first dose of study treatment, and

b. agree to use a *highly effective method of contraception* during the study and for at least 3 months following the last dose of olaratumab and 6 months following the last dose of doxorubicin or ifosfamide.

Refer to Appendix 1 for the definitions of *highly effective method of contraception* and *effective method of contraception*.

Females not of child-bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause are permitted on the study.

A post-menopausal woman is a woman meeting either of the following criteria:

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

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

6.2. Exclusion Criteria

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

[15] Are currently enrolled in a clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[16] Have participated within the past 30 days in a clinical trial involving an investigational product. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed.

[17] Have previously completed or withdrawn from any study investigating olaratumab.

[18] Have received prior treatment with olaratumab, doxorubicin, or ifosfamide, or have participated in other trials investigating olaratumab.

[19] Have received prior radiotherapy of the mediastinal/pericardial area or whole pelvis radiation.

[20] Have known urinary outflow obstruction, or inflammation of the urinary bladder (cystitis).

[21] Are diagnosed with gastrointestinal stromal tumor or Kaposi sarcoma.

[22] Have active central nervous system (CNS) or leptomeningeal metastasis (brain metastasis) at the time of enrollment. Patients with a history of CNS metastasis (previously treated with curative intent [for example, stereotactic radiation or surgery]) that has not progressed on follow-up imaging, have been asymptomatic for at least 60 days, and are not receiving systemic corticosteroids and/or anticonvulsants are eligible. Patients with signs or symptoms of neurological compromise should have appropriate radiographic imaging performed before enrollment to rule out brain metastasis.

[23] Have a history of another primary malignancy, with the exception of:

a. curatively treated non-melanomatous skin cancer

b. curatively treated cervical carcinoma in situ

c. non-metastatic prostate cancer, or

d. other primary nonhematologic malignancies treated with curative intent, no known active disease, and no treatment administered during the last 3 years prior to enrollment, that the investigator and Lilly Medical representative agree will not affect interpretation of study results or would be unsuitable for participation in the study.

[24] Have an active fungal, bacterial and/or known viral infection including human immunodeficiency virus or viral (A, B, or C) hepatitis (screening is not required).

[25] Have Grade 3 or 4 peripheral neuropathy per NCI-CTCAE Version 4.0.

[26] Have a serious cardiac condition, such as:

- unstable angina pectoris
- angioplasty, cardiac stenting or myocardial infarction within 6 months of enrollment
- valvulopathy that is severe, moderate, or deemed clinically significant
- arrhythmias that are symptomatic or require treatment

[27] Have a resting heart rate of >100 bpm.

[28] Have a QTcF interval of >450 msec for males and >470 msec for females on screening electrocardiogram (ECG) utilizing Fridericia's correction (refer to formula in Appendix 7).

[29] Have uncontrolled intercurrent illness including, but not limited to, an ongoing/active infection requiring parenteral antibiotics.

[30] Have a psychiatric illness/social situation that would limit compliance with study requirements.

[31] Have electively planned or will require major surgery during the course of the study.

[32] Are females who are pregnant or breastfeeding.

6.3. Screen Failures

The duration of the screening period is 14 days for the majority of procedures (see Section 2); certain noted procedures may be performed within 28 days of enrollment. Individuals who do not meet the criteria for participation in this study within the extended 28-day screening period (screen failure) may be re-screened after discussion with the Lilly CRP. Individuals may be re-screened a maximum of 1 time. The interval between re-screenings should be at least 28 days. If re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

Repeating laboratory tests during the 28-day screening period does not constitute re-screening. Screening laboratory tests may not be repeated more than once in order to meet eligibility during the 28-day screening period. If a repeat screening laboratory value meets eligibility, it is recommended that the test is rechecked to confirm stability.

7. Treatments

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drugs and planned duration of each individual's treatment to the patient and study site personnel
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless Lilly and sites have agreed all unused medications have to be destroyed by the site, as allowed by local law.

7.1. Treatment Administered (Dosing Schedule)

Table JGDR.6 shows the treatment regimens. On days where multiple study drugs are to be administered, the drugs should be administered in the order shown in Table JGDR.6.

Table JGDR.6. Treatments Administered (Dosing Schedule)

Phase and Dose Cohort		Drug Name and Dose	Day of 21-day (±3 days) cycle	Total dose	Route and duration of administration	Notes
Dose-Finding Phase	Olara 15 mg/kg	Olaratumab 15 mg/kg[a]	D1 and D8		IV over 60 (±5) min Infusion rate should not exceed 25 mg/min	See Section 7.1.1 for premedication requirements and Section 7.8.1 for IRR monitoring period requirements
		Doxorubicin 25 mg/m^2 per day[a]	D1, D2, D3	75 mg/m^2	IV over less than 60 min or continuous IV infusion (according to institutional practice)	Administer after olara on D1 and after any required observation period
		Ifosfamide 2.5 g/m^2 per day[a]	D1, D2, D3, D4[b]	10[b] g/m^2	IV over 3 hours (±15 min)	Administer after dox on D1, D2, D3
		Mesna dose ≥60% of ifos dose[a]	D1, D2, D3, D4[b]		According to institutional practice	
	Olara Loading Dose Cycle	Olaratumab 20 mg/kg Cycle 1 Olaratumab 15 mg/kg Cycles 2 to 6[a]	D1 and D8 D1 and D8		IV over 60 (±5) min Infusion rate should not exceed 25 mg/min	See Section 7.1.1 for premedication requirements and Section 7.8.1 for IRR monitoring period requirements
		Doxorubicin 25 mg/m^2 per day[a]	D1, D2, D3	75 mg/m^2	IV over less than 60 min or continuous IV infusion (according to institutional practice)	Administer after olara on D1 and after any required observation period
		Ifosfamide 2.5 g/m^2 per day[a]	D1, D2, D3, D4[b]	10[b] g/m^2	IV over 3 hours (±15 min)	Administer after dox on D1, D2, D3
		Mesna dose ≥60% of ifos dose[a]	D1, D2, D3, D4[b]		According to institutional practice	
Dose Confirmation Phase	Recommended Olara Dose	Olaratumab dose determined from Dose-Finding Phase[a]	D1 and D8		IV over 60 (±5) min Infusion rate should not exceed 25 mg/min	See Section 7.1.1 for premedication requirements and Section 7.8.1 for IRR monitoring period requirements
		Doxorubicin 25 mg/m^2 per day[a]	D1, D2, D3	75 mg/m^2	IV over less than 60 min or continuous IV infusion (according to institutional practice)	Administer after olara on D1 and after any required observation period
		Ifosfamide 2.5 g/m^2 per day[a]	D1, D2, D3, D4[b]	10[b] g/m^2	IV over 3 hours (±15 min)	Administer after dox on D1, D2, D3
		Mesna dose ≥60% of ifos dose[a]	D1, D2, D3, D4[b]		According to institutional practice	

Abbreviations: C = cycle; CRP = clinical research physician; D = day; DLT = dose-limiting toxicity; dox = doxorubicin; g = grams; ifos = ifosfamide; IRR= infusion-related reaction; IV = intravenous; kg = kilogram; m^2 = square meters; mg = milligrams; min = minutes; olara = olaratumab.

a All patients will receive study therapy (olaratumab + doxorubicin/ifosfamide/mesna) for a maximum of 6 cycles, or until a discontinuation criterion is met. Patients who discontinue doxorubicin, ifosfamide and mesna treatment without evidence of disease progression will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met.

b If DLT rules (see Section 7.2.2.1) are exceeded in the olaratumab 15-mg/kg cohort, a reduced dose of ifosfamide (7.5 g/m2 total dose) will be explored. This reduced dose will be communicated by the Lilly CRP and will be accomplished by omitting the Day 4 dose (that is, ifosfamide will be administered at a dose of 2.5 g/m2 on D1, D2 and D3). The Day 4 dose of mesna will be correspondingly omitted. A Loading Dose Cycle of olaratumab (20 mg/kg on Days 1 and 8 of C1, then 15 mg/kg on Days 1 and 8 of subsequent cycles) may also be explored in combination with the reduced dose of ifosfamide.

7.1.1. Olaratumab Premedications and Required Monitoring

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

Premedicate patients prior to administration of olaratumab as below:

- On Days 1 and 8 of Cycle 1: **Mandatory** administration of a histamine H1 antagonist (for example, diphenhydramine) and dexamethasone prior to the start of the olaratumab infusion.
- For subsequent cycles, premedication with a histamine H1 antagonist (for example, diphenhydramine) is recommended prior to each dose of olaratumab.

Additional premedication(s) may be provided at the investigator's discretion. Premedication must be provided in the setting of a prior Grade 1 or 2 olaratumab IRR, as detailed in Section 7.8.1. All premedications administered must be adequately documented in the electronic case report form (eCRF).

Patients are required to be monitored for 1 hour after the olaratumab infusion in Cycles 1 and 2 for signs or symptoms of IRRs; see Section 7.8.1 for full description of required olaratumab monitoring period in Cycles 1 and 2. Patients should complete the required monitoring period prior to the start of the doxorubicin administration.

7.1.2. Doxorubicin Premedications and Dexrazoxane Administration

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

If antiemetic 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.

Patients may receive dexrazoxane for the prevention of cardiotoxicity at the discretion of the investigator according to institutional protocol.

7.1.3. Ifosfamide Premedications and Mesna Administration

Mesna must be administered to all patients for the prevention of ifosfamide-induced hemorrhagic cystitis. Mesna should be administered at a minimum dose equal to 60% of the ifosfamide dose according to institutional guidelines. 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 dose = minimum 60% of ifosfamide dose).

Ifosfamide should be given with extensive hydration consisting of oral or IV fluid (≥2 L/m^2 per day IV) to prevent bladder toxicity or according to institutional guidelines.

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

If ifosfamide premedication is required, it should be administered together with any doxorubicin premedications prior to doxorubicin administration.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be assigned to receive olaratumab in combination with doxorubicin, ifosfamide and mesna in this study. After the patient signs the ICF, the site will register the patient in the interactive web response system (IWRS), which is web-based and accessible 24 hours a day. The IWRS registration consists of assigning the patient a unique study identification number. Once the patient is registered through the IWRS, he/she is considered to be enrolled in the study.

7.2.1. Selection and Timing of Doses

A cycle is defined as an interval of 21 days. In Cycle 2 and beyond, up to 3 days delay of a cycle (that is, Day 1) or Day 8 will be permitted due to holidays, weekends, bad weather, or other unforeseen circumstances and will not count as a protocol deviation. In exceptional cases, longer delays may be allowed in later cycles following consultation with Lilly medical representative.

The actual dose of olaratumab to be administered will be determined by measuring the patient's weight in kilograms on Days 1 and 8 of each cycle. See also Section 7.5 for further details on olaratumab. The actual doses of doxorubicin, ifosfamide and mesna to be administered will be determined by calculating the patient's body surface area at the beginning of each cycle. If the patient's weight does not fluctuate by ±10% from the weight used to calculate prior doses, the olaratumab and doxorubicin, ifosfamide and mesna doses will not need to be recalculated, unless deemed clinically meaningful. A ±5% variance in the calculated total doses will be allowed for ease of dose administration.

Patients will continue treatment for a maximum of 6 cycles, or until there is documented disease progression, unacceptable toxicity, death, or other discontinuation criteria are met (Section 8). Patients who discontinue doxorubicin, ifosfamide and mesna treatment without evidence of disease progression will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met (Section 8). Patients who undergo surgical tumor resection following study treatment are not eligible to receive olaratumab as monotherapy.

7.2.2. Dose-Finding Phase

7.2.2.1. Dose-Limiting Toxicity Determination

Because of the relatively high rate of DLT-level toxicity with the backbone doxorubicin, ifosfamide and mesna regimen (Judson et al. 2014) and the generally acceptable toxicity profile

of the 15-mg/kg dose of olaratumab (Days 1 and 8 every 21 days) in combination with other chemotherapeutic agents including doxorubicin, approximately 15 patients will be enrolled at the first dose level of olaratumab (provided safety data confirms the required number of patients without DLTs have been met for each DLT threshold as described in Table JGDR.7) to allow sufficient patient numbers to judge initial tolerability of olaratumab in combination with doxorubicin, ifosfamide and mesna.

In the Dose-Finding Phase, DLT assessment will be performed. A DLT is defined as events such as the following, graded according to the NCI-CTCAE Version 4.0, when it occurs within Cycle 1 and is considered to be related to study treatment by the investigator in conjunction with the sponsor:

1. Grade 3 or 4 febrile neutropenia, or sepsis.
2. Grade 4 neutropenia lasting 7 days or longer.
3. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia complicated by hemorrhage.
4. Nonhematologic Grade ≥3 toxicity, except for toxicities (such as nausea, vomiting, transient electrolyte abnormalities, diarrhea) that can be controlled with optimal medical management within 48 hours or clinically non-significant laboratory abnormalities.

A dose-limiting equivalent toxicity is an AE that meets the DLT criteria as defined above and occurs in any cycle *other than Cycle 1*. In addition to the DLT assessment period in Cycle 1, available safety data beyond Cycle 1 may also be taken into consideration prior to a decision to advance to the next dose level or the determination of the Confirmation Phase dose.

Note: Infusion-related reactions will not be considered as DLTs, as they occur independent of dose level.

Table JGDR.7 shows the DLT thresholds that will be used to determine study progression.

Table JGDR.7. Dose-Limiting Toxicity Thresholds for Study JGDR

Dose Level	Regimen	If…	Then[b]…
Olara 15 mg/kg (Starting Dose Level)	**Olara** 15 mg/kg D1, D8 **Ifos** 10 g/m^2 D1 to D4[a] **Dox** 75 mg/m^2 D1 to D3	6 DLTs in first 6 patients	Proceed to Olara 15 mg/kg with Ifos Reduction Dose Level (new cohort of approximately 15 patients).
		≤5 DLTs in first 6 patients	Enroll 3 additional patients and evaluate DLTs in this group of first 9 patients.
		≤5 DLTs in first 9 patients	Enroll full cohort of 15 patients.
		≥6 DLTs in first 9 patients	Proceed to Olara 15 mg/kg with Ifos Reduction Dose Level (new cohort of approximately 15 patients).
		≥9 DLTs in full 15 patients	Proceed to Olara 15 mg/kg with Ifos Reduction Dose Level (new cohort of approximately 15 patients).
		≤8 DLTs in full 15 patients	Proceed to Olara 20-mg/kg Loading Dose Cycle Dose Level.
Olara 15 mg/kg with Ifos Reduction	**Olara** 15 mg/kg D1, D8 **Ifos** 7.5 g/m^2 D1 to D3[a] **Dox** 75 mg/m^2 D1 to D3	6 DLTs in first 6 patients	Halt study. No further patients enrolled.
		≤5 DLTs in first 6 patients	Enroll 3 additional patients and evaluate DLTs in this group of first 9 patients.
		≤5 DLTs in first 9 patients	Enroll full cohort of 15 patients.
		≥6 DLTs in first 9 patients	Halt study. No further patients enrolled.
		≥9 DLTs in full 15 patients	Halt study. No further patients enrolled.
		≤8 DLTs in full 15 patients	Proceed to Olara 20-mg/kg Loading Dose Cycle Dose Level with Ifos Reduction.
Olara 20-mg/kg Loading Dose Cycle	**Olara** 20 mg/kg D1, D8 of C1; then 15 mg/kg D1, D8 of C2 to C6 **Ifos** 10 g/m^2 D1 to D4[a] **Dox** 75 mg/m^2 D1 to D3	6 DLTs in first 6 patients	Discontinue enrollment into cohort. Proceed to Recommended Dosing Regimen cohort with Olara 15 mg/kg as recommended dose.
		≤5 DLTs in first 6 patients	Enroll 3 additional patients and evaluate DLTs in this group of first 9 patients.
		≤5 DLTs in first 9 patients	Enroll full cohort of 15 patients.
		≥6 DLTs in first 9 patients	Discontinue enrollment into cohort. Proceed to Recommended Dosing Regimen cohort with Olara 15 mg/kg as recommended dose.
		≥9 DLTs in full 15 patients	Discontinue enrollment into cohort. Proceed to Recommended Dosing Regimen cohort with Olara 15 mg/kg as recommended dose.
		≤8 DLTs in full 15 patients	Proceed to Recommended Dosing Regimen cohort with Olara 20-mg/kg Loading Dose Cycle as recommended dose.

