Protocol I5B-MC-JGDP(e)

A Phase 1b (Open-Label) / Phase 2 (Randomized, Double-Blinded) Study Evaluating Nab-Paclitaxel and Gemcitabine With or Without Olaratumab in the Treatment of First-Line Metastatic Pancreatic Cancer

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Olaratumab (LY3012207)

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1. Synopsis

Protocol Title:

A Phase 1b (Open-Label) / Phase 2 (Randomized, Double-Blinded) Study Evaluating Nab-Paclitaxel and Gemcitabine With or Without Olaratumab in the First-Line Treatment of Metastatic Pancreatic Cancer

Rationale:

Study I5B-MC-JGDP (JGDP) is designed to evaluate the safety and efficacy of olaratumab in combination with nab-paclitaxel and gemcitabine.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Phase 1b: • to determine a recommended Phase 2 dose of olaratumab in combination with nab-paclitaxel and gemcitabine **Phase 2**: • to compare the efficacy of olaratumab plus nab-paclitaxel and gemcitabine with placebo plus nab-paclitaxel and gemcitabine	**Phase 1b** • DLTs • Safety (including but not limited to) TEAEs, SAEs, and clinical laboratory abnormalities **Phase 2** • OS
Secondary	
Phase 1b • to characterize the safety and toxicity profile of olaratumab plus nab-paclitaxel and gemcitabine • to evaluate the PK and immunogenicity of olaratumab plus nab-paclitaxel and gemcitabine • to document the antitumor activity observed with olaratumab plus nab-paclitaxel and gemcitabine **Phase 2** • to assess time-to-event variables • to document the antitumor activity observed with olaratumab plus nab-paclitaxel and gemcitabine • to assess PROs: pain, HRQoL, and health status • to determine safety and tolerability of olaratumab in combination with nab-paclitaxel and gemcitabine • to assess the PK and immunogenicity of olaratumab plus nab-paclitaxel and gemcitabine	**Phase 1b** • Safety monitoring, including TEAEs, SAE, and deaths • Minimum serum/plasma concentration of olaratumab plus nab-paclitaxel and gemcitabine • OS, PFS, ORR, and DoR **Phase 2** • PFS, DoR • ORR • mBPI-sf, EORTC-QLQ-C30, and EQ-5D-5L • TEAEs, AESI, SAEs, clinical laboratory tests, vital signs, physical examinations, hospitalization, and deaths • Minimum serum/plasma concentration of olaratumab plus nab-paclitaxel and gemcitabine

Abbreviations: AESI = adverse event of special interest; DLT = dose-limiting toxicity; DoR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer HRQoL = Health-related Quality of Life; mBPI-sf = modified brief pain index-short form; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PRO = patient-reported outcomes; SAE = serious adverse events; TEAE = treatment-emergent adverse events.

Overall Design:

Study JGDP is an open-label, multicenter, nonrandomized Phase 1b study of olaratumab in combination with nab-paclitaxel and gemcitabine followed by a randomized, double-blinded, placebo-controlled, Phase 2 study of

olaratumab plus nab-paclitaxel and gemcitabine versus placebo plus nab-paclitaxel and gemcitabine in patients with metastatic (Stage IV) unresectable pancreatic cancer, who have not received prior treatment for metastatic disease.

Number of Patients:

Entered: Approximately 207 (Phase 1b: 27; Phase 2: 180)

Enrolled/Randomized (1:1 randomization [Phase 2 only]): 186 (Phase 1b: 24; Phase 2: 162) Phase 1b: Approximately 24 patients evaluable for dose-limiting toxicities (DLTs). Patients who are not evaluable for DLTs will be replaced.

- Phase 2: approximately 81 patients per treatment arm

Treatment Arms and Duration:

All patients enrolled in this study will receive olaratumab/placebo administered via intravenous (I.V.) infusion in combination with nab-paclitaxel and gemcitabine. After study completion, patients on study treatment who continue to experience clinical benefit and no undue risks, in the opinion of the investigator, may continue to receive study treatment until one of the criteria for discontinuation is met (see Section 8 for details).

Postdiscontinuation Follow-Up Period Assessments

Terms used to describe the postdiscontinuation of study treatment are defined below:

- Postdiscontinuation Follow-Up: begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.
    - The short-term follow-up period begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days.
    - The long-term follow-up period begins 1 day after the short-term follow-up period is completed and continues until death or end of trial.

Continued Access/ Follow-Up

The continued access period will apply to this study as long as 1 patient is still on study treatment when study completion occurs. Lilly will notify investigators when the continued access begins. Continued access follow-up (Visit 901) 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.

Study Schedule of Activities (Section 2) describes all assessments for the postdiscontinuation, continued access, and follow-up periods.

Study Completion and End of Trial

This study will be considered complete following the final analysis/evaluation of OS after approximately 113 events (deaths) have been recorded.

The end of trial occurs after study completion and after the last patient has discontinued from the study for one of the following reasons: death, lost to follow-up, patient or investigator decision to withdraw the patient, or Lilly decision to stop the study. Investigators will continue to follow the study schedule of activities for all patients until notified by Lilly that the end of trial has occurred.

2. Schedule of Activities

Table JGDP.1. Baseline Schedule of Activities

Relative Day Prior to C1D1	≤28	≤7	Instructions
Procedure			
Informed consent	X		ICF must be signed before any protocol-specific procedures are performed.
Physical examination	X		Including height, weight, and vital signs (temperature, blood pressure, pulse rate, and respiration rate)
ECOG performance status	X		(Oken et al. 1982) Refer to Section 6.1
Medical history	X		Including assessment of preexisting conditions, historical illnesses, and substance usage (such as tobacco, alcohol, or caffeine)
Prior and current medication	X		Current medications (including analgesic use) and those received within 30 days prior to study treatment will be recorded after eligibility is confirmed.
AE Collection	X		After consent, collect AEs continuously throughout pretreatment period. See Section 9.2.2
Radiologic imaging and, as applicable, measurement of palpable or visible lesions	X		Perform according to RECIST 1.1 (Eisenhauer et al. 2009). • Spiral CT with contrast or MRI of the abdomen, chest, and pelvis as clinically indicated • On scans available, assess for presence of lung, liver, bone and brain metastases. Radiologic assessments obtained prior to the date of consent may be used if performed within 28 days prior to enrollment.
ECG	X		See Section 9.4.1
Hematology	X		See Appendix 3
Coagulation	X		See Appendix 3 for designation of local or central testing.
Clinical chemistry	X		See Appendix 3 for designation of local or central testing.
Urinalysis	X		See Appendix 3 for designation of local or central testing.
Serum pregnancy test		X	Applies only to women of childbearing potential. See Appendix 3 for designation of local or central testing.

PRO assessment (mBPI-sf) **Phase 2 only**		X	Two baseline assessments will be collected, the first one within 7 days of the first cycle and the second one at Day 1 of the first cycle prior to study treatment administration. Questionnaires should be administered to the patient prior to extensive interaction with site staff. See Section 9.9
Tumor Tissue (archival or newly obtained biopsy)	X		Any time prior to the first infusion. Optional collection for Phase 1b, mandatory collection for Phase 2. See Section 9.8.2

Abbreviations: AE = adverse event; C1D1 = Cycle 1 Day 1; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ICF = informed consent form; mBPI-sf = modified Brief Pain Inventory-short form; PRO = patient-reported outcome; RECIST 1.1 = Response Criteria In Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

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

Day within Cycle (±3 days)	Cycle 1 and beyond				
	D1	D8	D15	D22 (Phase 1b Only)	
Procedure					**Instructions**
Physical examination	X				• Symptom-directed examination • Perform prior to administration of study drug(s). • Including weight, height, and vital signs (temperature, blood pressure, pulse rate, and respiration rate)
Concomitant medication	X	X	X	X[a]	Refer to Section 7.7
AE collection	X	X	X	X[a]	Refer to Section 9.2.2
ECOG performance status	X				Refer to Section 6.1
Radiologic imaging and measurement of palpable or visible lesions	X				• Perform according to RECIST 1.1, by the same method used at baseline, every 8 weeks (±7 days), from the start of study treatment in Phase 1 and from randomization in Phase 2 until radiographic disease progression, death, or study completion, whichever occurs first. (See Section 5.1) • Perform as scheduled, even if study treatment is delayed or omitted. • Spiral CT with contrast or MRI of the abdomen, chest, and pelvis as clinically indicated • At PD, assess scans available for presence of tumor lesions in lung, liver, bone and brain
ECG	X				Cycle 1 only. Perform additional evaluations in the setting of cardiac symptoms and/or at the discretion of the investigator. Refer to Section 9.4.1
Hematology	X	X	X	X[a]	≤3 days prior to administration of study treatment, unless more frequent assessment is clinically indicated. See Appendix 3
Coagulation	X				Perform within ≤3 days prior to administration of study treatment on Day 1 of every other cycle, unless more frequent assessment is clinically indicated. See Appendix 3
Clinical chemistry	X	X	X	X[a]	≤3 days prior to administration of study treatment, unless more frequent assessment is clinically indicated. CA-19.9 collected only on Day 1 of each cycle. See Appendix 3
Pregnancy test	X				Serum or urine pregnany test. Applies only to women of childbearing potential. Perform on Day 1 of each cycle or per local practice (whichever is shorter duration). If the urine pregnancy test performed on Day 1 of the cycle is positive, confirm with a serum pregnancy test (pregnancy test results are not recorded on the eCRF).

Day within Cycle (±3 days)	Cycle 1 and beyond				
	D1	D8	D15	D22 (Phase 1b Only)	
Procedure					**Instructions**
PRO assessments (mBPI-sf; EQ-5D-5L; EORTC QLQ C30) - **Phase 2 only**	X				Questionnaires should be administered to the patient prior to extensive interaction with site staff and must be completed prior to study drug administration in sequential order, at the beginning of the visit prior to other study procedures, with the mBPI-sf presented first, followed by the EORTC QLQ-C30 and continuing with the EQ-5D-5L. See Section 9.9.1
Administer olaratumab	X	X	X		Phase 1b, Cohorts 1 and 2, administered I.V. on Days 1, 8, and 15. Cohorts 3 and 4, administered I.V. on Days 1 and 15. For **Phase 2** portion, olaratumab will be administered on Days 1, 8 and 15. For additional detail, (see Table JGDP.6).
Administer nab-paclitaxel	X	X	X		See Section 7.1
Administer gemcitabine	X	X	X		See Section 7.1
Sample collection for					
Pharmacodynamics/Biomarkers			X		For all sample collection, see Appendix 4.
Pharmacokinetics					
Immunogenicity					
Pharmacogenomics					

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; EQ = EuroQol; IG = immunogenicity; I.V. = intravenous(ly); mBPI-sf = modified Brief Pain Inventory-short form; PD = progressive disease; PG = pharmacogenomics; PK = pharmacokinetics; PRO = patient-reported outcome; RECIST 1.1 = Response Criteria In Solid Tumors Version 1.1.

[a] Activities performed only in the Phase 1b portion of the study. Omit for the Phase 2 portion.