Dose Level	Regimen	If…	Then[b] …
Olara 20-mg/kg Loading Dose Cycle with Ifos Reduction	**Olara** 20 mg/kg D1, D8 of C1; then 15 mg/kg D1, D8 of C2 to C6 **Ifos** 7.5 g/m^2 D1 to D3[a] **Dox** 75 mg/m^2 D1 to D3	6 DLTs in first 6 patients	Discontinue enrollment into cohort. Proceed to Recommended Dosing Regimen cohort with Olara 15 mg/kg with Ifos reduction as recommended dose.
		≤5 DLTs in first 6 patients	Enroll 3 additional patients and evaluate DLTs in this group of first 9 patients.
		≤5 DLTs in first 9 patients	Enroll full cohort of 15 patients.
		≥6 DLTs in first 9 patients	Discontinue enrollment into cohort. Proceed to Recommended Dosing Regimen cohort with Olara 15 mg/kg and Ifos 7.5 g/m^2 as recommended doses.
		≥9 DLTs in full 15 patients	Discontinue enrollment into cohort. Proceed to Recommended Dosing Regimen cohort with Olara 15 mg/kg and Ifos 7.5 g/m^2 as recommended doses.
		≤8 DLTs in full 15 patients	Proceed to Recommended Dosing Regimen cohort with Olara 20 mg/kg Loading Dose Cycle and Ifos 7.5 g/m^2 as recommended doses.
Recommended Dosing Regimen	**Olara** dose TBD **Ifos** dose TBD **Dox** 75 mg/m^2 D1 to D3	Enroll 15 patients and treat with Recommended Dosing Regimen.	

Abbreviations: D = day; DLT = patients experiencing a dose-limiting toxicity; dox = doxorubicin; g = grams; Ifos = ifosfamide; kg = kilogram; m^2 = square meters; mg = milligrams; Olara = olaratumab; TBD = to be determined.

[a] With concomitant mesna administration.

[b] If a sufficient number of patients successfully complete the DLT period at a given dose level (ensuring the DLT threshold will not be exceeded), further enrollment may proceed as described in Table JGDR.7, upon agreement of the Sponsor and Investigators.

7.3. Blinding

This is an open-label study.

7.4. Dosage Delays, Discontinuations and Modifications

To begin dosing at Cycle 2 and each Day 1 thereafter (for cycles in which olaratumab is administered with doxorubicin and ifosfamide), the following criteria must be fulfilled (see Table JGDR.9 for hematological parameters for dosing olaratumab on Day 8):

- ANC ≥1.5 × 10^3 cells/μL (≥1500 cells/μL; ≥1.5 × 10^9/L)
- Platelets ≥100 × 10^3 cells/μL (≥100,000 cells/μL; ≥100 × 10^9 cells/L)
- Hemoglobin ≥8.0 g/dL. Note: For study inclusion, hemoglobin ≥9.0 g/dL
- Total bilirubin below ULN. In patients with Gilbert's syndrome, total bilirubin should be <3 mg/dL
- Serum creatinine ≤1.5 times ULN. If creatinine is above ULN, the patient's creatinine clearance is ≥60 mL/min (refer to Appendix 6 for the Cockcroft-Gault formula for creatinine clearance)
- AST and ALT ≤3 × ULN, or ≤5 × ULN if the transaminase elevation is due to liver metastases
- Nonhematologic toxicity must be Grade ≤2 or must have returned to baseline, unless the toxicity is deemed not clinically significant by the investigator or is a laboratory abnormality that is manageable by institutional standards (for example, low serum potassium, magnesium, or phosphate).

In addition, patients should be monitored for evidence of micro- and/or macroscopic hematuria and treated according to institutional standards.

7.4.1. Delays

In general, dose delays of 1 study drug (olaratumab, doxorubicin, or ifosfamide/mesna) due to toxicities outlined in Section 7.4.3 will not necessitate delays of the other study drugs. However, close consideration must be made by the investigator to administer all study treatments per the schedule outlined in Section 7.1.

Treatment may be delayed for up to 14 days to allow a patient sufficient time for recovery from study drug-related toxicity. If Day 8 treatment is delayed >7 days, treatment may be resumed with planned Day 1 treatment of the next cycle.

Dosing delay beyond 14 days may be permissible if AEs are not considered to be primarily related to olaratumab and the investigator deems continuation of study treatment to have clinical benefit for the patient. This decision has to be documented and be jointly made by the investigator and the Lilly team.

In the event of unforeseen circumstances or scheduling issues that require adjustments to the schedule, appropriate adjustments or delays to the schedule may be made following discussion between the investigator and the sponsor and written approval by the Lilly medical representative.

7.4.2. Discontinuations

The need to permanently discontinue doxorubicin and/or ifosfamide due to drug-related toxicity should be done according to local standard of care and labels. Criteria for olaratumab discontinuation are discussed in the olaratumab dose modification section (7.4.3.1) and in the olaratumab infusion-related reaction section (7.8.1).

Patients whose disease has not progressed at the time of doxorubicin, ifosfamide and mesna discontinuation will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met (Section 8). These patients will continue study assessments as outlined in Table JGDR.2. Patients who undergo surgical tumor resection following study treatment are not eligible to receive olaratumab as monotherapy.

Patients who exhibit disease progression at the time of doxorubicin, ifosfamide and mesna discontinuation will receive post-treatment follow-up assessments as outlined in Table JGDR.3.

7.4.3. Dose Modifications

General guidelines for dose modifications are provided below. Sections 7.4.3.2 and 7.4.3.3 outline guidelines for dose modifications of doxorubicin and ifosfamide, respectively; variations from these guidelines may be allowed according to local standard of care and labels.

7.4.3.1. Olaratumab Dose Modifications

A reduction in the dose of olaratumab will be permitted if the doses of doxorubicin and ifosfamide have been previously reduced for toxicity, and the same or similar toxicity has recurred despite reduction of doxorubicin, ifosfamide and mesna, and the toxicity is deemed potentially related to the addition of olaratumab in combination with doxorubicin, ifosfamide and mesna. In this scenario, an olaratumab dose reduction should occur in conjunction with a reduction in the doxorubicin and ifosfamide doses according to the guidance outlined in Sections 7.4.3.1.1 and 7.4.3.1.2.

A second reduction in the olaratumab dose will not be permitted during treatment with combination therapy of olaratumab plus doxorubicin and ifosfamide.

Patients who have not progressed on study will receive olaratumab as monotherapy following discontinuation of the combination therapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met. Patients receiving olaratumab as monotherapy will have assessments performed as per Table JGDR.2

Patients who have a dose reduction of olaratumab during the combination therapy portion and then proceeding to receive olaratumab monotherapy after discontinuation of doxorubicin and ifosfamide combination may have their dose of olaratumab re-escalated to the original dose level at the investigator's discretion.

7.4.3.1.1. Hematologic Toxicity

Table JGDR.8 shows olaratumab dose modifications that should be made for hematologic toxicities judged as potentially related to olaratumab in combination with doxorubicin, ifosfamide and mesna, and that have recurred or failed to improve/resolve despite 1 reduction in doxorubicin and ifosfamide doses. These guidelines should be used for olaratumab dosing, when given in combination with doxorubicin and ifosfamide.

Table JGDR.8. General Guidelines for Olaratumab Dose Modification due to Hematologic Toxicities

Toxicity	Dose Modification
Neutropenia	
ANC Grades 1-3	No dose modification required
ANC <500 cells/µL (Grade ≥4)	No treatment administered; treatment cycle delayed
At re-treatment: If ≥Grade 3 neutropenic fever/infection has occurred and 1 reduction in doxorubicin, ifosfamide and mesna doses has already occurred	Withhold dose until ANC is ≥1500 cells/µL; • 15-mg/kg Dose Level: Reduce dose to 12 mg/kg • 20-mg/kg Loading Dose Cycle Level: Reduce dose to 15 mg/kg
If Grade 4 neutropenia lasting ≥1 week has occurred and 1 reduction in doxorubicin, ifosfamide and mesna doses has already occurred	Withhold dose until ANC is ≥1500 cells/µL; • 15-mg/kg Dose Level: Reduce dose to 12 mg/kg • 20-mg/kg Loading Dose Cycle Level: Reduce dose to 15 mg/kg
Grade 4 ANC without fever/infection lasting ≤1 week	Administer next olaratumab at full dose, at investigator's discretion
After 1 reduction of olaratumab and 2 reductions of doxorubicin, ifosfamide and mesna, recurrence of either: 1) ≥Grade 3 neutropenic fever/infection 2) Grade 4 neutropenia lasting ≥1 week	Discontinue combination therapy (olaratumab + doxorubicin/ifosfamide/mesna). Patients who have not progressed will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met.

Abbreviation: ANC = absolute neutrophil count.

Omitting the Day 8 dose of olaratumab based on ANC and platelet counts judged as potentially related to olaratumab in combination with doxorubicin, ifosfamide, and mesna is permissible as shown in Table JGDR.9.

Table JGDR.9. Olaratumab Day 8 Dosing Algorithm Based on ANC and Platelet Count

Treatment Day	ANC (cells/µL)		Platelet Count (cells/µL)	Olaratumab
Day 8	≥500	and	≥75,000	Administer
	<500	and	Any	Omit[a]
	Any	and	<75,000	Omit

Abbreviations: ANC = absolute neutrophil count; µL = microliter.

[a] Day 8 administration of olaratumab may be delayed for a maximum of 7 days. If the ANC level has not increased to ≥500 cells/µL within 7 days, then the Day 8 olaratumab dose in that cycle should be skipped and dosing resumed on Day 1 of the following cycle (if criteria for dosing are met). If all dosing criteria are met, a delay or omission of the Day 8 olaratumab dose should not result in a delay of the Day 1 olaratumab dose of the following cycle.

7.4.3.1.2. Nonhematologic Toxicity

Specific guidelines for dose adjustments in patients who experience olaratumab-related IRRs may be found in Section 7.8.1.

Table JGDR.10 shows olaratumab dose modifications that should be made for nonhematologic toxicities judged as potentially related to olaratumab in combination with doxorubicin, ifosfamide and mesna and that have recurred despite 1 reduction in doxorubicin, ifosfamide and mesna dose.

Table JGDR.10. General Guidelines for Olaratumab Dose Modification due to Nonhematologic Toxicities

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 at the full dose, provided the event does not pose a serious health risk or is easily treated.
Grade 3 and 1 reduction in doxorubicin, ifosfamide and mesna doses has already occurred	If not adequately controlled with appropriate supportive care, withhold dose until ≤Grade 1 or has returned to pretreatment baseline. Treatment may resume as follows: • 15-mg/kg Dose Level: Reduce dose to 12 mg/kg • 20-mg/kg Loading Dose Cycle Level: Reduce dose to 15 mg/kg If toxicity recurs after therapy resumes, discontinue combination therapy (olaratumab + doxorubicin/ifosfamide/mesna). Patients who have not progressed will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met.
Grade 4 and 1 reduction in doxorubicin, ifosfamide and mesna doses has already occurred	Withhold dose until toxicity is ≤Grade 1 or has returned to pretreatment baseline. Permanent discontinuation of olaratumab should be considered for any patient experiencing Grade 4 nonhematologic 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 CRP as follows: • 15-mg/kg Dose Level: Reduce dose to 12 mg/kg • 20-mg/kg Loading Dose Cycle Level: Reduce dose to 15 mg/kg If toxicity recurs after therapy resumes, discontinue combination therapy (olaratumab + doxorubicin/ifosfamide/mesna). Patients who have not progressed will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met.

7.4.3.2. Doxorubicin Dose Modifications

Dose modifications of doxorubicin will follow the guidelines outlined below and may be adjusted according to local standard of care and label.

7.4.3.2.1. Hematologic Toxicity

Doxorubicin will not be administered after the initial dose if the patient's ANC is <1500 cells/µL or if the platelet count is <100,000 cells/µL. When necessary, the next treatment cycle should be delayed until the ANC is ≥1500 cells/µL and the platelet count is ≥100,000 cells/µL and any nonhematologic toxicities have resolved. For patients who experience ≥Grade 3 neutropenic fever or infection or Grade 4 neutropenia without fever lasting more than 1 week, doxorubicin should be reduced to 75% of the starting dose (that is, to approximately 60 mg/m^2). If a patient experiences a second incidence of neutropenic fever/infection or has another episode of Grade 4 neutropenia lasting >1 week, then a second dose reduction to 45 mg/m^2 should occur.

Therapeutic and prophylactic use of pegfilgrastim or other G-CSFs is required per current American Society of Clinical Oncology (ASCO; Smith et al. 2006) and National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2014). In general, G-CSF products like filgrastim or pegfilgrastim should be administered approximately 24 hours after the completion of cytotoxic chemotherapy (for example, on Day 5 for patients in full-dose ifosfamide cohorts or Day 4 for patients in reduced-dose ifosfamide cohorts). For patients with Grade 4 ANC without fever/infection lasting less than 1 week, re-treatment will be allowed at the investigator's discretion with the full dose of doxorubicin (75 mg/m^2) with required use of G-CSFs per current ASCO guidelines (Smith et al. 2006). See Table JGDR.11 for doxorubicin dose modification for neutropenia.

Table JGDR.11. General Guidelines for Doxorubicin Dose Modification Due to Neutropenia

Toxicity	Required Dose Modification
ANC <1500 cells/µL	No doxorubicin administered; entire treatment cycle delayed.
At re-treatment: If ≥Grade 3 neutropenic fever/infection has occurred	Approximately 60 mg/m^2 doxorubicin.
If Grade 4 neutropenia lasting longer than 1 week has occurred	Approximately 60 mg/m^2 doxorubicin.
If Grade 4 neutropenia without fever/infection lasting less than 1 week has occurred	Retreatment with doxorubicin at full dose at investigator's discretion with required use of G-CSFs.
Second incidence of either: 1) ≥Grade 3 neutropenic fever/infection 2) Grade 4 neutropenia lasting longer than 1 week	Second dose reduction to 45 mg/m^2.
Third incidence of either: 1) ≥Grade 3 neutropenic fever/infection 2) Grade 4 neutropenia lasting longer than 1 week	Discontinue combination therapy (olaratumab + doxorubicin/ifosfamide/mesna) and follow per Section 7.4.2.

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

7.4.3.2.2. Nonhematologic Toxicity

Permanent discontinuation of doxorubicin should be considered for any patient experiencing Grade 4 nonhematologic toxicity assessed as related to doxorubicin. If the investigator feels re-dosing of doxorubicin is appropriate (except for Grade 4 cardiotoxicities, which require mandatory discontinuation (see Section 7.4.3.2.3), treatment may only resume after consultation with the Lilly CRP, with the dose reduced to 60 mg/m² (or less if agreed by the investigator and Lilly CRP). If Grade 4 nonhematological toxicity recurs after therapy resumes, doxorubicin (in combination with ifosfamide and mesna) will be permanently discontinued and the patient will be followed as outlined in Section 7.4.2.

For appropriate management of cardiac toxicities, refer to Section 7.4.3.2.3.

7.4.3.2.3. 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 echocardiogram (ECHO)/multiple-gated acquisition (MUGA) scan.

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

Patients will undergo baseline LVEF determination using ECHO or MUGA scan. This evaluation may be repeated at any time during the study if clinically indicated. A decrease in LVEF of ≥10% and below the lower limit of normal, or an absolute decrease of 20%, or if the absolute LVEF decreases to or below 40%, then doxorubicin will be discontinued. Doxorubicin should also be discontinued if the patient develops Grade 3 or 4 left ventricular systolic dysfunction (symptomatic congestive heart failure).

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.

7.4.3.3. Ifosfamide Toxicities and Dose Modifications

Dose modifications of ifosfamide will follow the guidelines outlined below and may be adjusted according to local standard of care and label. Two reductions in ifosfamide dose for toxicity will be permitted during the study. If a third dose reduction is necessary, the patient will be discontinued from the combination therapy (olaratumab + doxorubicin/ifosfamide/mesna) and followed as outlined in Section 7.4.2.

General guidelines for ifosfamide dose modification are shown in Table JGDR.12. Dose modifications of ifosfamide due to hepatic impairment are shown in Table JGDR.13.

Table JGDR.12. 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 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	Discontinue combination therapy (olaratumab + doxorubicin/ifosfamide/mesna) and follow per Section 7.4.2. Administer methylene blue 50 mg intravenously every 4 hours until resolution.
Grade 3 or 4 neurotoxicity other than encephalopathy	Discontinue combination therapy (olaratumab + doxorubicin/ifosfamide/mesna) and follow per Section 7.4.2.
Grade 3 related organ toxicity/nonhematologic	Decrease 20%
Grade 4 related organ toxicity/nonhematologic	Discontinue combination therapy (olaratumab + doxorubicin/ifosfamide/mesna) and follow per Section 7.4.2.

Abbreviation: mg = milligrams.

[a] Do not re-treat until criteria in Section 7.4 are met.

Table JGDR.13. Dose Modification of Ifosfamide due to Hepatic Impairment

Bilirubin		AST/ALT	Ifosfamide Dose Reduction[a]
1-2 × ULN		<2 × ULN	Full dose
2-4 × ULN	**and/or**	2-5 × ULN	75% of initial dose
>4 × ULN		>5 ULN	Discontinue combination therapy (olaratumab + doxorubicin/ifosfamide/mesna) and follow per Section 7.4.2.

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.

7.4.3.3.1. Ifosfamide-Associated Central Nervous System Toxicity

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 chloroacetaldehyde formation, has been suggested as treatment or prophylaxis for ifosfamide-induced encephalopathy. Due to the potential for additive effects, drugs acting on the CNS (such as antiemetics, sedatives, narcotics, or antihistamines) must be used with particular caution or, if necessary, be discontinued in case of ifosfamide-induced encephalopathy.

7.4.3.3.2. Ifosfamide-Associated Urotoxic Effects

The incidence of urotoxic effects without an uroprotector can be up to 40% and is dose dependent; coadministration of mesna and adequate hydration are mandatory in this study. 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 with or without surgical intervention (electrocautery, cryosurgery, diversion of urine flow, hypogastric artery ligation, or cystectomy). Discontinuation or dose reduction of ifosfamide should follow local standard of care and label for patients with macroscopic hematuria.

7.4.3.3.3. Ifosfamide-Associated 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 preexisting renal impairment, concurrent use of nephrotoxic drugs, reduced renal reserve (unilateral nephrectomy), 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 guidelines of ifosfamide due to renal impairment are shown in Table JGDR.14.

Table JGDR.14. Dose Modification of Ifosfamide due to Renal Impairment

Creatinine Clearance (mL/min)[a]	Ifosfamide Dose Reduction
>60	Full dose
40-60	Reduce to 75% of initial dose
20-40	Reduce to 50% of initial dose
<20	Discontinue combination therapy (olaratumab + doxorubicin/ifosfamide/mesna) and follow per Section 7.4.2.

Abbreviations: min = minutes; mL = milliliters.

[a] Calculated using Cockcroft and Gault formula (see Appendix 6).

7.5. Packaging and Labeling

7.5.1. Olaratumab

Olaratumab will be provided to study sites by Lilly. Clinical trial materials will be labeled according to the country's regulatory requirements.

Olaratumab will be supplied as a sterile preservative-free solution for IV infusion in single-use vials containing 500 mg/50 mL of olaratumab (10 mg/mL).

Olaratumab is formulated in 10 mM histidine, 100 mM glycine, 50 mM sodium chloride, 75 mM mannitol and 0.02% polysorbate-20, with a pH of 5.5. All excipients used in the formulation of olaratumab drug product are of pharmacopoeia grade.

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

7.5.2. Doxorubicin, Ifosfamide and Mesna

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

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

7.5.3. Granulocyte-Colony Stimulating Factors

G-CSFs will be purchased by the sites.

7.5.4. Dexrazoxane

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

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

7.6. Preparation/Handling/Storage/Accountability

7.6.1. Olaratumab

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

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

7.6.2. Doxorubicin

Investigators should consult the approved doxorubicin hydrochloride package insert for complete preparation, handling and storage requirements. If a patient should have an IRR to doxorubicin, the investigator should follow the manufacturer's recommendations and clinical guidelines in the management of the patient.

Doxorubicin is administered as an IV infusion. Doxorubicin may be administered either as a bolus over 60 minutes or less, or as a 24-hour continuous infusion, depending on institutional protocol.

If erythematous streaking along the vein proximal to the site of infusion or facial flushing occur, decrease the rate of doxorubicin administration.

Doxorubicin must be reconstituted prior to infusion. The reconstituted solution is stable for 7 days at room temperature and under normal room light and 15 days under refrigeration (2°C to 8°C). It should be protected from exposure to sunlight.

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

7.6.3. Ifosfamide

Investigators should consult the approved ifosfamide package insert for complete preparation, handling and storage requirements.

Ifosfamide single-dose vials should be stored at controlled room temperature from 20°C to 25°C (68°F to 77°F) and protected from temperatures above 30°C (86°F).

Exercise caution while handling ifosfamide. The handling and preparation of ifosfamide should always be in accordance with current guidelines on safe handling of cytotoxic agents. Several

guidelines on this subject have been published (OSHA 1999; NIOSH 2004; ASHP 2006; Polovich et al. 2014). Skin reactions associated with accidental exposure to ifosfamide may occur. To minimize the risk of dermal exposure, always wear impervious gloves while handling vials and solutions containing ifosfamide. If ifosfamide solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water.

7.6.4. Mesna

Investigators should consult the approved mesna package insert for complete preparation, handling and storage requirements.

Mesna injection solution should be stored at 20°C to 25°C (68°F to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F).

7.7. Treatment Compliance

The study medication will be administered only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is ensured.

7.8. Concomitant Therapy and Supportive Care

7.8.1. Olaratumab Infusion-Related Reactions

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

A 1-hour observation period is required after the administration of olaratumab in the first and second cycles. If there is no evidence of an IRR during the initial 2 cycles of olaratumab, then no observation period is required for subsequent treatment cycles. In the event that a Grade 1 or 2 IRR occurs after Cycle 2, the 1-hour observation period will be reinstituted for a minimum of 2 cycles. The reinstituted observation period may be suspended after 2 cycles if the patient shows no further signs or symptoms of an IRR. During the observation period, patients treated with olaratumab should be closely monitored for signs and symptoms indicative of an IRR by the medical staff from the start of the infusion until at least 1 hour after the end of the infusion in an area where emergency medical resuscitation equipment and other agents (epinephrine, prednisolone equivalents, etc.) are available.

Treatment guidelines for olaratumab IRRs as well as premedications for subsequent infusions are described in Table JGDR.15.

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

Symptoms occurring during or following infusion of investigational therapy may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome (NCI-CTCAE Version 4.0 Section “Immune system disorders”). In the setting of symptoms 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.

Table JGDR.15. Olaratumab Infusion-Related Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Infusions
Grade 1 or 2	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy should be given according to standard medical practice; may include, but is not limited to: • antihistamines (for example, diphenhydramine HCl) • steroids (for example, dexamethasone) • acetaminophen • oxygen After recovery, the infusion rate should be decreased 50% for the duration of the infusion.	Patients should be premedicated with antihistamines, steroids, acetaminophen, etc., as appropriate.
Grades 3 or 4	**Stop infusion.** Administer immediate treatment; may include, but is not limited to: • epinephrine • bronchodilators and/or glucocorticoids for symptomatic bronchospasm • IV fluids and/or pressors for hypotension **Treatment with olaratumab should be immediately and permanently discontinued.**	No subsequent dosing

All attempts should be made to obtain an 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.

Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

Abbreviations: HCl = hydrochloride; IV = intravenous; NCI CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events.

7.8.2. Granulocyte-Colony-Stimulating Factors and Erythroid Growth Factors

Because the doxorubicin, ifosfamide and mesna regimen is known to be highly suppressive of the bone marrow, G-CSFs such as pegfilgrastim must be used at each cycle and should be

administered according to ASCO guidelines (Smith et al. 2006) and NCCN guidelines (NCCN 2014). In general, G-CSF products like filgrastim or pegfilgrastim should be administered approximately 24 hours after the completion of cytotoxic chemotherapy (for example, on Day 5 for patients in full-dose ifosfamide cohorts or Day 4 for patients in reduced-dose ifosfamide cohorts). Erythroid-stimulating factors (such as erythropoietin) may be used at the discretion of the investigator and should also be administered according to ASCO and NCCN guidelines.

7.8.3. Transfusion of Blood Products

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

7.8.4. Antiemetic Therapy

Both prophylactic and symptom-directed antiemetic therapy are recommended and should be used in accordance with institutional guidelines and/or at the investigator's discretion.

7.8.5. Inducers and Inhibitors of CYP3A4, CYP2D6 and P-gp

Avoid concurrent use of doxorubicin HCl with inhibitors and inducers of cytochrome (CYP)3A4, CYP2D6 and/or P-gp. Doxorubicin is a major substrate of CYP450, CYP3A4 and CYP2D6, and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4, CYP2D6 and/or P-gp (for example, verapamil), resulting in increased concentration and clinical effect of doxorubicin. Inducers of CYP3A4 (for example, phenobarbital, phenytoin, St. John's Wort) and P-gp inducers may decrease the concentration of doxorubicin.

Ifosfamide is a substrate for both CYP3A4 and CYP2B6. CYP3A4 inducers (for example, carbamazepine, phenytoin, fosphenytoin, phenobarbital, rifampin, St. John's Wort) may increase the metabolism of ifosfamide to its active alkylating metabolites. CYP3A4 inducers may increase the formation of the neurotoxic/nephrotoxic ifosfamide metabolite, chloroacetaldehyde. Closely monitor patients taking ifosfamide with CYP3A4 inducers for toxicities and consider dose adjustment. CYP3A4 inhibitors (for example, ketoconazole, fluconazole, itraconazole, sorafenib, aprepitant, fosaprepitant, grapefruit, grapefruit juice) may decrease the metabolism of ifosfamide to its active alkylating metabolites, perhaps decreasing the effectiveness of ifosfamide treatment.

7.8.6. Other Concomitant Therapies

No other chemotherapy, radiotherapy, immunotherapy, cancer-related hormone therapy, or experimental drugs will be permitted while the patients are on this study. An exception will be made for:

- prostate cancer patients continuing GnRH agonist therapy or breast cancer patients continuing anti-estrogen therapy (for example, an aromatase inhibitor) as long as those

therapies have been installed for at least 3 months and are known to have been well tolerated

- bisphosphonate osteoclast inhibitors (for example, zoledronic acid or pamidronate) for treatment of bone metastases will be permitted while patients are on study treatment. The osteoclast inhibitor denosumab is also allowed. Denosumab is a monoclonal antibody and is associated with a risk of hypersensitivity reactions. Therefore, denosumab should not be administered within 3 days of olaratumab administration.
- palliative local treatment (for example, radiotherapy of ≤14 calendar days) in Cycles 2 and beyond following discussions between the investigators and the sponsor (for example, for pain control of a solitary [non-skull] skeletal metastasis) and written approval by the sponsor, as long as the patient has not developed another reason for study discontinuation.

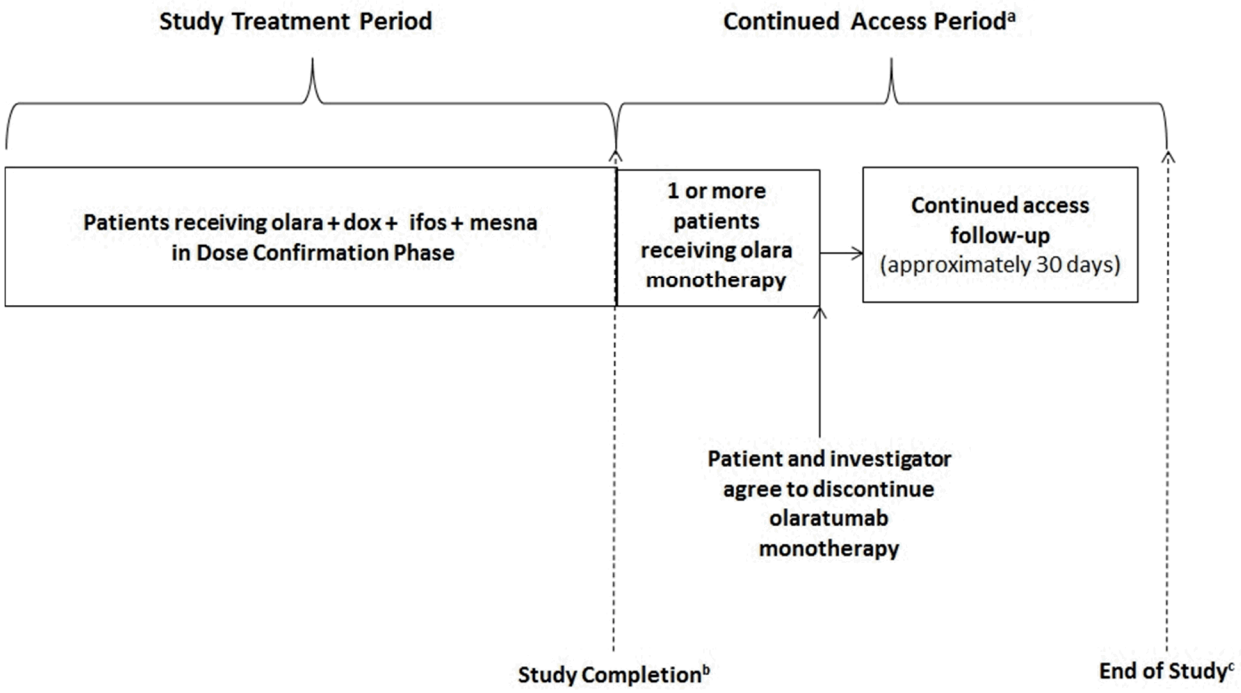
7.9. Treatment after the End of the Study

7.9.1. Continued Access

Patients who are still on olaratumab monotherapy at the time of study completion may continue to receive olaratumab monotherapy if they are experiencing clinical benefit.

A continued access period will apply to this study only if at least 1 patient is still on olaratumab monotherapy when study completion occurs. Lilly will notify investigators when the continued access period begins.

The patient's continued access to olaratumab study drug will end when a criterion for discontinuation is met (Section 8). Continued access follow-up will begin the day after the patient and the investigator agree to discontinue olaratumab monotherapy and last approximately 30±7 days (see Figure JGDR.2). Follow-up procedures will be performed as shown in the Continued Access Schedule of Activities (Table JGDR.4).



[a] Lilly will notify sites when the continued access period begins and ends.
[b] Lilly will notify sites when study completion occurs.
[c] End of study occurs at the last visit or last scheduled procedure for the last patient.

Abbreviations: dox = doxorubicin; ifos = ifosfamide; olara = olaratumab.

Figure JGDR.2. Continued access diagram.

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Patients will be discontinued from study treatment under the following circumstances:

- the patient is enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- the patient becomes pregnant during the study
- the patient is significantly noncompliant with study procedures and/or treatment
- the patient demonstrates disease progression
- the patient has unacceptable toxicity
- 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 study treatment will occur prior to introduction of the new agent
- the patient undergoes surgical tumor resection
- the investigator decides that the patient should be discontinued from study treatment
- the patient requests to be discontinued from study treatment
- the patient's designee (for example, legal guardian or caregiver) requests that the patient be discontinued from study treatment

Patients who are discontinued from study treatment will have follow-up procedures performed as shown in the Schedule of Activities (Section 2).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If Lilly or the investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate 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 study treatment.

8.2. Discontinuation from the Study

Patients will be discontinued from the study under the following circumstances:

- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations and good clinical practice (GCP)
- the patient requests to be discontinued from the study

Patients who discontinue from the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Study site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow-up.

Study site personnel, or an independent third party, will attempt to collect the survival status for all enrolled patients who are lost to follow-up, including enrolled patients who do not receive study treatment, within legal and ethical boundaries. Public sources may be searched for survival status information. If the patient's survival status is determined, the survival status will be documented, and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect survival status information.

9. Study Assessments and Procedures

Section 2 provides the Schedule of Activities for this study.

Appendix 3 provides a list of laboratory tests that will be performed for this study.

Appendix 4 provides the schedule for collection of samples in this study.

Unless otherwise stated in the following subsections, all samples collected for specified laboratory tests will be destroyed within 60 days after receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

9.1.1. Secondary Efficacy Assessments

Tumor assessments will be performed for each patient at the times shown in the Schedule of Activities (Section 2).