Table JGDP.3. Post-Study-Treatment Follow-Up Schedule of Activities

Procedure	Short-Term Follow-Up[a]	Long-Term Follow-Up[b]	Instructions
Physical examination	X		Including weight, and vital signs (temperature, blood pressure, pulse rate, and respiration rate)
Concomitant medication	X		Refer to Section 7.7
AE collection	X		Refer to Section 9.2.2
ECOG performance status	X		Refer to Section 6.1
Radiologic imaging and measurement of palpable or visible lesions	X	X	**For patients who discontinue study treatment for reasons other than documented radiographic disease progression**, imaging studies and tumor assessments are to be obtained q 8 weeks (±7 days) according to RECIST 1.1 (See Section 5.1), irrespective of treatment cycles as calculated from enrollment in Phase 1b or from randomization for Phase 2, until: • the patient has documented radiographic disease progression, or • study completion, or • start of a new anticancer therapy After the patient has documented disease progression, radiologic tests are no longer required. • Spiral CT with contrast or MRI of the abdomen, chest, and pelvis as clinically indicated • At PD, assess scans available for presence of tumor lesions in lung, liver, bone and brain
ECG	X		See Section 9.4.1
Collection of survival information		X	Perform q 12 weeks (±14 days). Although preferable to collect during a clinic visit, survival information may be collected by contacting the patient or family directly (for example, via telephone).
Collection of post-study-treatment anticancer therapy information	X	X	Perform q 12 weeks (±14 days) for the first 2 years after discontinuation from study treatment and q 6 mo (±14 days) thereafter until death or study completion.
Hematology	X		See Appendix 3
Coagulation	X		See Appendix 3

Procedure	Short-Term Follow-Up[a]	Long-Term Follow-Up[b]	Instructions
Pregnancy test	X		Serum or urine pregnancy test. Applies only to women of childbearing potential. If the urine test is positive, confirm with a serum pregnancy test (pregnancy test results are not recorded on the eCRF). Additional pregnancy tests may be done after short-term follow-up if required by local regulation.
Clinical chemistry	X		See Appendix 3
Urinalysis	X		
PRO assessments (mBPI-sf; EQ-5D-5L; EORTC QLQ C30) **Phase 2 only**	X	X	PROs will be assessed at the short-term follow-up visit and once during the first long-term follow-up visit. Questionnaires should be administered to the patient prior to extensive interaction with site staff and must be completed prior to study drug administration in sequential order, at the beginning of the visit prior to other study procedures, with the mBPI-sf presented first, followed by the EORTC QLQ-C30 and continuing with the EQ-5D-5L. See Section 9.9.1 A written copy of each PRO will be given to the patient at the 30 Days Follow-Up visit with instructions for completion as part of the first long-term follow-up visit. The PROs should be completed in the order described for the short-term follow-up visit. The completed PROs should be placed in an envelope addressed and stamped for return to the study site. If long-term follow-up visit is conducted via a phone call, every effort should be made for the patient to complete the questionnaires during the call, preferably before other study questions are asked. Once completed, the questionnaires should be mailed or returned back to the site as soon as possible.
Sample collection for:	X		For all sample collection, see Appendix 4.
Pharmacodynamics/Biomarkers			
Pharmacokinetics			
Immunogenicity			
Pharmacogenomics			

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Event; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC = European Organisation for Research and Treatment of Cancer; EQ = EuroQol; mBPI-sf = modified Brief Pain Inventory-short form; PD = progressive disease; PRO = patient-reported outcome; q = every; RECIST 1.1 = Response Criteria In Solid Tumors Version 1.1.

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

[b] Long-term follow-up period begins the day after the short-term follow-up period is completed and continues until the patient's death or overall study completion. Follow-up should be attempted at regularly scheduled intervals (q 12 weeks [±14 days]). This follow-up might be conducted via a request to the patient's doctor or by contacting the patient, his/her family by telephone/mail. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent to allow for follow-up.

Table JGDP.4. Continued Access Schedule of Activities

	Study Treatment	Follow-Up[a]	
Visit	**501-5XX**	**901**	
Procedure[b]			**Instructions**
AE collection	X	X	Refer to Section 9.2.2
Pharmacokinetics and Immunogenicity	X	X	Only if a patient experiences an IRR, collect blood samples for PK and IG 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 study drugs	X		

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

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

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

3. Introduction

3.1. Study Rationale

Study I5B-MC-JGDP (JGDP) is a Phase 1b/2 trial designed to evaluate the safety and efficacy of olaratumab in combination with nab-paclitaxel and gemcitabine in patients with unresectable metastatic pancreatic cancer, who had not previously been treated for metastatic disease.

Platelet-derived growth factor receptor (PDGFR)/platelet-derived growth factor (PDGF) signaling has been shown to be an important signaling regulator in epithelial mesenchymal transition in several types of cancer. Platelet-derived growth factor receptor / platelet-derived growth factor signaling has been shown to create an autocrine signaling loop in pancreatic cancer that is an active participant in the formation of desmoplastic reaction as well as the activation of pancreatic stellate cells – hallmarks of pancreatic cancer and important contributors to the pancreatic cancer microenvironment (Mahadevan and Von Hoff 2007). Thus, the use of neutralizing monoclonal antibody specific to human PDGFRα could provide a therapeutic target in metastatic pancreatic cancer.

Across numerous cancers evaluated based on data from The Cancer Genome Atlas (TCGA) research, overexpression of PDGFRα in tumors relative to normal tissue was highest in soft tissue sarcoma (STS) (37.1% overexpression) and pancreatic cancer (41.1% overexpression). Overexpression of PDGFRα ligands (PDGF-A, -B, and -C) was observed in sarcoma relative to normal tissue (PDGF-A 7.6%, PDGF-B 6.7%, and PDGF-C 20%). Though little to no overexpression was observed in pancreatic cancer tumors relative to normal pancreas tissue (PDGF-A 0%, PDGF-B 0%, and PDGF-C 5.4%), expression levels in normal pancreas were notably higher than expression levels in normal soft tissue, suggesting that despite little to no overexpression of PDGF ligands in pancreatic tumors, there are PDGF ligands present and overexpression of PDGFRα demonstrates necessary components for PDGF signaling within the tumor microenvironment.

Tissue array from human pancreatic cancer tumors show that while not directly expressed on the tumor, PDGFRα is expressed in pancreatic cancer tumor stroma (9 of 12 samples) (data in-house). The strong stromal component to pancreatic cancer and the associated PDGFRα staining seen may provide an opportunity to disrupt the tumor growth and support provided by PDGFRα signaling by blocking PDGFRα in pancreatic cancer and its associated tumor stroma (Olaratumab Bioinformatic Study Report 2015).

3.2. Background

3.2.1. Olaratumab

Olaratumab is a recombinant human immunoglobulin G subclass 1 (IgG1)-type monoclonal antibody that binds to PDGFRα. This antibody possesses high affinity binding for PDGFRα and blocks PDGF-AA, -BB, and -CC from binding to the receptor. In addition to blocking ligand-induced cell mitogenesis and receptor autophosphorylation, olaratumab inhibits ligand-induced

phosphorylation of the downstream signaling molecules Akt and mitogen-activated protein kinase (Loizos et al. 2005).

In 2 Phase 1 dose-escalation trials in patients with solid tumors (I5B-IE-JGDC and I5B-IE-JGDF) and in the 2 Phase 2 monotherapy studies (I5B-IE-JGDE [glioblastoma] and I5B-IE-JGDH [GIST]), single-agent olaratumab has consistently been well tolerated, with no dose-limiting toxicities (DLTs) observed up to a dose of 20 mg/kg administered every 2 weeks (q2w) and up to a dose of 16 mg/kg administered weekly for 4 weeks followed by 2 weeks off treatment for observation. Olaratumab has been safely administered in combination with liposomal doxorubicin in Study I5B-MC-JGDA (olaratumab 20 mg/kg q2w) in patients with ovarian cancer, and with paclitaxel/carboplatin in Study I5B-IE-JGDB (olaratumab 15 mg/kg on Days 1 and 8 of a 3-week cycle) in patients with NSCLC. However, certain toxicities, such as neutropenia and infections, were observed at a higher rate for olaratumab plus chemotherapy compared with the chemotherapy alone.

In the randomized, double-blind Phase 2 study (I5B-MC-JGDG [JGDG]) in patients with soft tissue sarcoma (STS), the combination of olaratumab and doxorubicin had an acceptable, monitorable, and manageable safety profile even in light of a significantly higher median cumulative doxorubicin exposure in the olaratumab plus doxorubicin arm. An increase in neutropenia, but not in neutropenic sepsis or febrile neutropenia, has been observed in the olaratumab plus doxorubicin arm compared with doxorubicin alone. A higher rate of some known doxorubicin-induced toxicities, such as, mucositis, nausea/vomiting, and diarrhea, in the olaratumab plus doxorubicin arm was observed; however, these toxicities were readily monitored and manageable and were predominantly Grade $\leq$2 in severity.

The combination of olaratumab and doxorubicin resulted in a statistically significant and clinically meaningful improvement in median overall survival (OS; 11.8-month improvement; hazard ratio [HR] = 0.463, p=0.0003). An improvement in median progression-free survival (PFS) of 2.5 months was observed for olaratumab plus doxorubicin over doxorubicin alone; (stratified HR=0.672, p=0.0615) and the study met the protocol-defined significance level for the primary endpoint. Exposure-response analysis from Study JGDG showed that when trough concentration at the end of the first cycle (C_{min1}) was used as the pharmacokinetic (PK) endpoint, the model predicted an minimum half-maximal effective concentration at the end of the first cycle ($EC_{min1}50$) of approximately 66 µg/mL, which corresponds to the 25th percentile of C_{min1} in the JGDG population. Patients with C_{min1} concentrations below the $EC_{min1}50$ progressed earlier and had shorter OS than patients with C_{min1} above the $EC_{min1}50$.

3.2.2. Pancreatic Cancers

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States (US; ACS 2016). Incidence rates in both sex are highest in North America and Europe and lowest in Asia and Africa (World Cancer Research Fund International [WWW]). In 2016, the number of new cases and deaths of pancreatic cancer in the US for both sexes are estimated to be 53,070 and 41,780, respectively (Siegel et al. 2016). In 2013, there were estimated to be 9,408 new

cases of pancreatic cancer in the United Kingdom (UK) in 2013 and 8817 deaths in 2014 (Cancer Research UK [WWW]).

Pancreatic ductal adenocarcinoma and its variants account for more than 90% of pancreatic malignancies (Tempero et al. 2010). Difficulty in early detection is a significant factor in the overall poor prognosis for patients with pancreatic cancer. At the time of diagnosis, the tumor that is confined to the pancreas is fewer than 10%, and over 50% have distant spread (Howard 1996), limiting the number of patients who are able to seek surgical resection as a treatment option.

Gemcitabine was approved by US Food and Drug Administration in 1996 as treatment for metastatic pancreatic cancer and was the standard of care for first-line metastatic pancreatic patients. Since that time, 2 regimens, FOLFIRINOX (Conroy et al. 2011) and gemcitabine plus nab-paclitaxel (Von Hoff et al. 2011, 2013), have supplanted gemcitabine as the current standard of care for first-line metastatic pancreatic cancer for patients with good performance status (0-1). Nab-paclitaxel in combination with gemcitabine was approved in the US in 2013 and in the European Union (EU) in 2014 for use in patients with metastatic pancreatic cancer.

The high-level results of the randomized Phase 3 clinical trial conducted in 861 patients with metastatic pancreatic cancer, which compared gemcitabine with a combination of gemcitabine and nab-paclitaxel (Von Hoff et al. 2013), demonstrated a median OS of 8.5 months in the gemcitabine plus nab-paclitaxel arm compared with 6.7 months in the gemcitabine alone. The HR for death was 0.72 (95% CI: 0.62 to 0.83; $p < .001$). Other end points, including PFS and response rate (RR), were superior with the combination. Grade ≥ 3 neutropenia occurred in 38% of the patients treated with gemcitabine plus nab-paclitaxel, with 3% of these instances resulting in febrile neutropenia. Twenty-six percent of the patients received growth factors (GFs). Cumulative peripheral neuropathy occurred in 17% of the patients treated with gemcitabine plus nab-paclitaxel, and it was managed with temporary discontinuation of nab-paclitaxel followed by a reduction in dose. Despite available options for the treatment of metastatic pancreatic cancer, there is still a poor prognosis for patients with metastatic disease as evidenced by a 5-year survival rate that is less than 3% (SEER 2016).

3.3. Benefit/Risk Assessment

Olaratumab has demonstrated efficacy in combination with doxorubicin in patients with STS. Pancreatic cancer, like STS, is another highly stromal tumor type and preclinical data has suggested increased PDGFRα levels in malignant pancreatic tissue, suggesting olaratumab may be able to affect PDGFR signaling in pancreatic cancer. Olaratumab has been used in several studies in combination with chemotherapies and has been generally well tolerated, with some increase in hematologic toxicity observed. The current study will evaluate the safety of olaratumab in combination with nab-paclitaxel and gemcitabine. Weekly monitoring of hematologic parameters will be conducted to ensure patient safety during the dose escalation/Phase 1b portion of the study. The Phase 2 randomized portion will evaluate nab-paclitaxel and gemcitabine with or without olaratumab, so all patients will receive standard of care treatment in this study.

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 JGDP.5 shows the objectives and endpoints of the study.