Computed tomography (CT) scans, including spiral CT, are the preferred methods of measurement (CT scan thickness recommended to be ≤5 mm); however, magnetic resonance imaging is also acceptable in certain situations, such as when body scans are indicated or if there is a concern about radiation exposure associated with CT. Intravenous and oral contrast is required unless medically contraindicated.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST Version 1.1 (Eisenhauer et al. 2009).

The method of tumor assessment used at baseline must be used consistently throughout the study. Radiological imaging of the chest, abdomen and pelvis and other areas, as clinically indicated, is required.

See Section 10.3.1 for definitions of the efficacy endpoints.

9.1.2. Appropriateness of Assessments

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

9.2. Adverse Events

The investigator will use NCI-CTCAE Version 4.0 (NCI 2009) to assign AE terms and severity grades.

Investigators are responsible for:

- monitoring the safety of patients in 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 appropriate medical care of patients during the study
- documenting their review of each laboratory safety report
- following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to study treatment or the study, or that caused the patient to discontinue study treatment before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, study site personnel will record via eCRF any change in the preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study procedure or study treatment via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatments, or pathologies. A "reasonable possibility" means that there is a cause and effect relationship between the study treatment and/or study procedure and the AE.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must report any dose modifications or treatment discontinuations that result from AEs to Lilly or its designee via eCRF, clarifying, if possible, the circumstances leading to the dose modification or discontinuation of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- 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 serious, based upon appropriate medical judgment.

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

Study site personnel must notify Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Lilly-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.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE but should be reported. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

All AEs and SAEs, regardless of relatedness to study drugs or protocol procedures, occurring during the safety follow-up visit (Visit 801; approximately 30 days after completion of study therapy) must be reported to Lilly or its designee. Investigators are not obligated to actively seek AEs or SAEs in patients beyond Visit 801. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Planned hospitalizations or procedures for preexisting conditions that were recorded in the patient's medical history at the time of enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study treatment or other protocol-required procedure) should not be considered SAEs.

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

9.2.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study treatment or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

9.2.3. Adverse Events of Special Interest

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

The following events will be considered as AESI for the combination of olaratumab and doxorubicin, ifosfamide and mesna:

infusion-related reactions
cardiac arrhythmias and cardiac dysfunction
encephalopathy
renal toxicity

Refer to Section 7.8.1 for treatment considerations relative to the occurrence of olaratumab IRRs. Refer to Section 7.4 for treatment considerations relative to dose delays, modifications and discontinuations from doxorubicin, including AEs of concern or AESI.

9.2.4. Complaint Handling

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

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

9.3. Treatment of Overdose

Refer to the olaratumab IB for information on the treatment of olaratumab overdose. Refer to the doxorubicin, ifosfamide and mesna product labels for information on overdose with these agents.

9.4. Safety

9.4.1. Other Safety Measures

For each patient, ECGs, vital signs, laboratory tests, or other tests should be collected as shown in the Schedule of Activities (Section 2).

Any clinically significant findings that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRF.

9.4.2. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods. In addition to the formal DLT period that occurs during Cycle 1, safety data from later

cycles that are available at the time of the DLT assessment may be used in the decision to move to the next cohort, or in the determination of the recommended Phase 2 dose.

Clinical and laboratory monitoring should be initiated by the investigator in the following circumstances:

1. The patient experiences elevation of serum ALT ≥10 × ULN
2. A patient without liver tumors or liver metastatis experiences elevated ALT ≥5 × ULN and elevated total bilirubin ≥2 × ULN
3. A patient with liver tumor or liver metastatis experiences elevated ALT ≥8 × ULN and elevated total bilirubin ≥2 × ULN
4. The patient is discontinued from treatment due to a hepatic event or abnormality of liver tests
5. The patient experiences a hepatic adverse event considered to be an SAE

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests (see Appendix 5).

9.5. Pharmacokinetics

At the visits and times specified in the Pharmacokinetic, Immunogenicity and Biomarker Research Sampling Schedule (Appendix 4), venous blood samples will be collected for all patients enrolled in the study. These samples will be used to determine the serum concentrations of olaratumab and the plasma concentrations of doxorubicin and ifosfamide.

A maximum of 5 additional samples (in addition to those shown in Appendix 4) may be collected at additional time points during the study if warranted and agreed upon between the investigator and Lilly.

Instructions for the collection and handling of blood samples will be provided by Lilly. It is preferred that the blood samples be obtained from a peripheral location. Blood samples can be collected via central access devices, but a sample drawn for PK from any type of central catheter cannot be diluted or it will not be viable for analysis. If multiple samples are obtained centrally, the PK sample should be the last specimen drawn to reduce the potential for a diluted or improperly drawn sample. The actual date and time (24-hour clock time) of each sampling will be recorded.

These samples will be analyzed at 1 or more laboratories designated by Lilly. Serum concentrations of olaratumab will be assayed using a validated enzyme-linked immunosorbent assay method. Doxorubicin and ifosfamide concentrations in plasma will be analyzed using individual validated methods based on liquid chromatography with tandem mass spectrometry.

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

Bioanalytical samples collected to measure olaratumab concentrations will be retained for a maximum of 1 year following the last patient visit for the study.

9.6. Genetics

9.6.1. Whole Blood Samples for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in Appendix 4, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to study treatment and to investigate genetic variants thought to play a role in sarcoma. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

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

9.7. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety) and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid, ribonucleic acid, proteins, lipids and other cellular elements. Required samples for biomarker research to be collected from all patients in this study are the following:

- blood (plasma) (see Section 9.7.1)
- tumor tissue (see Section 9.7.2)

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

- newly obtained tumor specimens collected during or after the treatment period or at disease progression if medically feasible (see Section 9.7.2)

Samples for biomarker research will be collected as specified in Appendix 4, where local regulations allow.

It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed prior to enrollment in this trial. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described below.

9.7.1. Samples for Nonpharmacogenetic Biomarker Research

Blood samples for nonpharmacogenetic biomarker research will be collected as specified in Appendix 4 where local regulations allow.

Samples will be examined for biomarkers related to, but not limited to drug targets, disease process, immune cells/immune and tumor microenvironment functioning within the disease state and cancer-related conditions, pathways associated with cancer and study drugs, variable response to study drugs, the mechanism of action of study drugs and/or for research-related methods, or validating diagnostic tools or assays.

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

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

9.7.2. Tissue Samples for Biomarker Research

Tumor tissue will be examined for biomarkers related to, but not limited to drug targets, disease process, immune cells/immune and tumor microenvironment functioning within the disease state and cancer-related conditions, pathways associated with cancer and study drugs, variable response to study drugs, the mechanism of action of study drugs and/or for research-related methods, or validating diagnostic tools or assays.

Collection of the following tumor tissue sample is **required** for all patients in order to participate in this study unless restricted by local regulations:

- To meet study eligibility criteria, and therefore mandatory for study participation, patients must have sufficient available material from an archived formalin-fixed paraffin-embedded tumor tissue. If such tissue is not available, a newly obtained core or excisional biopsy of a tumor lesion must be performed. Patients for whom it is inadvisable to undergo a new biopsy in the opinion of the investigator (for example, due to technically challenging tumor location) may be enrolled, after prior discussion with the Lilly CRP.

Collection of the following tumor tissue sample(s) is **optional** for all patients participating in this study:

- Newly obtained tumor specimens collected during or after the treatment period. If these additional samples are requested, they will be used to further investigate biomarkers that may explain treatment response and resistance mechanisms. A tumor tissue sample will be requested from patients who undergo surgical tumor resection subsequent to study treatment.

Details for the handling and shipping of the tumor tissue will be provided by the sponsor in a separate document. If additional tumor biopsies are collected as part of clinical care, they should be submitted, along with pathology reports, for further analysis. The tissue samples will be obtained using appropriate method. Tumor tissue should be submitted as a newly acquired excisional or core needle (minimum 18 gauge) biopsy in formalin. Cytological or fine-needle aspiration specimens and decalcified bone are not acceptable. Previously obtained formalin-fixed paraffin-embedded tumor tissue should be provided as a block or unstained slides. Due diligence should occur to ensure that tumor sample (not a normal adjacent or a tumor margin sample) is provided. The pathology report may also be requested to accompany the archival tissue sample. The report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission. Lilly has a right to retain a portion of the submitted tissue and archival blocks will be returned to the study site. Slides and tissue samples collected on-study will not be returned.

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

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

9.8. Immunogenicity Assessments

Blood samples for immunogenicity testing will be collected as shown in Appendix 4 to determine antibody production against olaratumab. Immunogenicity will be assessed using a validated assay designed to detect antidrug antibodies in the presence of olaratumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of olaratumab.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if regulations and ERBs/IRBs impose shorter time limits, at a facility selected by Lilly. The duration allows Lilly to respond to future regulatory requests related to olaratumab.

10. Statistical Considerations

10.1. Sample Size Determination

The primary objective is to determine whether olaratumab can be safely added to the doxorubicin, ifosfamide and mesna regimen in patients with advanced or metastatic STS. Section 5.1 outlines the study design. A total of approximately 45 to 60 patients will be enrolled; at least 15 patients will be treated in the olaratumab 15-mg/kg phase.

A traditional 3 + 3 study design is not appropriate for this trial because of the relatively high rate of DLT-level toxicity associated with the backbone doxorubicin, ifosfamide and mesna regimen (Judson et al. 2014). Instead, a total of approximately 15 patients will be enrolled at the first dose level of olaratumab (and incrementally evaluated after 6, 9 and 15 patients have received 1 cycle of therapy) to allow sufficient patient numbers to judge initial tolerability of olaratumab in combination with doxorubicin, ifosfamide and mesna.

Before enrolling the full 15 patients at a given dose level, the study design requires that an initial group of 6 will be enrolled and evaluated for DLTs. If 6 or more patents with DLTs are observed in the first 6 patients, enrollment at the current dose level will be stopped and appropriate dose de-escalation (or trial halt) will occur. Similarly, if 6 or more patients with DLTs are observed in the first 9 patients, enrollment at the current dose level will be stopped and appropriate dose de-escalation (or trial halt) will occur.

Assuming that the true DLT rate of olaratumab plus doxorubicin, ifosfamide and mesna is unacceptably high at 70%, this design will allow a 73% power to de-escalate the dose to an appropriate lower dose level. That is, when the true DLT rate is 70%, the probability of observing 6 or more DLT patients out of 9 patients is 0.73. Alternatively, assuming that the true DLT rate of olaratumab plus doxorubicin,ifosfamide and mesna is as low as 30%, then the probability of observing 6 or more DLT patients out of 9 patients is only 0.03 (false-positive rate when the true DLT rate is 30%).

Assuming the true DLT rate of olaratumab plus doxorubicin, ifosfamide and mesna is unacceptably high at 70%, the current design will allow an 87% power to de-escalate the dose to an appropriate lower dose level. That is, when the true DLT rate is 70%, the probability of observing 9 or more DLT patients out of 15 patients is 0.87. Alternatively, assuming the true DLT rate of olaratumab plus doxorubicin, ifosfamide and mesna is as low as 30%, then the probability of observing 9 or more DLT patients out of 15 patients is only 0.02 (false-positive rate when the true DLT rate is 30%).

Although the study sample size is limited, the overall design allows satisfactory power and false-positive rate.

10.2. Populations for Analyses

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

performed based on the actual initial therapy a patient has received. Efficacy analysis will be performed on the safety population unless otherwise specified.

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

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Lilly or its designee.

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

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

10.3.1. Efficacy Analyses

Efficacy analysis will be performed to investigate antitumor activity within each phase. The investigator-assessed objective response rate (complete response [CR]+partial response [PR]) and disease control rate (DCR = CR+PR+stable disease) and the 90% exact confidence interval (CI) will be tabulated for each phase. The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the median with 90% CI for PFS, OS and duration of response. Additional analyses may be performed as necessary. The details will be outlined in the SAP.

10.3.2. Safety Analyses

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

- Treatment-emergent adverse events will be summarized by MedDRA System Organ Class/preferred term, classified from verbatim terms. The incidence and percentage of patients with at least 1 occurrence of a preferred term will be included, according to the most severe NCI-CTCAE Version 4.0 grade. Causality (relationship to study drug), action taken, and outcome will be summarized separately. Duration of AE will be determined and included in the listings.
- Study drug exposure will be summarized for each arm with following variables: number of infusions, number of cycles, duration of therapy, cumulative dose, dose intensity, and relative dose intensity.
- Laboratory results will be classified according to NCI-CTCAE Version 4.0. Incidence of laboratory abnormalities will be summarized.
- Hospitalizations due to AEs, transfusions and vital signs will be summarized.

- DLTs will be summarized by phase in the patients who are evaluable for DLT assessments and listed by patient. ECG, ECHO/MUGA and immunogenicity data will also be summarized. Additional analyses may be performed as necessary. The details will be outlined in the SAP.

10.3.3. Other Analyses

10.3.3.1. Patient Disposition

A detailed description of patient disposition will be provided, including a summary of the number and percentage of patients who entered into the study, enrolled in the study and treated as well as the number and percentage of patients completing the study, as defined in the SAP, or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

10.3.3.2. Patient Characteristics

A summary of baseline patient and disease characteristics, historical diagnoses, preexisting conditions and prior therapies will be reported using descriptive statistics.

Other patient characteristics will be summarized as deemed appropriate.

10.3.3.3. Concomitant Therapy

A summary of prior and concomitant medications will be reported.

10.3.3.4. Post-study Treatment Discontinuation Therapy

The numbers and percentages of patients receiving post-study treatment discontinuation anticancer therapies will be provided by type of therapy (surgery, radiotherapy or systemic therapy), and by drug class and/or name, and overall.

10.3.3.5. Treatment Compliance

The number of cycles received, dose omissions, dose reductions, dose delays and dose intensity will be summarized for all treated patients by each phase.

Study treatment will be administered at the investigative site, therefore treatment compliance is assured.

10.3.4. Pharmacokinetic Analyses

Unless stated otherwise, the Lilly pharmacokineticist will be responsible for the PK and PK/PD analyses.

Pharmacokinetic parameter estimates for olaratumab will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be maximum concentration and area under the concentration-time curve ($AUC_{[0\text{-}tlast]}$, $AUC_{[0\text{-}\infty]}$) of olaratumab. Other noncompartmental parameters, such as half-life, apparent clearance and apparent volume of distribution may be reported.

Additional analyses such as population PK analyses may also be conducted if deemed appropriate. Other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global Pharmacokinetic management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

Plasma doxorubicin and ifosfamide concentrations at different time points will be summarized by descriptive statistics.

10.3.5. Biomarker Analyses

Biomarker assay results will be listed and summarized for all patients qualifying for the translational research portion of the study. Other exploratory analyses may also be undertaken to investigate the correlations and/or associations between marker status/level and drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety) and clinical outcomes. These assessments may include biomarker signatures consisting of marker status/levels of multiple biomarkers. For biomarkers that are serially measured, change from baseline to a subsequent time point may also be used as a potential explanatory variable in correlative assessments involving other trial data endpoints and as a dependent variable in PD analyses.

10.3.6. 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 antidrug antibody (ADA)-negative and treatment-emergent-ADA-positive patients at correspondent visits, or before and after treatment-emergent-ADA development for patients who developed treatment-emergent-ADA.

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

10.3.7. Subgroup Analyses

Subgroup analyses will be performed as deemed appropriate.

10.3.8. Interim Analyses

Since this is a safety study, data will be reviewed on at least a cohort-by-cohort basis during the study. The purpose of these safety reviews is to evaluate the safety data at each phase to determine if the current safety profile supports continual enrollment based on the study design. The investigators and the Lilly study team will make the determination regarding the patient enrollment based upon their review of the safety and tolerability data as described in this protocol.

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Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibody
AE	adverse event: any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
$AUC_{[0\text{-}tlast]}$	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
$AUC_{[0\text{-}\infty]}$	area under the first moment curve from zero to infinity
blinding/masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment. Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
CI	confidence interval
C_{min1}	trough serum level at the end of the first cycle of treatment
CNS	central nervous system
collection database	A computer database where clinical trial data are entered and validated.
CR	complete response
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist (CRS), global safety physician, or other medical officer.
CT	computed tomography

DLT	dose-limiting toxicity
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
effective method of contraception	male condom with spermicide, female condom with spermicide, diaphragm with spermicide, cervical sponge, or cervical cap with spermicide. Also see the definition of highly effective method of contraception.
EORTC	European Organisation for Research and Treatment of Cancer
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB/IRB	ethical review board/institutional review board: A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare and human rights of the patients participating in a clinical study are protected.
GCP	good clinical practice
G-CSF	granulocyte-colony-stimulating factor
highly effective method of contraception	combined oral contraceptive pill and mini-pill, NuvaRing®, implantable contraceptives, injectable contraceptives (such as Depo-Provera®), intrauterine device (such as Mirena® and ParaGard®), contraceptive patch for women <90 kg (<198 pounds), total abstinence, or vasectomy. Also see the definition of effective method of contraception.
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical trial data conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

IRR	infusion-related reaction
IV	intravenous/intravenously
IWRS	interactive web response system
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	multiple-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OS	overall survival
PD	pharmacodynamics(s)
PDGFR	platelet-derived growth factor receptor
PDGFRα	platelet-derived growth factor receptor alpha
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
QTc	corrected QT interval
QTcF	Fridericia's QT corrected interval
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	To screen a patient who was previously declared a screen failure for the same study.
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
screen failure	patient who does not meet one or more criteria required for participation in a trial
STS	soft tissue sarcoma

SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
US	United States

Appendix 2. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the potential risks and benefits of participating in the study
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study procedures and prior to the administration of study treatment
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

Ethical Review

Documentation of ERB/IRB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs/IRBs, before it is used at the investigative site(s). All ICFs must be compliant with the International Council for Harmonisation (ICH) guideline on GCP.

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

- the current IB and updates during the course of the study
- the ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical guidelines
- applicable ICH GCP guidelines
- applicable laws and regulations.

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

Investigator Information

Licensed physicians specializing in oncology will participate as investigators in this clinical trial.

Protocol Signatures

Lilly'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.

Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most enrolled patients will serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

Lilly'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.

Data Quality Assurance

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

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

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records and clinical notes. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs/IRBs with direct access to original source documents.

Data Capture System

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 Lilly-provided electronic data capture system.

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

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

Study and Site Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB/IRB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations and GCP.

Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations and GCP.

Appendix 3. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology - local and central laboratory[a]	
Leukocytes (WBC)	Erythrocytes (RBC)
Neutrophils[b]	Hemoglobin (HGB)
Lymphocytes	Hematocrit (HCT)
Monocytes	Mean corpuscular volume (MCV)
Eosinophils	Mean corpuscular hemoglobin concentration (MCHC)
Basophils	Platelets (PLT)
Coagulation - local laboratory	
Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT)	
International normalized ratio (INR) or prothrombin time (PT)	
Clinical Chemistry - local and central laboratory[a]	
Serum Concentrations of:	
Alanine aminotransferase (ALT)	Cholesterol
Albumin	Creatinine
Alkaline phosphatase	Glucose, random
Aspartate aminotransferase (AST)	Magnesium
Bilirubin, direct	Phosphorous
Bilirubin, total	Potassium
Blood urea nitrogen (BUN) or blood urea	Sodium
Calcium	Uric acid
Urinalysis - local laboratory	
Blood	Protein
Glucose	Specific gravity
Ketones	Urine leukocyte esterase
pH	
Pregnancy Test (for female patients of childbearing potential) - local laboratory	
Serum pregnancy test (screening)	
Serum or Urine pregnancy test (on study)	
Confirmation of Menopause (for female patients of menopausal age) – local laboratory	
Follicle-stimulating hormone (FSH)[c]	

Abbreviation: CRF = case report form.

[a] Treatment decisions will be based on local laboratory results.

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

[c] To be performed at screening only when needed to confirm post-menopausal status; applicable for women who have experienced spontaneous amenorrhea for 6 to 12 months.

Appendix 4. Pharmacokinetic, Biomarker, Pharmacogenetics and Immunogenicity Sampling Schedules

It is essential that the exact infusion start and stop times (actual clock readings) are recorded. The exact time of collection of each venous blood sample will be based on the clock used to record infusion times. It is essential that the PK blood samples not be drawn from the same site as the drug infusion.

Pharmacokinetic, Biomarker, Pharmacogenetic and Immunogenicity Sampling Schedule

Cycle	Day	Dosing	Sampling Time[a]	PK Sampling			Biomarker Sampling		PGx	IG[e,f]
				Olara PK[b,f]	Dox PK[c,l]	Ifos PK[d,l]	Plasma	Tumor Tissue[g]		
Baseline	-							X (mandatory)[g]		
1	1		≤60 min pre-olara	X[h]			X		X[i]	X
		Olara (1 hr)								
			≤5 min post-olara	X						
		Obs (1 hr)								
			60±10 min post-olara	X						
		Dox (<1 hr)[j]								
			≤5 min post-dox		X[j]					
		Ifos (3 hr)								
			≤5 min post-ifos	X		X				
	2	Dox (<1 hr)								
		Ifos (3 hr)								
			≤5 min post-ifos	X		X				
	3	Dox (<1 hr)[j]								
			≤5 min post-dox		X[j]					
		Ifos (3 hr)								
			≤5 min post-ifos			X				
	4	Ifos (3 hr)								
			≤5 min post-ifos	X		X				
	8		≤60 min pre-olara	X[h]			X			X
		Olara (1 hr)								
			≤5 min post-olara	X						
		Obs (1 hr)								
			60±10 min post-olara	X						
			4±0.5 hr post-olara	X						
	10		48±3 hr post-olara	X						
	15		Anytime	X						
2	1		≤60 min pre-olara	X[h]			X			X
		Olara (1 hr)								
			≤5 min post-olara	X						
	8		≤60 min pre-olara	X[h]						
		Olara (1 hr)								
			≤5 min post-olara	X						

3	1		≤60 min pre-olara	X[h]			X			X
		Olara (1 hr)								
			≤5 min post-olara	X						
		Dox (<1 hr)[i]								
			≤5 min post-dox	X	X[j]					
		Ifos (3 hr)								
			≤5 min post-ifos	X		X				
	2	Dox (<1 hr)								
		Ifos (3 hr)								
			≤5 min post-ifos	X[k]		X				
	3	Dox (<1 hr)[i]								
			≤5 min post-dox		X[j]					
		Ifos (3 hr)								
			≤5 min post-ifos			X				
	4	Ifos (3 hr)								
			≤5 min post-ifos	X[k]		X				
	8		≤60 min pre-olara	X[h]						
		Olara (1 hr)								
			≤5 min post-olara	X						
			60±10 min post-olara	X						
			4±0.5 hr post-olara	X						
	10		48±3 hr post-olara	X						
	15		Anytime	X						
4	1		≤60 min pre-olara	X[h]						
5 and then every other cycle	1		≤60 min pre-olara	X[h]						X
Visit 801			Anytime	X			X	X (optional; for patients who undergo surgical tumor resection subsequent to study treatment)		X

Abbreviations: C = cycle; D = day; dox = doxorubicin; hr = hour; ifos = ifosfamide; IG = immunogenicity; min = minute; IRR = infusion-related reaction; obs = observation; olara = olaratumab; PGx = pharmacogenetics; PK = pharmacokinetics.

a Post-infusion is defined as after the completion of the infusion.

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

[c] Samples of approximately 2 mL of whole blood will be drawn into plastic tubes with anticoagulant for measurement of ifosfamide in plasma.

[d] Samples of approximately 3 mL of whole blood will be drawn into plastic tubes with anticoagulant for measurement of doxorubicin in plasma.

[e] For the immunogenicity assay, approximately 5 mL of whole blood will be drawn into a serum separator tube without anticoagulant to generate serum samples.

[f] 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 (±3 days) after the IRR.

[g] Patients must have sufficient available material from an archived formalin-fixed paraffin-embedded tumor tissue. If such tissue is not available, a newly obtained core or excisional biopsy of a tumor lesion must be performed.

[h] Pretreatment samples may be collected any time during the day of the clinical visit, prior to the start of the olaratumab infusion and must be taken prior to administering any premedication.

[i] It is highly recommended to draw the PGx sample prior to the first dose of study drug (C1D1); however, it can be collected at a later time point, if necessary.

[j] If doxorubicin is administered as a 24 hour infusion, the doxorubicin PK sample should be collected at the same time as the ifosfamide PK sample (that is, approximately 3 to 4 hours after the start of the doxorubicin infusion).

[k] For patients who have discontinued doxorubicin/ifosfamide early, these samples may be omitted if there is no other reason for the patient to visit the clinic.

[l] Should a patient discontinue doxorubicin or ifosfamide, all subsequent PK samples for the corresponding chemotherapeutic agent can be omitted.

Appendix 5. 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 CRP.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin (HGB)	
Hematocrit (HCT)	**Hepatic Coagulation[a]**
Erythrocytes (RBC)	Prothrombin time (PT)
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils[b]	
Lymphocytes	**Hepatic Serologies[a,c]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets (PLT)	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
Alanine aminotransferase (ALT)	**Recommended Autoimmune Serology[a]**
Aspartate aminotransferase (AST)	Anti-nuclear antibody
Gamma-glutamyl transferase (GGT)	Anti-smooth muscle antibody
Creatine phosphokinase (CPK)	Anti-actin antibody

Abbreviations: CRF = case report form; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio.

[a] Assayed by Lilly-designated laboratory.

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

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

Appendix 6. Creatinine Clearance Formula

Note: This formula is to be used for calculating creatinine clearance (CrCl) from **local laboratory results only.**

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

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

Source: Cockcroft and Gault 1976.

Appendix 7. Fridericia's QT Correction Formula

Fridericia's QT Correction Formula

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

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

Appendix 8. Protocol Amendment I5B-MC-JGDR(a) Summary A Phase 1b Study of Olaratumab, Doxorubicin and Ifosfamide in the Treatment of Patients with Advanced or Metastatic Soft Tissue Sarcoma

Overview

Protocol I5B-MC-JGDR, A Phase 1b Study of Olaratumab, Doxorubicin and Ifosfamide in the Treatment of Patients with Advanced or Metastatic Soft Tissue Sarcoma has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- The Schedule of Activities was amended to remove visits and/or procedures not intended for patients receiving olaratumab monotherapy after completing 6 cycles of olaratumab plus doxorubicin and ifosfamide or otherwise having discontinued doxorubicin and ifosfamide. Changes are as follows:

  On-Study Treatment Schedule of Activities

  - Olaratumab monotherapy section added for Cycle 7 and beyond
  - Footnote was added to schedule to explain olaratumab monotherapy schedule for Cycle 7 and beyond
  - Vital sign assessments were reduced to just Day 1
  - Radiologic imaging and measurement of palpable or visible lesions procedure note was modified, deleting the 12-week timing for patients receiving olaratumab as monotherapy following discontinuation of combination therapy
  - For ECGs, language was added for timing of ECGs in Cycle 7 and beyond, which will be performed Day 1 of Cycle 7 and approximately 6 months and 12 months after discontinuation of of doxorubicin and ifosfamide treatment.
  - For patients receiving olaratumab as monotherapy following discontinuation of combination therapy, echocardiograms will be performed approximately 6 months (±14 days) and 12 months (±14 days) after discontinuation of doxorubicin and ifosfamide treatment
  - For urinalysis, patients will be monitored for evidence of micro- and/or macroscopic hematuria and treated according to institutional standards. For patients receiving olaratumab monotherapy Cycle 7 and beyond, urinalysis is not performed.

  Post-Treatment Follow-Up Schedule of Activities

- ECGs were added during short- and long-term follow up. All patients should have a 12-lead ECG performed at short-term follow-up. Patients should also have a 12-lead ECG performed approximately 6 months (±7 days) and 12 months (±7 days) after the end of treatment with doxorubicin and ifosfamide.
- For echo and MUGA, clarifying language was added to make clear the after the end of treatment with doxorubicin and ifosfamide, specificially.

Section 6.1 Inclusion Criteria

- Clarifying language was added to inclusion criterion [7] explicitly stating that adjuvant or neo-adjuvant treatment will not be counted as a prior line of therapy
- Inclusion criterion [12] was modified to delete general language and add treatment-specific duration requirements related to male contraception
- Female pregnancy testing and contraception language in [13] was modified, increasing the prior-to-treatment pregnancy testing window to 7 days, and making the duration of contraception requirements treatment specific - at least 3 months following the last dose of olaratumab and 6 months following the last dose of doxorubicin or ifosfamide.

Section 6.2 Exclusion Criteria

- Additional language was added to [23] regarding patients' history of prior malignancies as follows:
    - non-metastatic prostate cancer, or
    - other primary nonhematologic malignancies treated with curative intent, no known active disease, and no treatment administered during the last 3 years prior to enrollment, that the investigator and Lilly Medical representative agree will not affect interpretation of study results or would be unsuitable for participation in the study
- In Section 7.1, Table JGDR.6, for clarity, footnote "b" was added to the ifosfamide rows in the Total Dose column (that is, 10b g/m2 ifosfamide)
- Clarifying edits related to premedication were added in Section 7.1.1
- In Section 7.2.1 clarifying language was added for delays for Cycle 2 and beyond
- Clarifying language was added in Section 7.2.2.1 to explain DLTs in relation to further enrollment and patients. A note was added making it clear that IRR are not considered DLTs.
- A footnote was added to Table JGDR.7 to clarify threshholds patients experiencing DLTs and further patient enrollment.
- In Section 7.4, text was added to make clear the section is referring to patients being treating with olaratumab plus doxorubicin and ifosfamide. Additional text was inserted to state monitoring for hematuria.

- In Section 7.4.1, text was inserted to further detail guidance around dose delays. If Day 8 treatment is delayed >7 days, treatment may be resumed with planned Day 1 treatment of the next cycle. Dosing delay beyond 14 days may be permissible if AEs are not considered to be primarily related to olaratumab and the investigator deems continuation of study treatment to have clinical benefit for the patient. Dose delays do to unforeseen circumstances or scheduling issues are also addressed.
- In Section 7.4.2, clarifying text was added to address discontinuations.
- Section 7.4.3 was modified related to guidance for dose modification – referring the reader to specific subsections, and addressing potential for variations from guidelines with respect to local standard of care and labels.
- In Section 7.4.3.1, text related to number of and specifics of olaratumab dose modifications.
- Section 7.4.3.1.1 was edited, indicating that the guidelines for dose modifications due to hematologic toxicities are outlined in Table JGDR.8 and should be used when olaratumab is given in combination with doxorubicin and ifosfamide.
- Clarifying text was added to Section 7.4.3.2 explaining that doxorubicin dose modifications will follow guidelines outlined in the protocol, and that adjustments may be made based on local standard of care and label.
- Section 7.4.3.3 was edited to explain that dose modifications will follow guidelines outlined in the protocol, and that adjustments may be made based on local standard of care and label.
- Section 7.8.6 was added to provide detailed guidance regarding other concomitant therapies during Study JGDR.
- Minor clarifying text was added to Section 9.1.1 regarding secondary efficacy assessment.
- Serum pregnancy test was added as an option to urine pregnancy test in Appendix 3 for on-study pregnancy testing.
- Footnotes were added to the the sampling table in Appendix 4.

Revised Protocol Sections

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

2. Schedule of Activities

Table JGDR.2. On-Study Treatment Schedule of Activities

Day within Cycle / Procedure	~~Every Cycle~~Cycles 1-6 (olaratumab + doxorubicin + ifosfamide; (Cycle = 21 days)						Cycles 7-N Olaratumab Monotherapy [a] (Cycle = 21 days)		Instructions
	1	2	3	4	8	15	1	8	
Physical examination	X				X		X		• Perform prior to infusion of study drug(s) ~~on Day 1~~. • Includes weight and BSA. • ~~For patients receiving olaratumab as monotherapy following discontinuation of combination therapy, perform on D1 of every cycle.~~
Vital signs	X	X	X	X	X	X	X		Vital signs include temperature, blood pressure, pulse rate, respiration rate.
Concomitant medication	X						X		Concomitant medications will be recorded continuously throughout the treatment period.
AE collection	X						X		Collect continuously throughout the treatment period; CTCAE Version 4.0.
ECOG performance status	X						X		
Radiologic imaging and measurement of palpable or visible lesions	X ~~q 6 weeks~~						X		• Perform according to RECIST 1.1, by the same method used at baseline, q 6 weeks (-7 days) from the start of treatment until radiographic disease progression, death, or study completion, whichever occurs first. • Perform as scheduled, even if study treatment is delayed or omitted. ~~For patients receiving olaratumab as monotherapy following discontinuation of combination therapy, perform every 12 weeks (-7 days).~~
ECG	X ~~C1 - C6~~						X		• Perform local 12-lead ECG on Day 1 of Cycle 1 through Cycle 6. • Perform local 12-lead ECG on Day 1 of Cycle 7 and approximately 6 months (±14 days) and 12 months (±14 days) after discontinuation of doxorubicin and ifosfamide treatment
Echocardiogram and/or MUGA scan	X C4 and C6						X		• Perform at the end of C4 and C6; perform additional evaluations in the setting of cardiac symptoms and/or at the discretion of the investigator. • For patients receiving olaratumab as monotherapy following discontinuation of combination therapy, perform approximately 6 months (±14 days) and 12 months (±14 days) after discontinuation of doxorubicin and ifosfamide treatment.