Table JGDP.5. Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1b: • to determine a recommended Phase 2 dose of olaratumab in combination with nab-paclitaxel and gemcitabine **Phase 2**: • to compare the efficacy of olaratumab plus nab-paclitaxel and gemcitabine with placebo plus gemcitabine and nab-paclitaxel	**Phase 1b** • DLTs • Safety (including but not limited to) TEAEs, SAEs, and clinical laboratory abnormalities **Phase 2** • OS
Secondary	
Phase 1b • to characterize the safety and toxicity profile of olaratumab plus nab-paclitaxel and gemcitabine • to evaluate the PK and immunogenicity of olaratumab plus nab-paclitaxel and gemcitabine • to document the antitumor activity observed with olaratumab plus nab-paclitaxel and gemcitabine **Phase 2** • to assess time-to-event variables • to document the antitumor activity observed with olaratumab plus nab-paclitaxel and gemcitabine • to assess the following PROs: • to determine safety and tolerability of olaratumab in combination with nab-paclitaxel and gemcitabine • to assess the PK and immunogenicity of olaratumab plus nab-paclitaxel and gemcitabine	**Phase 1b** • Safety monitoring, including TEAEs, SAE, and deaths • Minimum serum/plasma concentration of olaratumab plus nab-paclitaxel and gemcitabine • Anti-drug antibody concentration • OS, PFS, DoR, ORR **Phase 2** • PFS, DoR • ORR • mBPI-sf, EORTC-QLQ-C30, and EQ-5D-5L • TEAEs, AESIs, SAEs, clinical laboratory tests, vital signs, physical examinations, hospitalizations, and death • Minimum serum/plasma concentration of olaratumab plus nab-paclitaxel and gemcitabine • Anti-drug antibody concentration
Tertiary/Exploratory	
• to characterize tumor tissue and blood biomarkers relevant to study drugs including but not limited to immune cells/immune and tumor microenvironment functioning, mechanism of action of study drugs, cancer-related pathways, and disease state • to assess the relationship between biomarkers and clinical outcomes	• Markers of immune function, tumor microenvironment, drug targets, signaling pathways, and disease status

Abbreviations: AESIs = adverse events of special interest; DLT = dose-limiting toxicity; DoR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; EQ = EuroQol; HRQoL = Health-related Quality of Life; mBPI-sf = modified Brief Pain Inventory - short form; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PRO = patient-reported outcome; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.

5. Study Design

5.1. Overall Design

Study JGDP is Phase 1b/2 trial. The Phase 1b portion of the trial will consist of an open-label, dose-finding study and the Phase 2 portion will be a multicenter, randomized, double-blind, parallel, placebo-controlled study in patients with metastatic unresectable pancreatic cancer (Stage IV), who have not received prior treatment for metastatic disease.

Phase 1b:

The Phase 1b will commence prior to Phase 2. Study cycles will be 28 days in duration.

In the Phase 1b portion of the study, a 3 + 3 dose escalation design will be used to evaluate the safety and tolerability of olaratumab in combination with gemcitabine and nab-paclitaxel in patients with pancreatic cancer and determine a recommended Phase 2 dose of olaratumab.

Three patients will be treated initially at each dose level. If no DLTs occur in a cohort of 3 patients, a new cohort of 3 patients will be treated at the next higher dose level. If 1 of 3 patients at any dose level experiences a DLT, that cohort will be expanded to 6 patients.

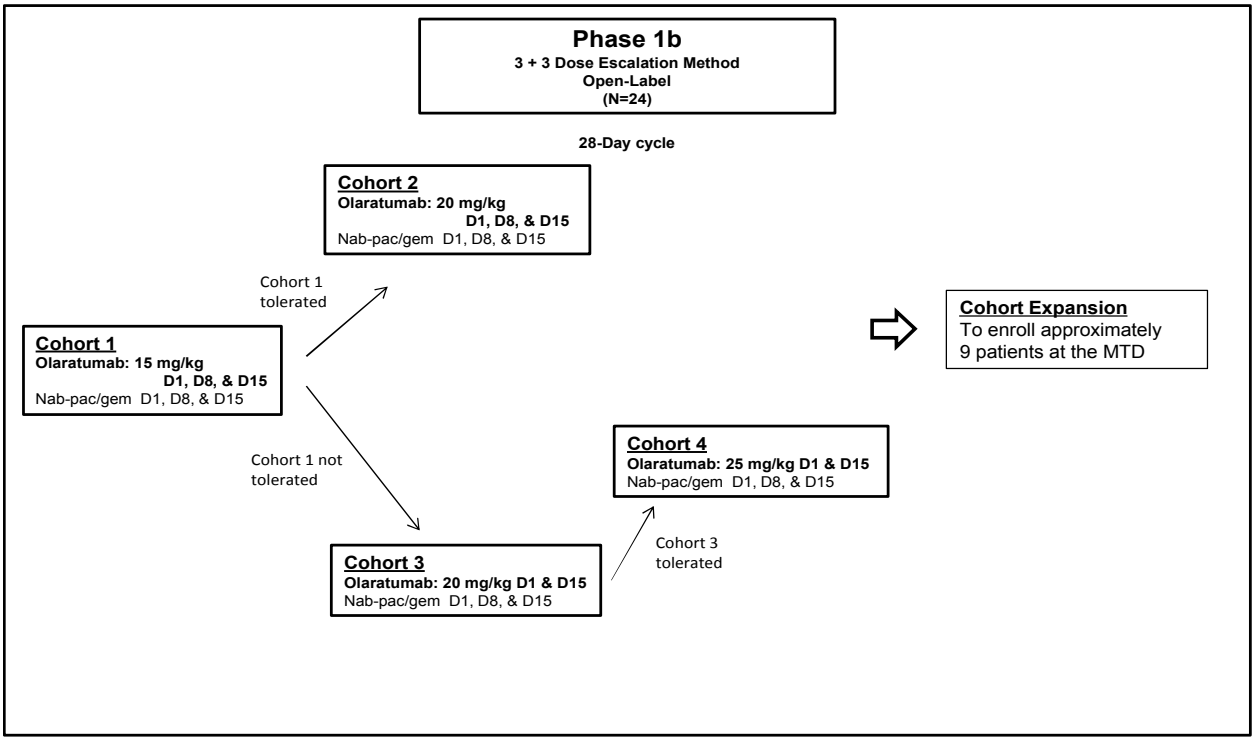
- If no further patient experiences a DLT, the dose escalation can proceed.
- If a DLT is observed in ≥2 out of a maximum of 6 patients at any given dose, dose escalation will cease and the next lower dose will be the maximum tolerated dose (MTD).
- The dose escalation can proceed if fewer than 2 out of 6 evaluable patients experience a DLT.

During the dose escalation, no more than one cohort will be open for enrollment at any given time.

After the MTD has been identified in the dose-escalation phase, approximately 9 patients will be enrolled in a cohort expansion. The purpose of the cohort expansion is to confirm the safety of the MTD in approximately 12 to 15 patients (including those in the dose escalation cohort) prior to proceeding to the Phase 2 portion of the study. Continuous evaluation of toxicity in the cohort expansion will be performed throughout enrolment in the cohort. If the rate of DLT-like events exceeds 33% in the first cycle, the findings will be discussed, and further enrolment may be interrupted. If the expansion cohort is discontinued because of toxicity, a new cohort may be initiated at a previously tested lower dose level.

In the first cohort, olaratumab will be dosed on Days 1, 8, and 15 (that is, on the same days as nab-paclitaxel and gemcitabine dosing as described in their United States Package Insert [USPI] and Summary of Product Characteristics [SmPC]) at a starting dose of 15 mg/kg. If the 15 mg/kg dose of olaratumab is tolerated, enrollment will commence in Cohort 2 at the 20 mg/kg dose of olaratumab dosed on Days 1, 8, and 15. If the 20 mg/kg dose is tolerated, approximately 9 to 12 additional patients will be enrolled in the cohort expansion to confirm the safety and tolerability of the dose.

If the Cohort 1 olaratumab dose of 15 mg/kg on Days 1, 8, and 15 is not tolerated, dosing of olaratumab at 20 mg/kg on Days 1 and 15 may be evaluated (Cohort 3) to determine if decreasing the frequency of olaratumab dosing improves the tolerability of olaratumab in combination with nab-paclitaxel and gemcitabine (see Figure JGDP.1). The dose of 20 mg/kg on Days 1 and 15 will decrease the total dose administered in the cycle from 15 mg/kg dosed on Days 1, 8, and 15 (in Cohort 1) while still providing exposures above the $EC_{min1}50$ (see Section 5.5 for further dose justification). If the 20 mg/kg dose of olaratumab is tolerated, enrollment will commence with planned dose escalation to 25 mg/kg olaratumab on Days 1 and 15 in the subsequent dose cohort (Cohort 4). If neither of the initial dose levels in the Day 1, 8, and 15 dosing schedule (Cohort 1) and the Days 1 and 15 dosing schedule (Cohort 3) are tolerated, enrollment in the study will be stopped.



Abbreviations: D = Day; MTD = maximum tolerated dose.
Note: Approximately 24 patients will be enrolled into the Phase 1b. A 3 + 3 dose-escalation design will be used. It is planned that between 3 to 6 patients will be enrolled at each dose level. After determination of the MTD, a cohort expansion will further evaluate the MTD in approximately 9 additional patients.

Figure JGDP.1. Illustration of study design of Phase 1b.

After determination of the MTD in the dose escalation portion of the study and confirmation of the safety and tolerability of that dose in the cohort expansion, a review of safety data, including the number and type of DLTs, other safety information, and relevant PK, will be conducted prior to proceeding to Phase 2. The decision to proceed to Phase 2 and selection of the recommended Phase 2 dose will be made following discussions between the investigators and Lilly clinical research personnel.

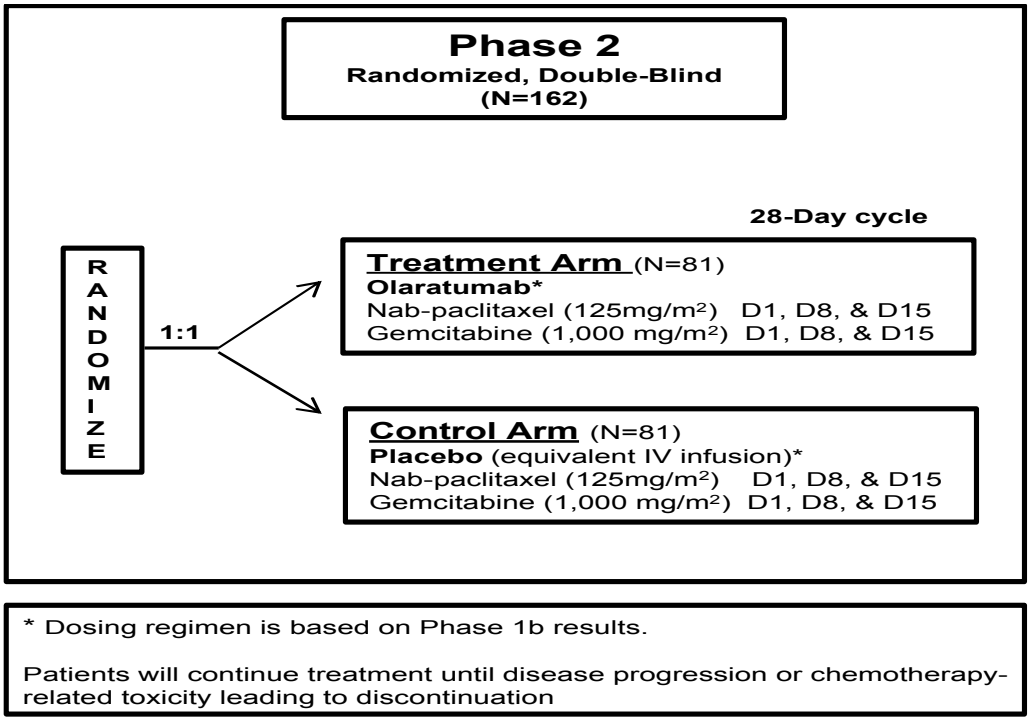
Phase 2:

The Phase 2 portion of the study is a 1:1 randomized, double-blinded, 2-arm study of olaratumab at a dose and schedule determined from Phase 1b in combination with nab-paclitaxel and gemcitabine (Treatment Arm) versus placebo plus nab-paclitaxel-gemcitabine (Control Arm) (see Section 5.4.4). Patients will receive nab-paclitaxel (125 mg/m^2) via infusion followed by gemcitabine (1000 mg/m^2) infusion on Days 1, 8, and 15 of each 28-day cycle. Nab-paclitaxel and gemcitabine will be administered following olaratumab/placebo administration.