Day within Cycle Procedure	~~Every Cycle~~Cycles 1-6 (olaratumab + doxorubicin + ifosfamide; (Cycle = 21 days) 1	2	3	4	8	15	Cycles 7-N Olaratumab Monotherapy [a] (Cycle = 21 days) 1	8	Instructions
Hematology	X				X	X	X	X	≤3 days prior to administration of study treatment on D1 and ≤1 day prior to administration of study treatment on D8, unless more frequent assessment is clinically indicated. Day 15 labs may be drawn within ±1 day of Day 15. See Appendix 3. To be performed locally for patient management and centrally for analysis purposes.
Coagulation	X						X		≤3 days prior to administration of study treatment on D1, unless more frequent assessment is clinically indicated. For patients receiving olaratumab as monotherapy following combination therapy discontinuation, perform on D1 of every other cycle. See Appendix 3. To be performed locally.
Clinical chemistry	X				X	X	X		≤3 days prior to administration of study treatment on D1 and ≤1 day prior to administration of study treatment on D8, unless more frequent assessment is clinically indicated. Day 15 labs may be drawn within ±1 day of Day 15. See Appendix 3. To be performed locally for patient management and centrally for analysis purposes.
Urinalysis	X	X	X	X					Monitor patients for evidence of micro- and/or macroscopic hematuria and treat according to institutional standards. ~~Prior to administration of study treatment on each treatment day. Patients must have ≤10 RBCs per high-power field present in urinalysis in order to proceed with ifosfamide dosing. For patients receiving olaratumab as monotherapy following discontinuation of combination therapy, perform on D1 of every other cycle. See Appendix 3. To be performed locally.~~
~~Urine pregnancy~~ Pregnancy test	X						X		• Applies only to women of childbearing potential • Where required by local law or regulation, perform once every 21 days (-7 days) prior to administration of study treatment. • To be performed locally

Day within Cycle Procedure	~~Every Cycle~~Cycles 1-6 (olaratumab + doxorubicin + ifosfamide; (Cycle = 21 days) 1	2	3	4	8	15	Cycles 7-N Olaratumab Monotherapy [a] (Cycle = 21 days) 1	8	Instructions
Administer olaratumab	X				X		X	X	Administer IV over 60 (±5) min. Administer until a maximum of 6 cycles is complete, or until PD, unacceptable toxicity, death, or other withdrawal criteria are met. Patients who discontinue doxorubicin, ifosfamide and mesna treatment without evidence of disease progression will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met. Patients who undergo surgical tumor resection following study treatment are not eligible to receive olaratumab as monotherapy. See section 7.1.1 for olaratumab premedication requirements. See section 7.8.1 for olaratumab IRR monitoring period requirements.
Administer doxorubicin	X	X	X						Administer IV over less than 60 (±5) min or as a continuous IV infusion (according to institutional guidelines) after completion of olaratumab infusion and any required observation period. Administer until a maximum of 6 cycles is complete, or until PD, unacceptable toxicity, death, or other withdrawal criteria are met. See Section 7.1.2 for details of dexrazoxane administration.
Administer ifosfamide	X	X	X	X *					Administer IV over 3 hours (±15 min) ~~after completion of doxorubicin administration.~~ Administer until a maximum of 6 cycles is complete, or until PD, unacceptable toxicity, death, or other withdrawal criteria are met. *Patients treated in cohorts with ifosfamide dose reduction will have the Day 4 dose omitted (that is, ifosfamide will be administered at a dose of 2.5 g/m^2 on D1, D2 and D3).
Administer mesna	X	X	X	X					See Section 7.1.3 for details of mesna administration.
G-CSF	X								The use of G-CSFs is required. Administer according to ASCO and NCCN guidelines. In general, G-CSF products like filgrastim or pegfilgrastim should be administered approximately 24 hours after the completion of cytotoxic chemotherapy (for example, on Day 5 for patients in full-dose ifosfamide cohorts or Day 4 for patients in reduced-dose ifosfamide cohorts).
Sample collection									For all sample collection, see Appendix 4.
Pharmacodynamics									
Pharmacokinetics									
Immunogenicity									
Pharmacogenetics									
Other biomarkers									

Abbreviations: AE = adverse event; ASCO = American Society of Clinical Oncology; BSA = body surface area; C = cycle; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); G-CSF = granulocyte-colony stimulating factor; IRR = infusion-related reaction; IV = intravenously; LVEF = left ventricular ejection fraction; min = minutes; MUGA = multiple-gated acquisition; NCCN = National Comprehensive Cancer Network; PD = progressive disease; q = every; RBC = red blood cell; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

[a] Olaratumab monotherapy schedule applies to patients who have completed 6 cycles of olaratumab plus doxorubicin and ifosfamide and are continuing treatment with olaratumab monotherapy or have discontinued doxorubicin plus ifosfamide and are continuing with olaratumab monotherapy. Note: if a patient discontinues doxorubicin plus ifosfamide treatment prior to completing 6 cycles and is continuing treatment with olaratumab monotherapy, perform procedures according to the olaratumab monotherapy schedule beginning the next cycle after the patient discontinues doxorubicin/ifosfamide.

Table JGDR.3. Post-Treatment Follow-Up Schedule of Activities

Procedure	Short-Term Follow-Up[a]	Long-Term Follow-Up	Instructions
Visit	**801**	**802–8XX**	
Physical examination	X		Including weight and vital signs (temperature, blood pressure, pulse rate, respiration rate)
Concomitant medication	X		
AE collection	X		CTCAE Version 4.0.
ECOG performance status	X		
Radiologic imaging and measurement of palpable or visible lesions	X	X*	*__**For patients whose disease has not progressed:**__ Perform q 6 weeks × 2, then q 3 mo until: • the patient has objective disease progression according to RECIST 1.1 or • the study's primary/final analysis Perform using the same method used at baseline and throughout the study. __**For patients who have had objective disease progression:**__ Radiologic tests and measurement of palpable or visible lesions are no longer required; these patients should be followed up for OS and collection of post-study treatment anticancer therapy information collection ~~approximately every 90 days (±14 days) until death or study completion~~ as indicated below.
Collection of survival information		X	Perform q 2 mo (±7 days) for the first 2 years after discontinuation from study treatment and q 6 mo (±14 days) thereafter until death or study completion. If an in-person visit is not possible, confirm survival by contacting the patient directly via phone.
Collection of post-study treatment anticancer therapy information	X	X	Perform q 2 mo (±7 days) for the first 2 years after discontinuation from study treatment and q 6 mo (±14 days) thereafter until death or study completion.
ECG	X	X	• All patients should have a 12-lead ECG performed at short-term follow-up. • Patients should also have a 12-lead ECG performed approximately 6 months (±7 days) and 12 months (±7 days) after the end of treatment with doxorubicin and ifosfamide.

Procedure	Short-Term Follow-Up[a]	Long-Term Follow-Up	Instructions
Visit	**801**	**802–8XX**	
Echocardiogram and/or MUGA scan		X	Perform at 6 months (±7 days) and 12 months (±7 days) after the end of ~~study~~ treatment with doxorubicin and ifosfamide. Echocardiograms/MUGA scans may be discontinued if the patient begins another anticancer therapy. Perform additional evaluations in the setting of cardiac symptoms and/or at the discretion of the investigator.
Hematology	X		See Appendix 3. To be performed locally for patient management and centrally for analysis purposes.
Coagulation	X		See Appendix 3. To be performed locally.
Clinical chemistry	X		See Appendix 3. To be performed locally for patient management and centrally for analysis purposes.
Urinalysis	X		See Appendix 3. To be performed locally.
Sample collection			For all sample collection, see Appendix 4.
Pharmacodynamics			
Pharmacokinetics			
Immunogenicity			
Pharmacogenetics			
Other biomarkers			

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); mo = month; MUGA = multiple-gated acquisition; OS = overall survival; q = every; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

[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). No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

3.2.1 Rationale for Amendment (a)

The original Study JGDR protocol, version dated 14 March 2017, was amended to remove visits and/or procedures not intended for patients receiving olaratumab monotherapy only after completing 6 cycles of olaratumab plus doxorubicin and ifosfamide (or discontinued doxorubicin and ifosfamide before). In particular, visits and procedures specifically used to administer and monitor for toxicity from the doxorubicin and ifosfamide combination have been removed for patients receiving olaratumab monotherapy.

The timing of ECHO/MUGA scans after discontinuation of doxorubicin plus ifosfamide treatment was clarified and ECG evaluations were added at the same frequency to ensure complete evaluation of any potential cardiotoxic effects following treatment with doxorubicin plus ifosfamide.

The wording pertaining to required contraceptive use following study treatment has been clarified to align with label requirement for doxorubicin.

In addition, some minor editorial changes have been made throughout the protocol to improve clarity and practicality of the protocol and secure alignment with the intended study design.

5. Study Design

5.1 Overall Design

Study JGDR is a multicenter, nonrandomized, open-label, ….

Olaratumab 15-mg/kg Dose Level: The first phase of the study (Dose-Finding Phase) will evaluate the safety and tolerability of adding olaratumab to the regimen of doxorubicin (75 mg/m^2 plus given as IV infusions of 25 mg/m^2 on Days 1 to 3), ifosfamide (10 g/m^2 given as IV infusions of 2.5 g/m^2 on Days 1 to 4) and mesna according to a 21-day cycle. Fifteen patients will be initially enrolled and treated with a 15-mg/kg dose of olaratumab (on Days 1 and 8 of a 21-day cycle) in combination with doxorubicin, ifosfamide and mesna and assessed for safety after 1 cycle of therapy. The full cohort of 15 patients will be enrolled if 5 or fewer patients with DLTs are observed in the first 6 and 9 patients, respectively.

Olaratumab 20-mg/kg Loading Dose Cycle Dose Level: Following an evaluation of safety in the full cohort of 15 patients (and provided 8 or fewer of these patients have experienced DLTs), the study will progress to evaluate a loading dose cycle of olaratumab (20 mg/kg IV on Days 1 and 8 of Cycle 1 only, then 15 mg/kg on Days 1 and 8 of subsequent cycles) in combination with doxorubicin, ifosfamide and mesna in a new cohort of 15 patients. Section 5.5.1 details the rationale for the loading dose. The full cohort of 15 patients will be enrolled if 5 or fewer patients with DLTs are observed in the first 6 and 9 patients, respectively.

Olaratumab 15-mg/kg Dose Level: Ifosfamide Dose Reduction Option
If during enrollment into the olaratumab 15-mg/kg dose level, DLTs are observed in 6 of the first 6 patients, in ≥6 of the first 9 patients, or in ≥9 of the full cohort of 15 patients, the study will proceed to explore a reduced ifosfamide dose (7.5 g/m^2 total dose) in combination with olaratumab 15 mg/kg and the same doxorubicin dose in a new cohort of 15 patients. If DLTs are observed in 6 of the first 6 patients, in ≥6 of the first 9 patients, or in ≥9 of the full cohort of 15 patients at this reduced ifosfamide dose, the study will halt and no further patients will be enrolled. If 8 or fewer patients with DLTs are observed in this full cohort of 15 patients, the study will progress to explore the olaratumab Loading Dose Cycle as previously described in combination with the reduced ifosfamide dose (and same doxorubicin dose) as previously described.

Olaratumab 20-mg/kg Loading Dose Cycle Dose Level: Ifosfamide Dose Reduction Option
If during enrollment into the olaratumab 20-mg/kg Loading Dose Cycle dose level, DLTs are observed in 6 of the first 6 patients, in ≥6 of the first 9 patients, or in ≥9 of the full cohort of 15 patients, no further patients will be enrolled at this dose level and olaratumab 15 mg/kg will be declared the recommended dose for combination with reduced-dose ifosfamide/mesna and doxorubicin. If 8 or fewer patients with DLTs are observed in this full cohort, the olaratumab 20-mg/kg loading dose cycle together with a reduced ifosfamide/mesna dose will be declared the recommended doses for combination with doxorubicin.

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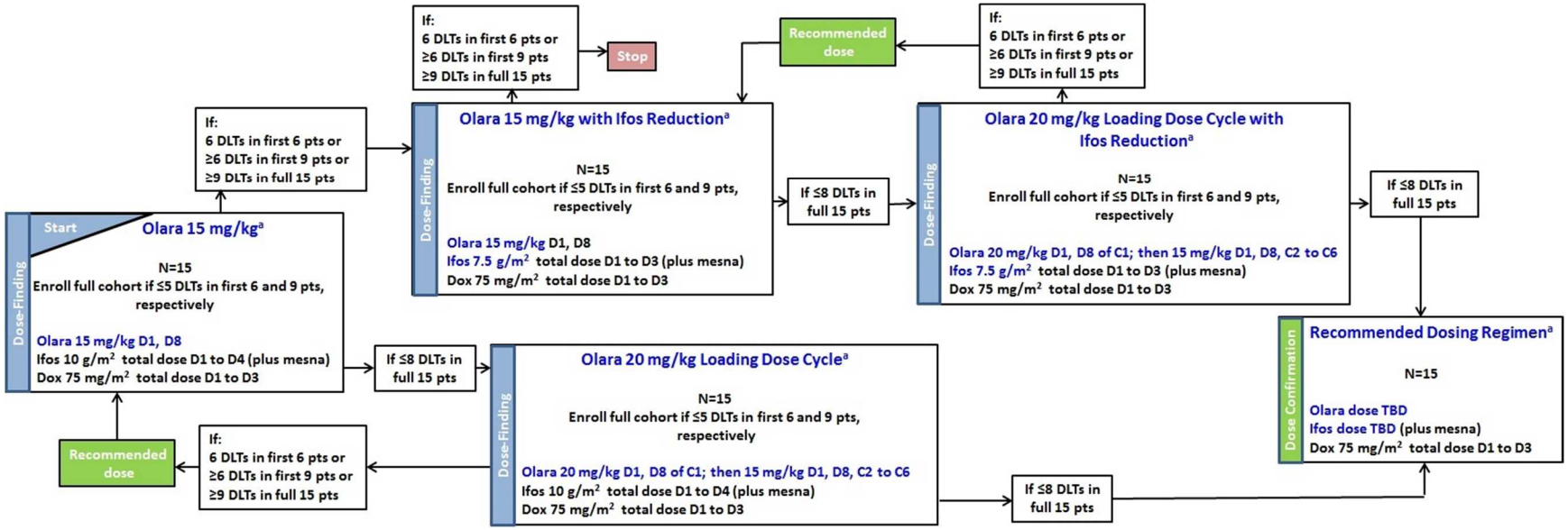

Abbreviations: D = day; DLT = patients experiencing a dose-limiting toxicity; Dox = doxorubicin; g = grams; Ifos = ifosfamide; kg = kilogram; m^2 = square meters; mg = milligrams; Olara = olaratumab; N = number; TBD = to be determined.

[a] Patients who discontinue combination study therapy without evidence of disease progression will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met.

Figure JGDR.1. Illustration of study design.

6. Study Population

All patients meeting the eligibility requirements will be considered for enrollment regardless of race, religion, or gender. The investigator or the sponsor will not grant exceptions to eligibility criteria. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

[7] Have received no prior lines of systemic therapy (adjuvant or neo-adjuvant treatment will not be counted as a prior line) and are suitable to receive doxorubicin, ifosfamide and mesna. All previous anticancer treatments must have completed ≥3 weeks (21 days) prior to the first dose of study treatment.

[12] If male, must be sterile or agree to use an *effective method of contraception* or a *highly effective method of contraception* during the study and for at least: ~~12 weeks following the last dose of study treatment.~~

- 3 months following the last dose of olaratumab
- 6 months following the last dose of doxorubicin or ifosfamide

Refer to Appendix 1 for definitions of *effective method of contraception* and *highly effective method of contraception*.

[13] If female and of child-bearing potential, must:

~~a. have a negative serum pregnancy test at the time of enrollment,~~

a. have a negative ~~urine~~serum pregnancy test within ~~24 hours~~7 days prior to the first dose of study treatment, and

b. agree to use a *highly effective method of contraception* during the study and for ~~3 months following the last dose of study treatment~~ at least 3 months following the last dose of olaratumab and 6 months following the last dose of doxorubicin or ifosfamide.

Refer to Appendix 1 for the definitions of *highly effective method of contraception* and *effective method of contraception*.

6.2. Exclusion Criteria

[23] Have a history of another primary malignancy, with the exception of:

a. curatively treated non-melanomatous skin cancer

b. curatively treated cervical carcinoma in situ

c. non-metastatic prostate cancer, or

d. other primary nonhematologic malignancies treated with curative intent, no known active disease, and no treatment administered during the last 3 years prior to enrollment, that the investigator and Lilly Medical representative agree will not affect interpretation of study results or would be unsuitable for participation in the study.

7.1. Treatment Administered (Dosing Schedule)

Table JGDR.6 shows the treatment regimens. On days where multiple study drugs are to be administered, the drugs should be administered in the order shown in Table JGDR.6.

Table JGDR.6. Treatments Administered (Dosing Schedule)

Phase and Dose Cohort		Drug Name and Dose	Day of 21-day (±3 days) cycle	Total dose	Route and duration of administration	Notes
Dose-Finding Phase	Olara 15 mg/kg	Olaratumab 15 mg/kg[a]	D1 and D8		IV over 60 (±5) min Infusion rate should not exceed 25 mg/min	See Section 7.1.1 for premedication requirements and Section 7.8.1 for IRR monitoring period requirements
		Doxorubicin 25 mg/m^2 per day[a]	D1, D2, D3	75 mg/m^2	IV over less than 60 min or continuous IV infusion (according to institutional practice)	Administer after olara on D1 and after any required observation period
		Ifosfamide 2.5 g/m^2 per day[a]	D1, D2, D3, D4[b]	10[b] g/m^2	IV over 3 hours (±15 min)	Administer after dox on D1, D2, D3
		Mesna dose ≥60% of ifos dose[a]	D1, D2, D3, D4[b]		According to institutional practice	
	Olara Loading Dose Cycle	Olaratumab 20 mg/kg Cycle 1 Olaratumab 15 mg/kg Cycles 2 to 6[a]	D1 and D8 D1 and D8		IV over 60 (±5) min Infusion rate should not exceed 25 mg/min	See Section 7.1.1 for premedication requirements and Section 7.8.1 for IRR monitoring period requirements
		Doxorubicin 25 mg/m^2 per day[a]	D1, D2, D3	75 mg/m^2	IV over less than 60 min or continuous IV infusion (according to institutional practice)	Administer after olara on D1 and after any required observation period
		Ifosfamide 2.5 g/m^2 per day[a]	D1, D2, D3, D4[b]	10[b] g/m^2	IV over 3 hours (±15 min)	Administer after dox on D1, D2, D3
		Mesna dose ≥60% of ifos dose[a]	D1, D2, D3, D4[b]		According to institutional practice	
Dose Confirmation Phase	Recommended Olara Dose	Olaratumab dose determined from Dose-Finding Phase[a]	D1 and D8		IV over 60 (±5) min Infusion rate should not exceed 25 mg/min	See Section 7.1.1 for premedication requirements and Section 7.8.1 for IRR monitoring period requirements
		Doxorubicin 25 mg/m^2 per day[a]	D1, D2, D3	75 mg/m^2	IV over less than 60 min or continuous IV infusion (according to institutional practice)	Administer after olara on D1 and after any required observation period
		Ifosfamide 2.5 g/m^2 per day[a]	D1, D2, D3, D4[b]	10[b] g/m^2	IV over 3 hours (±15 min)	Administer after dox on D1, D2, D3
		Mesna dose ≥60% of ifos dose[a]	D1, D2, D3, D4[b]		According to institutional practice	

Abbreviations: C = cycle; CRP = clinical research physician; D = day; DLT = dose-limiting toxicity; dox = doxorubicin; g = grams; ifos = ifosfamide; IRR= infusion-related reaction; IV = intravenous; kg = kilogram; m^2 = square meters; mg = milligrams; min = minutes; olara = olaratumab.

a All patients will receive study therapy (olaratumab + doxorubicin/ifosfamide/mesna) for a maximum of 6 cycles, or until a discontinuation criterion is met. Patients who discontinue doxorubicin, ifosfamide and mesna treatment without evidence of disease progression will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met.

b If DLT rules (see Section 7.2.2.1) are exceeded in the olaratumab 15-mg/kg cohort, a reduced dose of ifosfamide (7.5 g/m2 total dose) will be explored. This reduced dose will be communicated by the Lilly CRP and will be accomplished by omitting the Day 4 dose (that is, ifosfamide will be administered at a dose of 2.5 g/m2 on D1, D2 and D3). The Day 4 dose of mesna will be correspondingly omitted. A Loading Dose Cycle of olaratumab (20 mg/kg on Days 1 and 8 of C1, then 15 mg/kg on Days 1 and 8 of subsequent cycles) may also be explored in combination with the reduced dose of ifosfamide.

7.1.1. Olaratumab Premedications and Required Monitoring

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

~~All patients will receive the following (or equivalent) premedications~~Premedicate patients prior to administration of olaratumab as below:

- ~~on~~ On Days 1 and 8 of Cycle 1: **Mandatory** administration of a histamine H1 antagonist (for example, diphenhydramine) and dexamethasone ~~IV 30 to 60 min~~ prior to the start of the olaratumab infusion.
- For subsequent cycles, premedication ~~all patients will be premedicated~~with a histamine H1 antagonist (for example, diphenhydramine) ~~IV 30 to 60 min~~ is recommended prior to each dose of olaratumab.

Additional premedication(s) may be provided at the investigator's discretion. Premedication must be provided in the setting of a prior Grade 1 or 2 olaratumab IRR, as detailed in Section 7.8.1. All premedications administered must be adequately documented in the electronic case report form (eCRF).

Patients are required to be monitored for 1 hour after the olaratumab infusion in Cycles 1 and 2 for signs or symptoms of IRRs; see Section 7.8.1 for full description of required olaratumab monitoring period in Cycles 1 and 2. Patients should complete the required monitoring period prior to the start of the doxorubicin administration.

7.2.1. Selection and Timing of Doses

A cycle is defined as an interval of 21 days. In Cycle 2 and beyond, ~~(~~up to 3 days~~²~~ delay of a cycle (that is, Day 1) or Day 8 will be permitted due to holidays, weekends, bad weather, or other unforeseen circumstances and will not count as a protocol deviation~~)~~. In exceptional cases, longer delays may be allowed in later cycles following consultation with Lilly medical representative.

7.2.2. Dose-Finding Phase

7.2.2.1. Dose-Limiting Toxicity Determination

Because of the relatively high rate of DLT-level toxicity with the backbone doxorubicin, ifosfamide and mesna regimen (Judson et al. 2014) and the generally acceptable toxicity profile of the 15-mg/kg dose of olaratumab (Days 1 and 8 every 21 days) in combination with other chemotherapeutic agents including doxorubicin, approximately 15 patients will be enrolled at the first dose level of olaratumab (provided safety data confirms the required number of patients without DLTs have been met for each DLT threshold as described in Table JGDR.7 ~~and evaluated after 6, 9 and 15 patients have received 1 cycle of therapy~~) to allow sufficient patient

numbers to judge initial tolerability of olaratumab in combination with doxorubicin, ifosfamide and mesna.

In the Dose-Finding Phase, DLT assessment will be performed. A DLT is defined as events such as the following, graded according to the NCI-CTCAE Version 4.0, when it occurs within Cycle 1 and is considered to be related to study treatment by the investigator in conjunction with the sponsor:

1. Grade 3 or 4 febrile neutropenia, or sepsis.~~, or~~
2. Grade 4 neutropenia lasting 7 days or longer.
3. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia complicated by hemorrhage.
4. Nonhematologic Grade ≥3 toxicity, except for toxicities (such as nausea, vomiting, transient electrolyte abnormalities, ~~or~~ diarrhea) that can be controlled with optimal medical management within 48 hours or clinically non-significant laboratory abnormalities.

A dose-limiting equivalent toxicity is an AE that meets the DLT criteria as defined above and occurs in any cycle *other than Cycle 1*. In addition to the DLT assessment period in Cycle 1, available safety data beyond Cycle 1 may also be taken into consideration prior to a decision to advance to the next dose level or the determination of the Confirmation Phase dose.

Note: Infusion-related reactions will not be considered as DLTs, as they occur independent of dose level.

Table JGDR.7 shows the DLT thresholds that will be used to determine study progression.

Table JGDR.7. Dose-Limiting Toxicity Thresholds for Study JGDR

Dose Level	Regimen	If…	Then[b]…
Olara 15 mg/kg (Starting Dose Level)	**Olara** 15 mg/kg D1, D8 **Ifos** 10 g/m^2 D1 to D4[a] **Dox** 75 mg/m^2 D1 to D3	6 DLTs in first 6 patients	Proceed to Olara 15 mg/kg with Ifos Reduction Dose Level (new cohort of approximately 15 patients).
		≤5 DLTs in first 6 patients	Enroll 3 additional patients and evaluate DLTs in this group of first 9 patients.
		≤5 DLTs in first 9 patients	Enroll full cohort of 15 patients.
		≥6 DLTs in first 9 patients	Proceed to Olara 15 mg/kg with Ifos Reduction Dose Level (new cohort of approximately 15 patients).
		≥9 DLTs in full 15 patients	Proceed to Olara 15 mg/kg with Ifos Reduction Dose Level (new cohort of approximately 15 patients).
		≤8 DLTs in full 15 patients	Proceed to Olara 20-mg/kg Loading Dose Cycle Dose Level.
Olara 15 mg/kg with Ifos Reduction	**Olara** 15 mg/kg D1, D8 **Ifos** 7.5 g/m^2 D1 to D3[a] **Dox** 75 mg/m^2 D1 to D3	6 DLTs in first 6 patients	Halt study. No further patients enrolled.
		≤5 DLTs in first 6 patients	Enroll 3 additional patients and evaluate DLTs in this group of first 9 patients.
		≤5 DLTs in first 9 patients	Enroll full cohort of 15 patients.
		≥6 DLTs in first 9 patients	Halt study. No further patients enrolled.
		≥9 DLTs in full 15 patients	Halt study. No further patients enrolled.
		≤8 DLTs in full 15 patients	Proceed to Olara 20-mg/kg Loading Dose Cycle Dose Level with Ifos Reduction.
Olara 20-mg/kg Loading Dose Cycle	**Olara** 20 mg/kg D1, D8 of C1; then 15 mg/kg D1, D8 of C2 to C6 **Ifos** 10 g/m^2 D1 to D4[a] **Dox** 75 mg/m^2 D1 to D3	6 DLTs in first 6 patients	Discontinue enrollment into cohort. Proceed to Recommended Dosing Regimen cohort with Olara 15 mg/kg as recommended dose.
		≤5 DLTs in first 6 patients	Enroll 3 additional patients and evaluate DLTs in this group of first 9 patients.
		≤5 DLTs in first 9 patients	Enroll full cohort of 15 patients.
		≥6 DLTs in first 9 patients	Discontinue enrollment into cohort. Proceed to Recommended Dosing Regimen cohort with Olara 15 mg/kg as recommended dose.
		≥9 DLTs in full 15 patients	Discontinue enrollment into cohort. Proceed to Recommended Dosing Regimen cohort with Olara 15 mg/kg as recommended dose.
		≤8 DLTs in full 15 patients	Proceed to Recommended Dosing Regimen cohort with Olara 20-mg/kg Loading Dose Cycle as recommended dose.

Dose Level	Regimen	If…	Then[b] …
Olara 20-mg/kg Loading Dose Cycle with Ifos Reduction	**Olara** 20 mg/kg D1, D8 of C1; then 15 mg/kg D1, D8 of C2 to C6 **Ifos** 7.5 g/m^2 D1 to D3[a] **Dox** 75 mg/m^2 D1 to D3	6 DLTs in first 6 patients	Discontinue enrollment into cohort. Proceed to Recommended Dosing Regimen cohort with Olara 15 mg/kg with Ifos reduction as recommended dose.
		≤5 DLTs in first 6 patients	Enroll 3 additional patients and evaluate DLTs in this group of first 9 patients.
		≤5 DLTs in first 9 patients	Enroll full cohort of 15 patients.
		≥6 DLTs in first 9 patients	Discontinue enrollment into cohort. Proceed to Recommended Dosing Regimen cohort with Olara 15 mg/kg and Ifos 7.5 g/m^2 as recommended doses.
		≥9 DLTs in full 15 patients	Discontinue enrollment into cohort. Proceed to Recommended Dosing Regimen cohort with Olara 15 mg/kg and Ifos 7.5 g/m^2 as recommended doses.
		≤8 DLTs in full 15 patients	Proceed to Recommended Dosing Regimen cohort with Olara 20 mg/kg Loading Dose Cycle and Ifos 7.5 g/m^2 as recommended doses.
Recommended Dosing Regimen	**Olara** dose TBD **Ifos** dose TBD **Dox** 75 mg/m^2 D1 to D3	Enroll 15 patients and treat with Recommended Dosing Regimen.	

Abbreviations: D = day; DLT = patients experiencing a dose-limiting toxicity; dox = doxorubicin; g = grams; Ifos = ifosfamide; kg = kilogram; m^2 = square meters; mg = milligrams; Olara = olaratumab; TBD = to be determined.

[a] With concomitant mesna administration.

[b] If a sufficient number of patients successfully complete the DLT period at a given dose level (ensuring the DLT threshold will not be exceeded), further enrollment may proceed as described in Table JGDR.7, upon agreement of the Sponsor and Investigators.

7.4. Dosage Delays, Discontinuations and Modifications

To begin dosing at Cycle 2 and each ~~cycle(~~Day 1~~)~~ thereafter (for cycles in which olaratumab is administered with doxorubicin and ifosfamide), the following criteria must be fulfilled (see Table JGDR.9 for hematological parameters for dosing olaratumab on Day 8):

- ANC $\geq 1.5 \times 10^3$ cells/µL ($\geq$1500 cells/µL; $\geq 1.5 \times 10^9$/L)
- Platelets $\geq 100 \times 10^3$ cells/µL ($\geq$100,000 cells/µL; $\geq 100 \times 10^9$ cells/L)
- Hemoglobin ≥8.0 g/dL. Note: For study inclusion, hemoglobin ≥9.0 g/dL
- Total bilirubin below ULN. In patients with Gilbert's syndrome, total bilirubin should be <3 mg/dL
- Serum creatinine ≤1.5 times ULN. If creatinine is above ULN, the patient's creatinine clearance is ≥60 mL/min (refer to Appendix 6 for the Cockcroft-Gault formula for creatinine clearance)
- AST and ALT ≤3 × ULN, or ≤5 × ULN if the transaminase elevation is due to liver metastases
- Nonhematologic toxicity must be ~~less than~~Grade ≤2 or must have returned to baseline, unless the toxicity is deemed not clinically significant by the investigator or is a laboratory abnormality that is manageable by institutional standards (for example, low serum potassium, magnesium, or phosphate).

In addition, patients should be monitored for evidence of micro- and/or macroscopic hematuria and treated according to institutional standards.~~the following criteria must be fulfilled on each day of ifosfamide dosing (D1, D2, D3 and D4 of each cycle):~~

~~≤10 red blood cells per high-power field present in urinalysis.~~

7.4.1. Delays

In general, dose delays of 1 study drug (olaratumab, doxorubicin, or ifosfamide/mesna) due to toxicities outlined in Section 7.4.3 will not necessitate delays of the other study drugs. However, close consideration must be made by the investigator to administer all study treatments per the schedule outlined in Section 7.1.

Treatment may be delayed for up to 14 days to allow a patient sufficient time for recovery from study drug-related toxicity. If Day 8 treatment is delayed >7 days, treatment may be resumed with planned Day 1 treatment of the next cycle.

Dosing delay beyond 14 days may be permissible if AEs are not considered to be primarily related to olaratumab and the investigator deems continuation of study treatment to have clinical benefit for the patient. This decision has to be documented and be jointly made by the investigator and the Lilly team.