Patients will receive the study treatment until disease progression or a criterion for discontinuation is met. The primary end point is OS; secondary end points are PFS, duration of response (DoR), objective response rate (ORR), patient-reported outcomes (PROs), and safety.

Patients will be assessed for tumor response every 8 weeks. Patients without disease progression may continue to receive treatment until the development of unacceptable toxicity, death, or other discontinuation criteria are met.

Figure JGDP.2 illustrates the study design of Phase 2.



Abbreviations: D = Day; IV = intravenous; N = number of patients.
Note: Dose and schedule of olaratumab will be determined based upon tolerability in the Phase 1b portion of the study.

Figure JGDP.2. Illustration of study design of Phase 2.

After study completion, patients on study treatment who continue to experience clinical benefit and no undue risks, in the opinion of the investigator, may continue to receive study treatment (Continued Access period) until one of the criteria for discontinuation is met, as described in

Section 7.8.1. A continued access follow-up visit will occur 30 days (±7 days) after discontinuation.

5.2. Number of Patients

Planned enrollment for each phase is as follows:

Phase 1b: Approximately 24 patients with metastatic pancreatic cancer who have not received chemotherapy for metastatic disease will be evaluated for dose-limiting toxicities (DLTs). Patients who are not evaluable for DLTs will be replaced.

Phase 2: Approximately 162 patients with metastatic pancreatic cancer who have not received chemotherapy for metastatic disease will be randomized in a 1:1 ratio to receive either olaratumab plus nab-paclitaxel and gemcitabine (Treatment Arm) or placebo plus nab-paclitaxel and gemcitabine (Control Arm).

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure for the last patient.

5.4. Scientific Rationale for Study Design

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States (US; ACS 2016). Gemcitabine plus nab-paclitaxel (Von Hoff et al. 2011, 2013) and FOLFIRINOX (Conroy et al. 2011) are the 2 current standard of care regimens for first-line metastatic pancreatic cancer for patients with good performance status (0-1). Despite available options for the treatment of metastatic pancreatic cancer, there is still a poor prognosis for patients with metastatic disease as evidenced by a 5-year survival rate that is less than 3% (SEER 2016).

Pancreatic cancer is characterized by a highly stromal tumor microenvironment that is composed largely of extracellular matrix proteins, fibroblasts, and pancreatic stellate cells. This tumor microenvironment, or desplasmic reaction, has been associated with worse clinical outcomes in pancreatic cancer (Erkan et al. 2008) as well as other tumors (Hasebe et al. 1997). PDGFRα expression has been shown to be upregulated in malignant pancreas relative to normal tissue (Ebert et al. 1995). PDGF/PDGFRα signaling in the microenvironment may contribute to both the growth and maintenance of the dense tumor microenvironment as well as tumor growth.

Tissue microarrays have shown the presence of PDGFRα in the stroma (46.7% of 210 tissues evaluated) of pancreatic cancer in the tissues evaluated (data on file). The link between PDGF and tumor-associated angiogenesis is supported by its expression by tumor cells, and overexpression was found to be correlated with microvascular density and poor survival in a large variety of human cancers, including pancreatic cancer (Fujimoto et al. 1998).

Blocking PDGFRα by the use of olaratumab has been shown effective in another highly stromal tumor type, STS, with recent results showing improvement in OS and PFS. The ability to inhibit PDGFRα signaling in pancreatic cancer may represent an opportunity to disrupt signaling in the tumor microenvironment in a manner that could potentially enhance the antitumor activity

already observed with gemcitabine plus nab-paclitaxel, an established standard of care regimen for the treatment of metastatic pancreatic cancer.

5.4.1. Rationale for Amendment (a)

Amendment (a) updated the Phase 1b design to enroll patients in the Days 1, 8 and 15 cohort first, and begin enrollment in the Days 1 and 15 dosing cohorts if the Days 1, 8 and 15 cohort is not tolerable. In addition, the design was changed to add a cohort expansion to ensure an appropriate number of patients (12 to 15 patients) are evaluated for safety in Phase 1b at the highest tolerated dose.

5.4.2. Rationale for Amendment (b)

Amendment (b) revised the definition of DLT based on Food and Drug Administration (FDA) feedback to include toxicities related to the combination of olaratumab plus gemcitabine and nab-paclitaxel.

5.4.3. Rationale for Amendment (c)

Amendment (c) addresses several requests from FDA including language urging caution when administering nab-paclitaxel with CYP2C8 or CYP3A4 inhibitors or inducers as well as further details regarding the sample size justification.

In addition, this amendment adjusts the study entry criteria-related prior therapies. DLT wordings were clarified to ensure that clinically non-significant AEs are not included in the DLT definition. This amendment describes that a patient's dose may be re-escalated after a dose reduction. The schedule and timing of PROs in the follow-up periods (both long-term and short-term) have been updated. Plans for the Phase 2 interim analysis and the Internal Assessment Committee (IAC) have been updated. In addition, several administrative items have been updated to provide clarity or correct errors.

5.4.4. Rationale for Amendment (d)

Amendment D updates the protocol to include dose and schedule of olaratumab to be administered in the Phase 2 part, based on the results of the Phase 1b part of study JGDP.

In Part 1b of Study JGDP, a total of 22 patients were enrolled and treated with olaratumab plus gemcitabine/nab-paclitaxel as of 31 July 2018. Safety review revealed that the addition of olaratumab to the combination of gemcitabine and nab-paclitaxel in pancreatic patients is safe and tolerable with a monitorable and manageable side-effect profile. Both dose levels of olaratumab (i.e. 15 mg/kg and 20 mg/kg olaratumab [N = 3 and 19 patients, respectively]) were tolerated in combination with gemcitabine/nab-paclitaxel with one DLT reported at the 20 mg/kg olaratumab dose level (Grade 4 neutropenia lasting greater than 7 days). No maximum tolerated dose for olaratumab in combination with gemcitabine/nab-paclitaxel was identified. AEs reported were consistent in nature and within the frequency range expected for chemotherapy with gemcitabine plus nab-paclitaxel or olaratumab therapy. Though the MTD of olaratumab was not reached, a trend towards a higher number of early Grade ≥3 neutropenia and dose reductions in nab-paclitaxel and gemcitabine was noted among patients treated at the 20 mg/kg

dose level relative to the 15 mg/kg olaratumab dose level. Therefore, considering safety and exposure-response analyses across olaratumab studies, the recommended dose for the randomized part of Study JGDP for olaratumab in combination with gemcitabine plus nab-paclitaxel was determined as a 20 mg/kg olaratumab loading dose on Days 1, 8, and 15 in Cycle 1, followed by 15 mg/kg on Days 1, 8, and 15 in Cycles 2-n. This selected Phase 2 dose and schedule of olaratumab aims to maximize patients achieving concentrations above previously identified olaratumab serum levels associated with clinical activity, while also minimizing reductions/omissions of the standard-of-care chemotherapy backbone. This decision was mutually agreed upon following discussions between the sponsor and the Study JGDP Phase 1b investigators.

This amendment also formalizes a change from an IAC (internal assessment committee) to an IDMC (independent data monitoring committee) for the Phase 2 part of the study to enable monitoring of unblinded safety data by the IDMC while maintaining Lilly blinded to safety and efficacy interim data. This change is being made prior to any data being reviewed by the IAC.

In addition, clarifications to the inclusion/exclusion criteria # [1], [3], [5], [9], and [22]; olaratumab premedication; and infusion instructions in alignment with the recent investigators brochure are provided. 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.

5.4.5. Rationale for Amendment (e)

Amendment (e) updates the protocol to include screening criteria for Immunoglobulin E (IgE) antibodies against galactose-α-1-3-galactose (α-gal) and premedication requirements to mitigate the risk for an observed rate of Grade ≥3 infusion-related reactions (IRRs) on Study JGDP that was greater than the rate of 3.1% previously observed across the olaratumab program. Based on data from the Phase 1 and Phase 2 portion of Study JGDP, Grade ≥3 IRRs were observed at an approximate rate between 5% and 10% of olaratumab-treated patients.

Infusion related reactions are a known Adverse Drug Reaction for olaratumab, and the rate of IRR is 12.5% (all grades) and 3.1% (Grade ≥3). Grade ≥3 IRR occur within minutes of first infusion of olaratumab. The risk of anaphylactic reaction is associated with elevated IgE antibody levels. Across 8 studies with olaratumab (401 evaluable olaratumab-treated patients), IgE antibody levels greater than the manufacturer-specified ULN had a positive predictive value of 75% (34.9% - 96.8%) and a negative predictive value of 99% (98.2% - 99.9%) for Grade ≥3 IRRs, with sensitivity of 75% (34.9% - 96.8%) and specificity of 99% (98.2% - 99.9%). Two patients had Grade ≥3 IRR with an IgE antibody level ≤ ULN (0.28 kU/L and <0.10 kU/L, respectively). Prior to this amendment, patients in Study JGDP were tested for pre-existing IgE antibody against α-gal as pre-planned retrospective analysis. However, the results of these tests were not available prior to first dosing of olaratumab/placebo. Pre-testing for elevated IgE antibody levels against α-gal for all untreated patients as part of screening is being implemented as a risk mitigation strategy.

This amendment implements actions to mitigate the risk of increased Grade ≥3 IRRs observed in Study JGDP. Specifically, screening in the Phase 2 portion of the study was modified to include immuniogenicity testing, and the inclusion/exclusion criteria were updated to clarify that patients with IgE anti-α-gal antibody levels greater than the upper limit of normal will be excluded from this study. In addition, the required premedication regimen prior to Cycle 1 Day 1 of olaratumab/placebo was clarified to include: dexamethasone (or steroid equivalent); a histamine H1 antagonistist (for example, diphenhydramine); and a histamine H2 antagonist (for example, ranitidine).

5.5. Justification for Olaratumab Dose

Olaratumab will be initially dosed on Days 1, 8, and 15 to dose olaratumab coinciding with the dosing schedule of the gemcitabine and nab-paclitaxel backbone chemotherapy regimen. In the event the Day 1, 8, and 15 dosing schedule is not tolerated, dosing of olaratumab on Day 1 and 15 may be evaluated to determine if less frequent dosing of olaratumab may improve the feasibility of the combination.

The starting dose level of olaratumab administered on the Day 1, 8, and 15 schedule will be 15 mg/kg (Cohort 1). In monotherapy dose-escalation studies, no DLTs were observed up to olaratumab doses of 20 mg/kg every other week and 16 mg/kg weekly for 4 weeks followed by 2 weeks off treatment for observation.

In prior studies of olaratumab plus chemotherapies (doxorubicin in STS [JGDG], paclitaxel plus carboplatin in non-small cell lung cancer [JGDB], mitoxantrone in prostate cancer [JGDD], and liposomal doxorubicin in ovarian cancer [JGDA]), olaratumab was generally well tolerated with manageable toxicities. Some increase in hematological AEs (such as neutropenia) was noted over chemotherapy alone. In Studies JGDG and JGDA, despite an increase in neutropenia there was no increase in febrile neutropenia upon addition of olaratumab to the respective chemotherapies. In Study JGDB, Grade ≥4 febrile neutropenia was 3.0% on the olaratumab plus paclitaxel/carboplatin arm versus 0% on the paclitaxel/carboplatin arm.

In several ongoing studies, a Cycle 1 loading dose of 20 mg/kg has been safely administered in on Days 1 and 8 of Cycle 1 in combination with doxorubicin. The exposures anticipated from the starting dose of 15 mg/kg on Day 1, 8, and 15 would be anticipated to be similar to those achieved for patients receiving the 20-mg/kg loading dose on Days 1 and 8 of a 3-week cycle. Based upon the increase in hematological AEs observed when olaratumab was administered with previous chemotherapy regimens, it is anticipated that myelosuppression may be a key safety measure in determining the maximum tolerated dose of olaratumab with the combination of gemcitabine plus nab-paclitaxel. Weekly assessment of hematologic parameters will provide close monitoring of this toxicity and aid in determining the safety of this combination.

The second dose level, 20 mg/kg (Cohort 2), provides the opportunity to achieve higher serum concentrations of olaratumab. CCI

CCI [redacted]

In the event that the Day 1, 8, and 15 dosing schedule is not tolerated, an alternate dosing schedule with olaratumab administered on Day 1 and 15 may be explored.

For administration of olaratumab on the Day 1 and 15 schedule, the starting dose is 20 mg/kg (Cohort 3). This dose and schedule of olaratumab has been administered in prior studies (JGDA, in combination with liposomal doxorubicin in patients with ovarian cancer). In addition, a loading dose of 20 mg/kg in Cycle 1 (Days 1 and 8 of a 21-day cycle) has been safely administered in several ongoing studies (JGDJ, JGDI, and JGDK) in combination with doxorubicin. CCI [redacted]

After determination of the MTD in the dose escalation portion of the study and confirmation of the safety and tolerability of that dose in the cohort expansion, a review of safety data, including the number and type of DLTs, other safety information, and relevant PK, will be conducted prior to proceeding to Phase 2. The decision to proceed to Phase 2 and selection of the recommended Phase 2 dose will be made following discussions between the investigators and Lilly clinical research personnel.

6. Study Population

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 definitive histological or cytological diagnosis of adenocarcinoma of the exocrine pancreas that is metastatic (i.e. Stage IV according to AJCC v8) and not amenable to resection with curative intent (Amin et al. 2017). The definitive diagnosis of metastatic pancreatic adenocarcinoma will be made by integrating the histopathological data within the context of the clinical and radiographic data.

Eligible patients must be patients for whom nab-paclitaxel-gemcitabine therapy is considered by the investigator to be an appropriate treatment. Patients with previous radical surgery for pancreatic cancer are eligible after progression is documented.

[2] if present, clinically significant or symptomatic amounts of ascites should be drained prior to Day 1

[3] have sufficient available material from an archived formalin-fixed paraffin-embedded (FFPE) 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 in the Phase 2 portion of the study.

Patients who must undergo a new biopsy that is unsuccessful may not be required to have a second attempted biopsy, after consultation with the Lilly Medical representative.

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

[5] have had no prior systemic treatment for metastatic disease. Prior adjuvant or neo-adjuvant chemotherapy or radiochemotherapy (other than nab-paclitaxel) is allowed, if completed ≥3 months prior to enrollment and no lingering toxicities are present.

[6] prior radiation therapy for treatment of cancer is allowed to <25% of the bone marrow (Cristy and Eckerman 1987). Patients must have recovered from the acute toxic effects of their treatment prior to study enrollment.

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

[8] Patients must have discontinued from previous treatments for cancer (radiotherapy/major surgery, excluding biopsy) ≥4 weeks prior to study treatment.

[9] have adequate organ function, as defined below:

System	Laboratory Value
Hematologic	
ANC	≥1.5 × 10^9/L
Platelets	≥100 × 10^9/L Platelet transfusions to meet eligibility reruirements are not allowed within 2 weeks prior to the baseline hematology profile.
Hemoglobin	≥9 g/dL
	Transfusions to increase the patient's hemoglobin level to 9 g/dL are not permitted **within 2 weeks** prior to the baseline hematology profile.
Hepatic	
Total bilirubin	≤1.5 × ULN
ALT and AST	≤2.5 × ULN OR ≤5 × ULN if the liver has tumor involvement
Renal	
Serum creatinine OR Calculated creatinine clearance (see Appendix 6)	≤1.5 × ULN OR ≥60 mL/min
Coagulation	
INR or PT	Normalized ratio ≤1.5 × ULN or prothrombin time ≤1.5 × ULN
aPTT or PTT	PTT or aPTT ≤1.5 × ULN if not receiving anticoagulation therapy. For patients receiving anticoagulants, exceptions to these coagulation parameters, are allowed if they are within the intended or expected range for their therapeutic use.
For patients receiving anticoagulants, exceptions to these coagulation parameters are allowed if they are within the intended or expected range for their therapeutic use. Patients must have no history of active bleeding (defined as within 14 days of first dose of study drug) or pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known esophageal varices).	

Abbreviations: aPTT = activated partial thromboplastin time; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; PT = prothrombin time; ULN = upper limit of normal.

[10] are at least 18 years old at the time of screening/randomization

[11] If male, the patient is sterile (including vasectomy) or agrees to use an effective method of birth control. Refer to Appendix 1 for definitions of *effective method of contraception* and *highly effective method of contraception*.

[12] If female:

- is not of childbearing potential due to surgical sterilization confirmed by medical history (at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) or menopause
- is of childbearing potential, has a negative serum or urine pregnancy test within 72 hours prior to the first dose of study treatment, agrees to use a highly effective method of birth control during the study and for up to 3 months following the last dose of the study treatment, and is not breastfeeding. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Refer to Appendix 1 for definitions of *effective method of contraception* and *highly effective method of contraception*.

[13] have given written informed consent/assent prior to any study-specific procedures

[14] has a life expectancy of at least 3 months in the opinion of the investigators.

6.2. Exclusion Criteria

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

[15] have received first line treatment for metastatic pancreatic cancer.

[16] have received prior treatment with nab-paclitaxel.

[17] have a serious concomitant systemic disorder (for example, active infection including human immunodeficiency virus, or cardiac disease) or other condition that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol

[18] have known central nervous system (CNS) malignancy or metastasis (screening not required)

[19] have current hematologic malignancies, acute or chronic leukemia

[20] have participated within the last 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.

[21] are women with a positive pregnancy test or who are lactating

[22] have known endocrine pancreatic tumors or ampullary cancer

[23] 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

[24] have known additional malignancy that is progressing or required active treatments within the past 1 year

Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

[25] have known allergy to nab-paclitaxel, gemcitabine, or olaratumab (levels of IgE antibodies against α-gal that are above the upper limit of normal) or any ingredient of olaratumab, nab-paclitaxel, or gemcitabine formulations.

6.3. Lifestyle Restrictions

This section is not applicable.

6.4. Screen Failures

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

Repeating of laboratory tests during the screening period, after a patient has not met requisite criteria, does not constitute re-screening. Screening laboratory tests may not be repeated more than twice in order to meet eligibility during the screening period.

7. Treatments

7.1. Treatments Administered

Table JGDP.6 shows the treatment regimens. The dosing of nab-paclitaxel and gemcitabine will be the same for all cohorts. The dosing of olaratumab will vary based upon cohorts in the Phase 1b. The Phase 2 dose and schedule of olaratumab/placebo has been selected based upon results of the Phase 1b (Section 5.4.4).

Table JGDP.6. Treatment Regimens

Phase	Drug	Route	Dose	Schedule q 28-day cycle	Approximate Infusion Duration
Phase 1b					
Cohorts 1 and 2	Olaratumab[a]	I.V.	15, 20 mg/kg	D1, D8, D15	60 min
	nab-paclitaxel	I.V.	125 mg/m^2	D1, D8, D15	30 - 40 min
	Gemcitabine	I.V.	1000 mg/m^2	D1, D8, D15	30 min
Cohorts 3 and 4	Olaratumab[a]	I.V.	20, 25 mg/kg	D1, D15	60 min
	nab-paclitaxel	I.V.	125 mg/m^2	D1, D8, D15	30 - 40 min
	Gemcitabine	I.V.	1000 mg/m^2	D1, D8, D15	30 min
Phase 2	olaratumab/placebo[a]	I.V.	**Cycle 1:** 20 mg/kg	D1, D8, D15	60 min
		I.V.	**Cycle 2-n:** 15 mg/kg	D1, D8, D15	60 min
	nab-paclitaxel	I.V.	125 mg/m^2	D1, D8, D15	30 - 40 min
	gemcitabine	I.V.	1000 mg/m^2	D1, D8, D15	30 min

Abbreviations: D = day; I.V. = intravenous; q = every.

[a] For mandatory premedication requirements please see Section 7.1.1.

Patients will receive study treatments in the following order: olaratumab followed by nab-paclitaxel followed by gemcitabine. Omission or discontinuation of one component of the regimen may change that sequence, but remaining treatments should still be given in the same relative order.

Olaratumab will be administered as an approximately 60 minute I.V. infusion on Days 1, 8, and 15 of a 28-day cycle at the doses shown in Table JGDP.6. In certain instances, longer infusion times may be allowed; refer to Pharmacy Manual for more information.

Patients are required to be monitored for 1 hour after the olaratumab infusions in the first two treatment cycles for signs or symptoms of IRRs; see Section 7.4.4.3.1 for full description of required olaratumab monitoring period. Patients should complete the required monitoring period prior to the start of any other study treatment (gemcitabine or nab-paclitaxel) administration.

7.1.1. Premedication

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

7.1.1.1. Olaratumab/Placebo

Infusion-related reactions, including Grade ≥3 events, have been observed with olaratumab. To date, all Grade ≥3 IRR events have occurred during the first olaratumab infusion, most of them within 30 minutes from the start of infusion. Symptoms of IRRs have included flushing, shortness of breath, bronchospasm, fever/chills, and in severe cases have manifested as severe hypotension, anaphylactic shock, or cardiac arrest.

The following premedications need to be administered prior to olaratumab/placebo infusions in Study JGDP. Additional premedication may be provided at the investigator's discretion.

- **Premedication in Cycle 1:**
  Premedication is **mandatory** for all patients during Cycle 1 prior to each dose of olaratumab/placebo. Premedicate all patients with the following (or equivalent) medications 30-60 minutes prior to olaratumab/placebo dosing on Days 1, 8, and 15 of Cycle 1:
  - Histamine H1 antagonist (for example, diphenhydramine)
  - Dexamethasone intravenously
  - Histamine H2 antagonist (for example, ranitidine)

- **Premedication in Cycles 2-n:**
  For subsequent cycles, premedication with a histamine H1 antagonist (for example, diphenhydramine) is recommended prior to each dose of olaratumab/placebo.

In case of prior Grade 1 or 2 IRR to olaratumab, premedication is **mandatory** prior to subsequent infusions with olaratumab. After a Grade 1 or 2 IRR, patients should be premedicated with the following (or equivalent) medications prior to all subsequent olaratumab/placebo infusions:

- Histamine H1 antagonist (for example, diphenhydramine)
- Glucocorticoid (for example, dexamethasone) intravenously
- Acetaminophen orally

Treatment guidelines for olaratumab IRRs are described in Table JGDP.7.

Table JGDP.7. 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 to 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 • I.V. 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; I.V. = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

7.1.1.2. Nab-paclitaxel

Premedication to prevent hypersensitivity reactions is generally not needed prior to the administration of nab-paclitaxel. Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported (Abraxane® Prescribing Information 2015). Patients who experience a severe hypersensitivity reaction to nab-paclitaxel should not be re-challenged with it.

7.1.1.3. Gemcitabine

Prophylactic antiemetics may be routinely administered to patients during the course of the study as per the decision of the investigator. Additionally, premedication for gemcitabine may be administered according to institutional guidelines and/or clinical practice.

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

7.1.1.4. Granulocyte-Colony Stimulating Factors

Growth factors and erythropoietin are allowed per American Society of Clinical Oncology or National Comprehensive Cancer Network guidelines. Short-acting G-CSF (for example, filgrastim) should be administered at least 24 hours after the last dose of chemotherapy and must be discontinued at least 24 hours prior to the next dose of chemotherapy. Longer-acting G-CSF (for example, pegfilgrastim) should be given at least 24 hours after the last dose of chemotherapy in the cycle.

Duration of uncomplicated neutropenia before initiation of G-CSF treatment is left to the investigator's discretion. Transfusions are permitted. No other therapy, including routine use of GFs or experimental medications (for example, immunotherapy or other unapproved medication), will be permitted while the patients are on the study.