In the event of unforeseen circumstances or scheduling issues that require adjustments to the schedule, appropriate adjustments or delays to the schedule may be made following discussion between the investigator and the sponsor and written approval by the Lilly medical representative.

7.4.2. Discontinuations

The need to permanently discontinue doxorubicin and/or ifosfamide due to drug-related toxicity should be done according to local standard of care and labels. Criteria for olaratumab discontinuation are discussed in the olaratumab dose modification section (7.4.3.1) and in the olaratumab infusion-related reaction section (7.8.1) ~~The need to permanently discontinue doxorubicin, ifosfamide and mesna due to drug-related toxicity will result in the permanent discontinuation of all study drugs in the doxorubicin, ifosfamide and mesna regimen.~~

Patients whose disease has not progressed at the time of doxorubicin, ifosfamide and mesna discontinuation will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met (Section 8). These patients will continue study assessments as outlined in Table JGDR.2. Patients who undergo surgical tumor resection following study treatment are not eligible to receive olaratumab as monotherapy.

Patients who exhibit disease progression at the time of doxorubicin, ifosfamide and mesna discontinuation will receive post-treatment follow-up assessments as outlined in Table JGDR.3.

7.4.3. Dose Modifications

~~Any patient who requires a dose reduction for drug-related toxicity will continue to receive the reduced dose for the remainder of the study.~~

General guidelines for dose modifications are provided below. Sections 7.4.3.2 and 7.4.3.3 outline guidelines for dose modifications of doxorubicin and ifosfamide, respectively; variations from these guidelines may be allowed according to local standard of care and labels.

7.4.3.1. Olaratumab Dose Modifications

A ~~one-time~~ reduction in the dose of olaratumab will be permitted if the doses of doxorubicin and ifosfamide have been previously reduced ~~once~~ for toxicity, and the same or similar toxicity has recurred despite reduction of doxorubicin, ifosfamide and mesna, and the toxicity is deemed potentially related to the addition of olaratumab in combination with doxorubicin, ifosfamide and mesna. In this scenario, an olaratumab dose reduction should occur in conjunction with a ~~second~~reduction in the doxorubicin and ifosfamide doses according to the guidance outlined in Sections 7.4.3.2 and 7.4.3.3.

A second reduction in the olaratumab dose will not be permitted during treatment with combination therapy of olaratumab plus doxorubicin and ifosfamide.

Patients who have not progressed on study will receive olaratumab as monotherapy following discontinuation of the combination therapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met. Patients receiving olaratumab as monotherapy will have assessments performed as per Table JGDR.2.

Patients who have a dose reduction of olaratumab during the combination therapy portion and then proceeding to receive olaratumab monotherapy after discontinuation of doxorubicin and

ifosfamide combination may have their dose of olaratumab re-escalated to the original dose level at the investigator's discretion.

7.4.3.1.1. Hematologic Toxicity

Table JGDR.8 shows olaratumab dose modifications that should be made for hematologic toxicities judged as potentially related to olaratumab in combination with doxorubicin, ifosfamide and mesna, and that have recurred or failed to improve/resolve despite 1 reduction in doxorubicin and ifosfamide doses. These guidelines should be used for olaratumab dosing, when given in combination with doxorubicin and ifosfamide.

Table JGDR.8. General Guidelines for Olaratumab Dose Modification due to Hematologic Toxicities

Toxicity	~~Required~~ Dose Modification
Neutropenia	
ANC Grades 1-3	No dose modification required
ANC <500 cells/μL (Grade ≥4)	No treatment administered; treatment cycle delayed
At re-treatment: If ≥Grade 3 neutropenic fever/infection has occurred and 1 reduction in doxorubicin, ifosfamide and mesna doses has already occurred	Withhold dose until ANC is ≥1500 cells/μL; • 15-mg/kg Dose Level: Reduce dose to 12 mg/kg • 20-mg/kg Loading Dose Cycle Level: Reduce dose to 15 mg/kg
If Grade 4 neutropenia lasting ≥1 week has occurred and 1 reduction in doxorubicin, ifosfamide and mesna doses has already occurred	Withhold dose until ANC is ≥1500 cells/μL; • 15-mg/kg Dose Level: Reduce dose to 12 mg/kg • 20-mg/kg Loading Dose Cycle Level: Reduce dose to 15 mg/kg
Grade 4 ANC without fever/infection lasting ≤1 week	Administer next olaratumab at full dose, at investigator's discretion
After 1 reduction of olaratumab and 2 reductions of doxorubicin, ifosfamide and mesna, recurrence of either: 1) ≥Grade 3 neutropenic fever/infection 2) Grade 4 neutropenia lasting ≥1 week	Discontinue combination therapy (olaratumab + doxorubicin/ifosfamide/mesna). Patients who have not progressed will receive olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met.

Abbreviation: ANC = absolute neutrophil count.

Omitting the Day 8 dose of olaratumab based on ANC and platelet counts judged as potentially related to olaratumab in combination with doxorubicin, ifosfamide, and mesna is permissible as shown in Table JGDR.9.

7.4.3.2. Doxorubicin Dose Modifications

Dose modifications of doxorubicin will follow the guidelines outlined below and may be adjusted according to local standard of care and label.~~Two reductions in doxorubicin dose will be permitted during the study according to the guidance outlined in Sections 7.4.3.5 and 7.4.3.6. If~~

~~a third dose reduction is necessary, the patient will be discontinued from the combination therapy (olaratumab + doxorubicin/ifosfamide/mesna) and will be followed as outlined in Section 7.4.2.~~

7.4.3.2.1. Hematologic Toxicity

Doxorubicin will not be administered after the initial dose if the patient's ANC is <1500 cells/µL or if the platelet count is <100,000 cells/µL. When necessary, the next treatment cycle should be delayed until the ANC is ≥1500 cells/µL and the platelet count is ≥100,000 cells/µL and any nonhematologic toxicities have resolved. For patients who experience ≥Grade 3 neutropenic fever or infection or Grade 4 neutropenia without fever lasting more than 1 week, doxorubicin should be reduced to 75% of the starting dose (that is, to approximately 60 mg/m^2). If a patient experiences a second incidence of neutropenic fever/infection or has another episode of Grade 4 neutropenia lasting >1 week, then a second dose reduction to 45 mg/m^2 should occur~~will be necessary~~.

7.4.3.3. Ifosfamide Toxicities and Dose Modifications

Dose modifications of ifosfamide will follow the guidelines outlined below and may be adjusted according to local standard of care and label. Two reductions in ifosfamide dose for toxicity will be permitted during the study. If a third dose reduction is necessary, the patient will be discontinued from the combination therapy (olaratumab + doxorubicin/ifosfamide/mesna) and followed as outlined in Section 7.4.2.

General guidelines for ifosfamide dose modification are shown in Table JGDR.12. Dose modifications of ifosfamide due to hepatic impairment are shown in Table JGDR.13.

7.4.3.3.2. Ifosfamide-Associated Urotoxic Effects

The incidence of urotoxic effects without an uroprotector can be up to 40% and is dose dependent; coadministration of mesna and adequate hydration are mandatory in this study. 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 with or without surgical intervention (electrocautery, cryosurgery, diversion of urine flow, hypogastric artery ligation, or cystectomy). ~~Ifosfamide should be discontinued or dose reduced~~Discontinuation or dose reduction of ifosfamide should follow local standard of care and label for patients with macroscopic hematuria.

7.4.3.3.3. Ifosfamide-Associated 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 preexisting renal impairment, concurrent use of nephrotoxic drugs, reduced renal reserve (unilateral nephrectomy), 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 guidelines of ifosfamide due to renal impairment are shown in Table JGDR.14.

7.7. Treatment Compliance

The study medication will be administered only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is ensured.

7.8.6. Other Concomitant Therapies

No other chemotherapy, radiotherapy, immunotherapy, cancer-related hormone therapy, or experimental drugs will be permitted while the patients are on this study. An exception will be made for:

- prostate cancer patients continuing GnRH agonist therapy or breast cancer patients continuing anti-estrogen therapy (for example, an aromatase inhibitor) as long as those therapies have been installed for at least 3 months and are known to have been well tolerated
- bisphosphonate osteoclast inhibitors (for example, zoledronic acid or pamidronate) for treatment of bone metastases will be permitted while patients are on study treatment. The osteoclast inhibitor denosumab is also allowed. Denosumab is a monoclonal antibody and is associated with a risk of hypersensitivity reactions. Therefore, denosumab should not be administered within 3 days of olaratumab administration.
- palliative local treatment (for example, radiotherapy of ≤14 calendar days) in Cycles 2 and beyond following discussions between the investigators and the sponsor (for example, for pain control of a solitary [non-skull] skeletal metastasis) and written approval by the sponsor, as long as the patient has not developed another reason for study discontinuation.

9.1. Efficacy Assessments

9.1.1. Secondary Efficacy Assessments

Tumor assessments will …

The method of tumor assessment used at baseline must be used consistently throughout the study. Radiological ~~scan~~ imaging of the chest~~thorax~~, abdomen and pelvis and other areas, as clinically indicated, is required.

See Section 10.3.1 for definitions of the efficacy endpoints.

10. Statistical Considerations

10.1. Sample Size Determination

The primary objective is to …

Before enrolling the full 15 patients at a given dose level, the study design requires that an initial group of 6 will be enrolled and evaluated for DLTs. If 6 or more patents with DLTs are observed in the first 6 patients, enrollment at the current dose level will be stopped and appropriate dose de-escalation (or trial halt) will occur. Similarly, if 6 or more patients with DLTs are observed in the first 9 patients, enrollment at the current dose level will be stopped and appropriate dose de-escalation (or trial halt) will occur.

Appendix 3. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology - local and central laboratory[a]	
Leukocytes (WBC)	Erythrocytes (RBC)
Neutrophils[b]	Hemoglobin (HGB)
Lymphocytes	Hematocrit (HCT)
Monocytes	Mean corpuscular volume (MCV)
Eosinophils	Mean corpuscular hemoglobin concentration (MCHC)
Basophils	Platelets (PLT)
Coagulation - local laboratory	
Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT)	
International normalized ratio (INR) or prothrombin time (PT)	
Clinical Chemistry - local and central laboratory[a]	
Serum Concentrations of:	
Alanine aminotransferase (ALT)	Cholesterol
Albumin	Creatinine
Alkaline phosphatase	Glucose, random
Aspartate aminotransferase (AST)	Magnesium
Bilirubin, direct	Phosphorous
Bilirubin, total	Potassium
Blood urea nitrogen (BUN) or blood urea	Sodium
Calcium	Uric acid
Urinalysis - local laboratory	
Blood	Protein
Glucose	Specific gravity
Ketones	Urine leukocyte esterase
pH	
Pregnancy Test (for female patients of childbearing potential) - local laboratory	
Serum pregnancy test (screening)	
Serum or Urine pregnancy test (on study)	
Confirmation of Menopause (for female patients of menopausal age) – local laboratory	
Follicle-stimulating hormone (FSH)[c]	

Abbreviation: CRF = case report form.

[a] Treatment decisions will be based on local laboratory results.

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

[c] To be performed at screening only when needed to confirm post-menopausal status; applicable for women who have experienced spontaneous amenorrhea for 6 to 12 months.

Appendix 4. Pharmacokinetic, Biomarker, Pharmacogenetics and Immunogenicity Sampling Schedules

It is essential that the exact infusion start and stop times (actual clock readings) are recorded. The exact time of collection of each venous blood sample will be based on the clock used to record infusion times. It is essential that the PK blood samples not be drawn from the same site as the drug infusion.

Pharmacokinetic, Biomarker, Pharmacogenetic and Immunogenicity Sampling Schedule

Cycle	Day	Dosing	Sampling Time[a]	PK Sampling			Biomarker Sampling		PGx	IG[e,f]
				Olara PK[b,f]	Dox PK[c,l]	Ifos PK[d,l]	Plasma	Tumor Tissue[g]		
Baseline	-							X (mandatory)[g]		
1	1		≤60 min pre-olara	X[h]			X		X[i]	X
		Olara (1 hr)								
			≤5 min post-olara	X						
		Obs (1 hr)								
			60±10 min post-olara	X						
		Dox (<1 hr)[j]								
			≤5 min post-dox		X[j]					
		Ifos (3 hr)								
			≤5 min post-ifos	X		X				
	2	Dox (<1 hr)								
		Ifos (3 hr)								
			≤5 min post-ifos	X		X				
	3	Dox (<1 hr)[j]								
			≤5 min post-dox		X[j]					
		Ifos (3 hr)								
			≤5 min post-ifos			X				
	4	Ifos (3 hr)								
			≤5 min post-ifos	X		X				
	8		≤60 min pre-olara	X[h]			X			X
		Olara (1 hr)								
			≤5 min post-olara	X						
		Obs (1 hr)								
			60±10 min post-olara	X						
			4±0.5 hr post-olara	X						
	10		48±3 hr post-olara	X						
	15		Anytime	X						
2	1		≤60 min pre-olara	X[h]			X			X
		Olara (1 hr)								
			≤5 min post-olara	X						
	8		≤60 min pre-olara	X[h]						
		Olara (1 hr)								
			≤5 min post-olara	X						

3	1		≤60 min pre-olara	X[h]			X			X
		Olara (1 hr)								
			≤5 min post-olara	X						
		Dox (<1 hr)[i]								
			≤5 min post-dox	X	X[j]					
		Ifos (3 hr)								
			≤5 min post-ifos	X		X				
	2	Dox (<1 hr)								
		Ifos (3 hr)								
			≤5 min post-ifos	X[k]		X				
	3	Dox (<1 hr)[i]								
			≤5 min post-dox		X[j]					
		Ifos (3 hr)								
			≤5 min post-ifos			X				
	4	Ifos (3 hr)								
			≤5 min post-ifos	X[k]		X				
	8		≤60 min pre-olara	X[h]						
		Olara (1 hr)								
			≤5 min post-olara	X						
			60±10 min post-olara	X						
			4±0.5 hr post-olara	X						
	10		48±3 hr post-olara	X						
	15		Anytime	X						
4	1		≤60 min pre-olara	X[h]						
5 and then every other cycle	1		≤60 min pre-olara	X[h]						X
Visit 801			Anytime	X			X	X (optional; for patients who undergo surgical tumor resection subsequent to study treatment)		X

Abbreviations: C = cycle; D = day; dox = doxorubicin; hr = hour; ifos = ifosfamide; IG = immunogenicity; min = minute; IRR = infusion-related reaction; obs = observation; olara = olaratumab; PGx = pharmacogenetics; PK = pharmacokinetics.

[a] Post-infusion is defined as after the completion of the infusion.

[b] Samples of approximately 3 mL of whole blood will be drawn without anticoagulant for measurement of olaratumab in serum.

[c] Samples of approximately 2 mL of whole blood will be drawn into plastic tubes with anticoagulant for measurement of ifosfamide in plasma.

[d] Samples of approximately 3 mL of whole blood will be drawn into plastic tubes with anticoagulant for measurement of doxorubicin in plasma.

[e] For the immunogenicity assay, approximately 5 mL of whole blood will be drawn into a serum separator tube without anticoagulant to generate serum samples.

[f] 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 (±3 days) after the IRR.

[g] Patients must have sufficient available material from an archived formalin-fixed paraffin-embedded tumor tissue. If such tissue is not available, a newly obtained core or excisional biopsy of a tumor lesion must be performed.

[h] ~~Pretreatment olaratumab PK samples may be collected up to 60 minutes prior to the olaratumab infusion and must be prior to administering any premedication.~~Pretreatment samples may be collected any time during the day of the clinical visit, prior to the start of the olaratumab infusion and must be taken prior to administering any premedication.

[i] It is highly recommended to draw the PGx sample prior to the first dose of study drug (C1D1); however, it can be collected at a later time point, if necessary.

[j] If doxorubicin is administered as a 24 hour infusion, the doxorubicin PK sample should be collected at the same time as the ifosfamide PK sample (that is, approximately 3 to 4 hours after the start of the doxorubicin infusion).

[k] For patients who have discontinued doxorubicin/ifosfamide early, these samples may be omitted if there is no other reason for the patient to visit the clinic.

[l] Should a patient discontinue doxorubicin or ifosfamide, all subsequent PK samples for the corresponding chemotherapeutic agent can be omitted.

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