7.1.2. Investigator Responsibilities

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 study site personnel, the patient, and/or the patient's legal representative
- verifying that instructions are followed properly
- maintaining accurate records of study treatment dispensing and collection
- following the protocol at all times
- at the end of the study, returning all unused medication to Lilly or its designee, unless Lilly and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law
- contacting Lilly clinical research personnel prior to screening a subject to ensure enrollment availability in the Phase 1b. Refer to Section 7.2.1.
- maintaining contact with the Lilly clinical research physician (CRP) to discuss DLTs and potential dose changes due to DLTs

The pharmacy manual contains information about preparation and administration of study treatment. Section 7.1.1 contains information about any required or suggested premedication.

7.1.3. Packaging and Labelling

Olaratumab/placebo, gemcitabine, and nab-Paclitaxel will be provided by Lilly. Olaratumab drug product is supplied in single-use, 50-mL nominal volume, United States Pharmacopeia Type I glass vials. Each vial contains 500 mg of olaratumab at a concentration of 10 mg/mL, in a sterile, preservative-free solution. Each vial is stoppered with a coated butyl rubber latex-free plug stopper and sealed with an aluminum seal and a flip-off cap.

In the event of regional restrictions or supply limitations, commercially available gemcitabine and nab-Paclitaxel may be purchased by study sites. Clinical trial materials will be labeled according to the country's regulatory requirements.

7.1.4. Dose-Limiting Toxicity Determination (Phase 1b)

Myelosuppression is expected with the nab-paclitaxel and gemcitabine regimen and can lead to complications such as fever and neutropenia, sepsis, infection, or bleeding. These adverse events are generally considered DLT-level toxicities and thus can confound DLT determination in the setting of combination with olaratumab. The criteria listed below will be used to determine the dose of olaratumab that can be added to nab-paclitaxel and gemcitabine without causing a significant increase in toxicity over that expected with nab-paclitaxel-gemcitabine alone.

A DLT is defined as events such as the following, graded according to the NCI-CTCAE version 4.03, when the event occurs within Cycle 1, and is considered to be related to olaratumab in combination with nab-paclitaxel plus gemcitabine by the investigator in conjuncture with Lilly:

- Any febrile neutropenia
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia complicated by clinically significant hemorrhage
- Grade 4 neutropenia lasting 7 days or longer
- nonhematologic Grade ≥3 toxicity, except for
  - toxicities such as nausea, vomiting, transient electrolyte abnormalities, diarrhea which can be controlled with optimal medical management within 48 hours;
  - non-clinically significant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, electrolytes, etc.
- Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose-limiting (e.g., any toxicity that is possibly related to the study medication that requires the withdrawal of the patient from the study during Cycle 1).

The MTD is defined as the highest olaratumab dose level at which no more than 33% of patients experience a DLT during Cycle 1.

Phase 1b

In addition to the DLT assessment period in Cycle 1, safety data beyond Cycle 1 may also be taken into consideration prior to a decision to dose escalation or determination of the Phase 2 dose. If both dosing regimens do not exceed DLT criteria, factors such as maintaining dose intensity of the standard of care treatment regimen and PK may be taken into consideration in selecting the dose recommended for use in the Phase 2 portion of the study.

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

7.2. Method of Treatment Assignment

The following treatments will be administered to enrolled patients in this study every 4 weeks (28-day cycle).

The Interactive Web Response System (IWRS), which is web-based and accessible 24 hours a day will be used in both the Phase 1b and Phase 2 portions of the study. 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. Phase 1b

Investigators are required to contact Lilly clinical research personnel prior to screening a patient in Phase 1b. Once enrollment availability is confirmed, sites may proceed with screening of patient and registration into Interactive Web Response System (IWRS), which is web-based and accessible 24 hours a day. No dose escalations (that is, to the next cohort) can occur without prior discussion and agreement with the responsible Lilly CRP or clinical research scientist.

Phase 1b patients will not be eligible to participate in the Phase 2 portion of the study.

7.2.2. Phase 2

Patients who meet all criteria for enrollment will be randomly assigned via IWRS to receive either olaratumab plus nab-paclitaxel and gemcitabine (Treatment Arm) or placebo plus nab-paclitaxel and gemcitabine (Control Arm). Approximately 162 patients will be randomized in a 1:1 ratio.

Randomization will be stratified into 4 groups, one for each combination of the following 2 baseline factors:

- Age group (<70 years versus ≥70 years)
- Prior adjuvant/neo-adjuvant therapy (yes versus no)

Once the patient is registered through the IWRS, he/she is considered to be enrolled in the study. After randomization, patients should receive their first dose of treatment within 72 hours (3 days) whenever possible. Up to 3 additional days delay of first dose of treatment will be permitted due to holidays, weekends, bad weather, or other unforeseen circumstances and will not count as a protocol deviation.

7.2.3. Selection and Timing of Doses

A cycle is defined as an interval of 28 days. A delay of a cycle due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 3 days and not counted as a protocol deviation.

The actual doses of olaratumab administered will be determined by measuring the patient's body weight in kilograms at the beginning of each cycle. If the patient's weight does not fluctuate by more than ±10% from the weight used to calculate the prior dose, the dose will not need to be recalculated. A ±5% variance in the calculated total dose will be allowed for ease of dose administration.

The actual doses of nab-paclitaxel and gemcitabine administered will be determined based on estimation of body surface area (BSA) in m^2 on Day 1 of each 28-day cycle. If the patient's weight does not fluctuate by more than ±10% from the weight used to calculate the prior dose, the BSA will not need to be recalculated, unless deemed clinically meaningful (recalculation

more frequently is allowed per local practice/standard). A ±5% variance in the calculated total dose will be allowed for ease of dose administration.

A patient may continue to receive study treatment until he or she meets one or more of the specified reasons for discontinuation (as described in Section 8).

7.3. Blinding

The Phase 1b portion of this study is open-label.

Phase 2 is a double-blind, placebo-controlled, randomized trial.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is completed.

Upon study completion, investigators may unblind patients to study treatment assignment.

7.3.1. Emergency Unblinding

Phase 2

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

Emergency unblinding for AEs must be performed through the IWRS. All actions resulting in an unblinding event are recorded and reported by the IWRS.

7.3.2. Inadvertent Unblinding

Every effort will be made to blind both the patient and the investigator to the identity of the treatment, but the inadvertent unblinding of a patient may occur. If an investigator, site personnel, or patient is inadvertently unblinded, the unblinding will not be sufficient cause for the patient to be discontinued from study treatment or excluded from study analyses.

Additionally, there may be ethical reasons for the patient to remain on the study treatment. In the event of unblinding, the investigator must obtain specific approval from a Lilly CRP for the patient to continue in the study.

7.4. Dosage Modification

Guidance for dose adjustment, delays, and discontinuation of blinded study drug (olaratuma/placebo), gemcitabine and nab-paclitaxel due to hematological and non-hematological toxicities are presented in Sections 7.4.2, 7.4.3, and 7.4.4, respectively. Gemcitabine and nab-paclitaxel are intended to be administered in accordance with standard-of-care in this study and dose modifications should follow the local labels. Investigators will interpret and document whether or not an AE has a reasonable possibility of being related to each

of the study drugs, taking into account the disease, concomitant treatments, or pathologies, in order to individually adjust study drug(s) doses.

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

- Absolute neutrophil count (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; 100 x 10^9/L)
- Total bilirubin ≤1.5 × upper limit of normal (ULN) for Cycle 1.
  For subsequent cycles, monitor and administer as per standard of care with dose adjustment based on individual tolerance.
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN, or ≤5 × ULN if the transaminase elevation is due to liver metastases
- Nonhematologic toxicity must be CTCAE < Grade 2 or must have returned to baseline, unless the toxicity is deemed not clinically significant by the investigator (such as alopecia) or is a laboratory abnormality that is manageable by institutional standards (such as asymptomatic electrolyte disturbances). Table JGDP.11 provides additional guidance for non-hematological toxicities of peripheral neuropathy, cutaneous toxicity and mucositis or diarrhea.

In the Phase 1b portion of the study, doses of olaratumab and/or nab-paclitaxel or gemcitabine may be delayed, omitted, or reduced if the patient experiences an AE or a DLT-equivalent toxicity.

In the Phase 2 portion, investigators will be blinded to treatment assignment (olaratumab versus placebo) and should adjust dosing of olaratumab/placebo as if all patients are receiving olaratumab.

In the event of an alteration in olaratumab/placebo dose due to an olaratumab/placebo-related toxicity, gemcitabine or nab-paclitaxel need not be altered, and the planned gemcitabine or nab-paclitaxel schedule should be maintained. Similarly, olaratumab/placebo therapy need not be altered for either gemcitabine- or nab-paclitaxel-related toxicity.

Omission or discontinuation of 1 of the study drugs in the combination does not prohibit dosing with other study drugs, provided the patient meets dosing criteria.

In case of difficulty in assigning relatedness to one study drug or the other, the doses of all study drugs may be delayed, reduced, or omitted.

7.4.1. Dosing and Dose Reductions

Given the known adverse profile of the gemcitabine and nab-paclitaxel combination, it is anticipated that bone marrow suppression will be a common reason for dose modification. In the case of toxicity related to myelosuppression and its complications, the relative roles of gemcitabine and nab-paclitaxel are often impossible to separate, and thus it is expected such toxicity would result in dose reductions of both agents. In cases where AEs, in the opinion of the investigator, are more likely due to one drug than another, adjustment of one of the chemotherapy agents and not the other is permissible.

Dose level reductions for nab-paclitaxel and gemcitabine are shown in Table JGDP.8.

Table JGDP.8. Dosing and Dose Reductions for Nab-paclitaxel and Gemcitabine

	Nab-paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Starting Dose	125	1000
1st Dose Reduction	100	800
2nd Dose Reduction	75	600

Table JGDP.9 summarizes dosing and dose reduction for olaratumab.

Table JGDP.9. Dosing and Dose Reductions for Olaratumab

Starting Dose (mg/kg)	**15**	**20**	**25**
1st Dose Reduction (mg/kg)	12	15	20
2nd Dose Reduction (mg/kg)	10	12	15

In the Phase 2 portion, patients will be started on a dose of 20 mg/kg in Cycle 1. In the event a patients toxicity in Cycle 1 requires an olaratumab dose reduction, the patient may start Cycle 2 at the dose of 15 mg/kg olaratumab, provided the toxicity necessitating dose reduction has adaequately resolved.

If a patient at the lowest dose level experiences toxicity that would necessitate additional dose reductions, the patient should discontinue that treatment.

Patients who undergo a dose reduction may be re-escalated at the discretion of the investigator once the toxicity requiring dose reduction has returned to Grade ≤1 or baseline.

In the case of recurrent, persistent toxicity, the investigator should consider permanent dose reduction.

7.4.2. Dose Modifications

7.4.2.1. Hematological Toxicites

General guidelines for dose modifications for hematologic toxicities are shown in Table JGDP.10.

Olaratumab has been safely administered without any DLTs or significant myelosuppressive toxicity in monotherapy studies. In studies with cytotoxic chemotherapies, olaratumab has shown some increase in myelosuppressive toxicities; however, these toxicities are principally driven by the profile of the backbone chemotherapy. In addition, exposure-response analysis of the Study JGDG demonstrated the importance of achieving and maintaining olaratumab serum concentrations in a potentially therapeutic range (see also Section 5.5). For these reasons, hematological toxicity management will focus on dose modification of gemcitabine and nab-paclitaxel per label guidelines, and not by olaratumab dose reductions (Table JGDP.10). In the case of toxicity related to myelosuppression and its complications, the relative roles of

gemcitabine and nab-paclitaxel are often impossible to separate, and thus it is expected such toxicity would result in dose reductions of both agents. In cases in which AEs, in the opinion of the investigator, are more likely due to 1 drug than another, adjustment of 1 of the chemotherapy agents and not the other is permissible. In the case of toxicities deemed potentially related to olaratumab, the investigator may deem it appropriate to reduce or modify olaratumab.

Table JGDP.10. Dose Recommended and Modifications for Neutropenia and/or Thrombocytopenia within a Cycle

Cycle Day	ANC[b] (cells/mm^3)		Platelet Count (cells/mm^3)	nab-Paclitaxel / Gemcitabine Dose	Olaratumab Dose
Day 1	<1500	OR	<100,000	Delay dosing until counts are above indicated level	Delay dosing until counts are above indicated level
Day 8	500 to <1000	OR	50,000 to <75,000	Reduce 1 dose level	Administer, no dose reduction[a]
	<500	OR	<50,000	Withhold doses	Withhold dose
Day 15: if Day 8 doses were reduced or given without modification:					
Day 15	500 to <1000	OR	50,000 to <75,000	Reduce 1 dose level from the dose level administered on Day 8	Administer, no dose reduction[a]
	<500	OR	<50,000	Withhold doses	Withhold dose
Day 15: if Day 8 doses were withheld:					
Day 15	≥1000	OR	≥75,000	Reduce 1 dose level from Day 1 dose	Administer, no dose reduction
	500 to <1000	OR	50,000 to <75,000	Reduce 2 dose levels from Day 1 dose	Administer, no dose reduction
	<500	OR	<50,000	Withhold doses	Withhold dose
Any Day	Febrile neutropenia	-	-	Withhold doses until fever resolves and ANC ≥1500 cell/mm^3; resume dosing with a 1 dose level reduction	

Abbreviations: ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor; Gem = gemcitabine; nab-P = nab-paclitaxel.

[a] At the investigator's discretion.

[b] Note that additional guidance for recommended dose delay/modifications for febrile neutropenia is shown in Table JGDP.11.

7.4.2.2. Non-Hematological Toxicities

Table JGDP.11 shows general guidelines for dose modifications due to non-hematological toxicities of study drugs.

For olaratumab IRRs, see Section 7.4.4.3.1. For IRRs to nab-paclitaxel see Section 7.4.4.2.3.

Table JGDP.11. Guidelines for Dose Modifications due to Non-Hematological Study Drugs-Related Toxicities

Toxicity	Nab-paclitaxel	Gemcitabine	Olaratumab
Peripheral neuropathy Grade ≥3	Withhold until improves to ≤ Grade 1; resume dosing with a 1 dose level reduction from prior dose	No dose reduction	No dose reduction[a]
Cutaneous toxicity Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists		No dose reduction[a]
Grade 3 mucositis or diarrhea	Withhold dosing until improves to ≤ Grade 1; resume at next lower dose level.		Investigator's discretion
Other Non –hematological Toxicity (except IRR to olaratumab)[c]			
Persistent or recurrent Grade 2 not resolved with best supportive care	Investigator discretion		Investigator discretion
Grade 3 or 4	Withhold either one or both drugs as clinically indicated[b]. Then resume treatment at the next lower dose level		Withhold until toxicity is ≤Grade 1 or has returned to pretreatment baseline [a,b]; If toxicity recurs or is Grade 4, treatment may resume at a reduced dose. If toxicity Grade 4 recurs, discontinue olaratumab treatment.

Abbreviation: ANC = absolute neutrophil count.

[a] Dose adjustments are allowed at discretion of investigator for toxicities deemed related to olaratumab/placebo.

[b] Except toxicities that can be adaequately controlled with supportive treatment such as asymptomatic electrolyte disturbances, hyperlipidemia, skin rash, nausea, or vomiting.

[c] Please see also specific discontinuation criteria for olaratumab (Section 7.4.4.3), gemcitabine (Section 7.4.4.1), and nab-paclitaxel (Section 7.4.4.2).

7.4.3. Dose Delays

Treatment may be delayed for up to 28 days to allow a patient sufficient time for recovery from study treatment-related toxicity. If a patient does not recover from the toxicity within 56 days from the time of last treatment, the patient must be discontinued from study treatment unless the investigator, in consultation with the Lilly CRP/CRS, agree that it is in the best interest of the patient to continue treatment.

Delays for nab-paclitaxel due to peripheral neuropathy are allowed to last longer than 28 days for toxicity to resolve (median duration of delay/resolution of AE to Grade ≤1 was 23 days in MPACT study of gemcitabine plus nab-paclitaxel [Von Hoff et al. 2013]). Gemcitabine and olaratumab/placebo should be dosed on the planned schedule during delays for nab-paclitaxel-related peripheral neuropathy.

If one (or more) study drugs will be withheld (omitted), Day 1 will be the day of administration of the first dose of any study drug in that cycle. If one (or more) study drugs will be withheld (omitted), the regular dosing interval for the non-affected study drug(s) should try to be maintained within or between cycles according to the planned treatment schedule (Section 7.1).

In certain instances, adjustments to planned dosing may be allowed upon consultation with the Sponsor (for instance if all study treatment on day 15 needs to be withhold/omitted that week may become the week of rest and the next dose (if counts and chemistries permit) Day 1 of a new cycle).

7.4.4. Dosing Discontinuation

7.4.4.1. Gemcitabine

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

Gemcitabine should be permanently discontinued for any of the following:

- unexplained new or worsening dyspnea or evidence of severe pulmonary toxicity
- severe hepatic toxicity
- Hemolytic Uremic Syndrome or severe renal impairment
- Capillary Leak Syndrome
- posterior reversible encephalopathy syndrome

7.4.4.2. Nab-paclitaxel

7.4.4.2.1. Hepatic Impairment

Exposure and toxicity of paclitaxel can be increased with hepatic impairment or administration of nab-paclitaxel in patients. Do not administer nab-paclitaxel to patients with total bilirubin > 5x ULN and/or AST > 10x ULN.

7.4.4.2.2. Sepsis

Sepsis, with or without neutropenia, has been reported with the use of nab-paclitaxel in combination with gemcitabine. Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis. If a patient becomes febrile (regardless of ANC), initiate treatment with broad-spectrum antibiotics. For febrile neutropenia, interrupt nab-paclitaxel and gemcitabine until fever resolves and ANC ≥ 1500, then resume treatment at reduced dose levels (see Table JGDP.11).

7.4.4.2.3. Pneumonitis

Pneumonitis, including some cases that were fatal, has been reported in patients receiving nab-paclitaxel in combination with gemcitabine. Monitor patients for signs and symptoms of pneumonitis and interrupt nab-paclitaxel and gemcitabine during evaluation of suspected pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with nab-paclitaxel and gemcitabine.

7.4.4.2.4. Infusion-related Reactions/Hypersensitivity Reactions

Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported in patients receiving nab-paclitaxel. Patients who experience a severe hypersensitivity reaction to nab-paclitaxel should not be rechallenged with this drug.

7.4.4.3. Olaratumab

For non-hematological toxicities, refer to Table JGDP.11.

7.4.4.3.1. Olaratumab Infusion-Related Reactions

Olaratumab should be immediately and permanently discontinued for Grade 3 or 4 IRR. For olaratumab IRR treatment guidelines see Table JGDP.7.

Due the observed rate of Grade ≥3 IRRs in the Phase 1 and Phase 2 portions of Study JGDP that was greater than the rate of 3.1% previously observed across the olaratumab program, testing for IgE anti-α-gal antibodies must be performed as part of screening, and patient with antibody levels >ULN should be excluded.

Patients treated with olaratumab (olaratumab/placebo in the Phase 2 portion of the study) should be closely monitored for signs and symptoms indicative of a hypersensitivity/infusion-related reaction 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 or equivalents, etc.) are available. No other study treatment (gemcitabine and/or nab-paclitaxel) should be administered during the observation period (premedications for gemcitabine and/or nab-paclitaxel are allowed to be administered during the observation period).

If there is no evidence of an IRR in the first 2 cycles, no observation period is required for subsequent treatment cycles. In the event that a Grade 1 or 2 IRR occurs after Cycle 2, the 1-hour observation period will be reinstituted for a minimum of 2 cycles. The reinstituted observation period may be suspended after 2 cycles if the patient shows no further signs or symptoms of an IRR. If a patient experiences an IRR, 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 (See Appendix 4 and Section 9.5).

Signs and symptoms of IRRs may vary in different patient populations and include rigors/tremor, back pain/spasms, chills, flushing, dyspnea, pruritus or rash (without urticaria), fever, headache, body aches, abdominal pain, nausea, vomiting, and blurred vision. In severe cases, symptoms have included wheezing, bronchospasm, hypoxia, chest pain and/or tightness, supraventricular tachycardia, hypotension, and paresthesia.

The Lilly medical monitor should be contacted immediately if questions arise concerning the grade of the reaction.

7.5. Preparation/Handling/Storage/Accountability

Refer to the IB or Pharmacy Manual for detailed storage information of olaratumab and gemcitabine. Investigators should consult the approved nab-paclitaxel package insert for complete storage and stability information.

It is the responsibility of the investigator or designee to ensure that a current record of investigational product disposition is maintained at each study site where investigational products are inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

7.6. Treatment Compliance

The study medication, which is administered intravenously, will be administered only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is ensured. The treatment administration data are recorded in the patient's medical record and eCRF.

7.7. Concomitant Therapy

Premedication guidelines are described in Section 7.1.1.

Patients may receive full supportive care therapies concomitantly during the study, including antiemetic treatment as per institutional guidelines. At each visit, appropriate documentation of all forms of premedication, supportive care, and concomitant medications must be captured on the study eCRF.

Concomitant medications and supportive care must also be documented until 30 days after the last dose of investigational product. No other chemotherapy, immunotherapy, radiation therapy, surgery for cancer, or experimental medications will be permitted while the patients are on study treatment or during short-term follow-up period. Any disease progression requiring other forms of specific antitumor therapy will be cause for discontinuation from the study.

7.7.1. Other Concomitant Medication (CYP2C8 and CYP3A4 Inhibitors or Inducers)

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to inhibit (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g., rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A4.

7.7.2. Supportive Care

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

7.7.2.1. Colony Stimulating Factors

Refer to Section 7.1.1.4.

7.7.2.2. Transfusion of Blood Product

Transfusions of red blood cells, platelets, or other blood products are permitted at the investigator's discretion, but may not be used to meet hematologic criteria for inclusion in the study (refer to Section 6.1, Inclusion Criterion [9]).

7.7.2.3. Antiemetic Therapy

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

7.7.3. Prohibited Therapies

Additional concurrent chemotherapy, radiation therapy, biologic response modifiers, or other investigational or approved anticancer agents may not be administered to patients on this study. Palliative radiation or surgery to symptomatic sites of disease will not be permitted while on study.

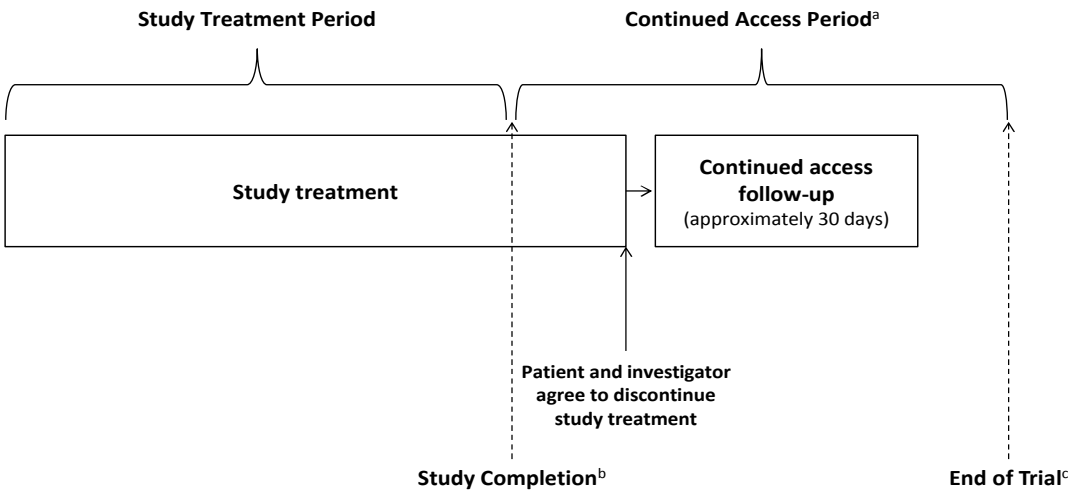
7.8. Treatment after the End of the Study

Study completion will occur when the primary analysis of OS has been completed. Investigators will continue to follow the Schedule of Activities (Section 2) for all patients until notified by Lilly that study completion has occurred.

Refer to Section 7.3 for unblinding that occurs after study completion.

7.8.1. Continued Access

After the final analysis of OS has been conducted, patients who are still on study treatment at the time of study completion may continue to receive study treatment if they are experiencing clinical benefit and no undue risks. Placebo will no longer be administered, and crossover will not be permitted. The continued access period (see Figure JGDP.3) will apply to this study only if at least 1 patient is still on study treatment when study completion occurs. Lilly will notify investigators when the continued access period begins.



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

Figure JGDP.3. Continued access diagram.

The patient's continued access to study treatment 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 study treatment and lasts approximately 30 (±7) days.

Follow-up procedures will be performed as shown in the Continued Access schedule of activities in Table JGDP.4.

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

8.1.1. Discontinuation of All Study Treatment

Patients will be discontinued from **all** study treatment in the following circumstances listed below. The reason for discontinuation and the date of discontinuation will be collected for all patients:

- 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
- disease progression
- 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 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, parents, 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).

8.1.2. Discontinuation of Olaratumab/Placebo

Patients will be discontinued from olaratumab if they experience unacceptable toxicity or experience an AE that would require a dose reduction below the doses listed in Table JGDP.9.

8.1.3. 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 in 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 investigator decides that the patient should be discontinued from the study

- the patient requests to be discontinued from the study
- the patient's designee (for example, parents, legal guardian, or caregiver) requests that the patient 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 documented 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 randomized patients who are lost to follow-up, including randomized 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

Refer to Section 2 for the Schedule of Activities. Appendix 3 provides a list of the laboratory tests that will be performed. 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

Tumor assessments will be performed according to Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST 1.1) for each patient at the times shown in the Schedule of Activities (Section 2). Digital images are to be sent to a third-party organization for storage.

For patients with solid tumors, 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 (MRI) is also acceptable in certain situations and 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 intravenous and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST v.1.1 (Eisenhauer et al. 2009).

Patients will be treated until there is documented radiological PD, toxicity requiring cessation of treatment, withdrawal of consent, or until other withdrawal criteria are met. In the event there is symptomatic deterioration resulting in treatment discontinuation, radiographic confirmation should be performed. For patients who discontinue treatment for any reason other than radiographically documented PD (for example, symptomatic deterioration), radiographic assessments should continue as scheduled every 8 weeks (±7 days) as calculated from randomization until objective radiographic evidence of PD.

The method of tumor assessment used at baseline must be used consistently throughout the study. Radiological scan of the thorax, abdomen, and pelvis is required.

See Section 10.3.1 for definitions of the efficacy endpoints.

9.1.1. 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

9.2.1. Definitions

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A treatment-emergent adverse event (TEAE) is 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.

9.2.2. AE Reporting

The investigator will use NCI-CTCAE version 4.03 (2010) to assign AE terms and severity grades. Documentation should include onset and resolution/stabilization dates, AE grade, seriousness, relationship to study treatment, and outcome of the event. AE reporting will begin after the patient signs the ICF.

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.

Adverse event will be collected until at least 30 days after the last dose of study treatment. After the 30-day short-term follow-up visit, only new and ongoing serious adverse events (SAEs) deemed related to study treatment will be collected.

9.2.3. Serious Adverse Events

An SAE is any AE from this study that results in one 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.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient summary eCRF has been completed). 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 an SAE.

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.

9.2.4. 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.

9.2.5. Adverse Events of Special Interest

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

- Infusion-related reactions (IRRs) to olaratumab. As with other monoclonal antibodies, hypersensitivity reactions (including fatal reactions) have been reported with olaratumab administration.
- IRRs to nab-paclitaxel. Severe and fatal hypersensitivity reactions have been reported with administration of nab-paclitaxel.
- Pneumonitis – Pneumonitis (including fatal cases) has been reported in patient receiving nab-paclitaxel and gemcitabine.

Refer to Section 7.4 for special treatment considerations for dose delays, modifications, and discontinuations from olaratumab/placebo and nab-paclitaxel/gemcitabine, including adverse events of concern or special interest. For olaratumab IRRs, refer to Section 7.4.4.3.1 for instructions on the monitoring and subsequent dosing and premedication adjustments for patients who experience an IRR to olaratumab.

9.2.6. 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

In case of olaratumab overdose, refer to the olaratumab IB. In case of overdose of the other chemotherapeutic agents, refer to the Product Label for the specific agent.

9.4. Safety

9.4.1. Other Safety Measures

For each patient, electrocardiograms (ECGs), vital signs, laboratory tests, or other tests should be collected as shown in the Schedule of Activities (Section 2). ECGs will be collected centrally for patients in the Phase 1 portion of the study and locally for patients in the Phase 2 portion. Refer to JGDP Manual of Operation for ECG storage requirement.

Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high quality records.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified. 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. The Lilly CRP will monitor safety data throughout the course of the study. The Lilly CRP will review trends in safety data, laboratory analytes, and AEs including monitoring of AESIs. Lilly will review SAEs within time frames mandated by company procedures.

A safety review committee (SRC) consisting of the Lilly CRP/CRS, Global Patient Safety (GPS) physician, statistician, the primary investigator, and ad hoc SCR members as needed will be responsible for review of safety data. The SRC will convene to review data at the end of the DLT observation period after Phase 1b is complete prior to initiation of Phase 2.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the Independent Data Monitoring Committee (IDMC) (refer to Section 10.3.5) can conduct additional analyses of the safety data.

During the study, Lilly will perform a blinded review of all reports of deaths and SAEs to ensure completeness and accuracy. If a death or other clinical AE is deemed serious, unexpected, and

possibly related to study treatment, a limited number of Lilly GPS representatives external to the study team will be unblinded for regulatory reporting and safety monitoring purposes. These measures will preserve the integrity of the data collected during this study and minimize any potential for bias while providing for appropriate safety monitoring.

9.4.2.1. Hepatic Monitoring

If a patient experiences elevated ALT ≥5 × ULN and elevated total bilirubin ≥2 × ULN, clinical and laboratory monitoring should be initiated by the investigator.

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

9.5. Pharmacokinetics

Pharmacokinetic samples will be collected as specified in the Pharmacokinetic, Immunogenicity, and Biomarker Research Sampling Schedule (Appendix 4). Based on the time and dates specified in Appendix 4, blood samples will be drawn for all patients for the assessment of olaratumab PK. Serum concentrations of olaratumab obtained at different time points will be summarized by descriptive statistics and noncompartmental analysis. Additional analysis utilizing the population pharmacokinetic approach may also be conducted, if deemed necessary.

At the visits and times specified in Appendix 4, venous blood samples of approximately 3 mL each will be collected to determine the concentrations of olaratumab in serum. A maximum of 5 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 both 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 one or more laboratories designated by Lilly. Serum concentrations of olaratumab will be assayed using a validated enzyme-linked immunosorbent assay method.

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

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

Refer to Section 9.8.

9.7. Genetics

9.7.1. 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 metastatic pancreatic cancer. 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) 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 olaratumab or after olaratumab becomes 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.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics (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 DNA, RNA, proteins, lipids, and other cellular elements.

Samples for biomarker research, described in Section 9.8.2, 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 enrolling 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 in Section 9.8.2.

In addition to the required tumor tissue and biomarker samples discussed below, patients may be asked to undergo collection of an additional biopsy specimen and blood sample after treatment with study drug(s) has been initiated, including potentially after disease progression. Such additional biopsies should be performed only if they do not create undue risk to the patient. If these additional samples are requested, they will be used to further investigate molecular features that may explain treatment response and resistance mechanisms.

9.8.1. 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 the drug targets, disease process, immune cells/immune and tumor microenvironment functioning within the disease state and/or cancer-related conditions, pathway associated with cancer and study drugs, variable response to olaratumab and/or nab-paclitaxel and gemcitabine, 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 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 olaratumab or after olaratumab becomes commercially available.

9.8.2. Tissue Samples for Research

Phase 1b

Collection of the following tumor tissue samples is **optional** for all patients participating in Phase 1b:

- an archived FFPE tumor tissue sample, if not restricted by local regulations and available. Note: if sufficient archival tissue not available, a new biopsy is not required.

Phase 2

Collection of the following tumor tissue samples is **required** for all randomized patients in Phase 2 in order to participate in this study:

- an archived FFPE tumor tissue sample; if such tissue is not available, a newly obtained core or excisional biopsy of a tumor lesion must be performed.

In addition to the required tumor tissue and biomarker samples discussed above, patients may be asked to undergo collection of an additional biopsy specimen and blood sample after treatment with study drug(s) has been initiated, including potentially after disease progression. Such additional biopsies should be performed only if they do not create undue risk to the patient. If

these additional samples are requested, they will be used to further investigate molecular features that may explain treatment response and resistance mechanisms.

Tumor tissue samples will be examined for biomarkers related to disease process, pathways associated with pancreatic cancer and/or cancer-related conditions, immune cells/immune and tumor microenvironment functioning within the disease state and/or cancer-related conditions, mechanism of action of olaratumab and/or gemcitabine, nab-paclitaxel, and/or research methods or in validating diagnostic tools or assay(s) related to cancer. The analysis of these tumor tissue samples may include the assessment of expression of PDGFRα, PDGFRβ, and canonical ligands (PDGFA, B, C, and D).

Formalin-fixed paraffin-embedded tumor tissue obtained from the primary tumor or metastatic site should be provided as a block or unstained slides. Due diligence should be used to make sure that tumor sample (not a normal adjacent or a tumor margin sample) is provided. Pathology report accompanying archival tissue may also be requested. The report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission. Archival blocks will be sectioned and returned to the study site. 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 impose shorter time limits, at a facility selected by Lilly or its designee. 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 olaratumab or after olaratumab becomes 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.

9.8.3. 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 by a validated assay designed to detect anti-drug antibodies in the presence of olaratumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of olaratumab.

When possible, immunogenicity analysis will be done from the same blood drawn for PK analysis. In the event of an olaratumab/placebo infusion reaction, additional blood samples will be collected for additional immunogenicity analysis. These additional samples will be collected as close as possible to the onset of the event, at the point of resolution from the event, and within 30 days after onset of the event.

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

9.9. Patient-Reported Outcomes/Resource Utilization (Phase 2 only)

9.9.1. Patient-Reported Outcomes

In the Phase 2 portion of this study, patient-reported outcome (PRO) for pain will be assessed using the Brief Pain Inventory Short Form, Modified (mBPI-sf; Cleeland 1991). Health-related quality of life will be assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30; Aaronson et al. 1993). Health status will be assessed using the EuroQol 5-Dimension 5-Level (EQ-5D-5L). For the mBPI-sf, 2 baseline assessments will be collected, the first one within 7 days of the first cycle (not on Cycle 1 Day 1) and the second one at Day 1 of the first cycle prior to study treatment administration. For patients who discontinued for reasons other than death or withdrawn consent, PRO data shall be collected at the short-term and first long-term follow-up visits in accordance with the Study Schedule of Activities.

Paper versions of the questionnaires will be used. It is recommended that the instruments be administered together and in sequence order, at the beginning of the visit prior to other study procedures, with the mBPI-sf presented first, followed by the EORTC QLQ-C30 and continuing with the EQ-5D-5L. Whenever possible, if administration is not possible prior to all other procedures, at least every effort should be made to administer at the same time point in each visit. Questionnaires should be administered to the patient prior to extensive interaction with site staff and must be completed prior to study drug administration.

Patient-reported questionnaires should be completed by patients when a language translation is available in which the patient is fluent or literate.

9.9.1.1. Pain assessments

The mBPI-sf is an 11-item instrument used as a multiple-item measure of cancer pain intensity. In addition to pain intensity (4 items), the mBPI-sf is designed for patients to record the presence of pain in general, pain relief, and pain interference with function (general activity, mood, ability to walk, ability to perform normal work, relations with others, sleep, and enjoyment of life). The mBPI-sf is administered per the Schedule of Activities (Section 2). The recall period is the past 24 hours or last week and completion time is typically 5 to 7 minutes.

Responses for the mBPI-sf items are captured through the use of 11-point numeric rating scales anchored at 0 (*no pain* or *does not interfere*) and ranged through 10 (*pain as bad as you can imagine* or *completely interferes*). The focus of the analysis will be on the "worst pain". "Worst pain" intensity has been shown to meaningfully impact patients' lives as indicated by a strong correlation with functional interference scores in various types of cancer (Daut et al. 1983; Serlin et al. 1995; Ger et al. 1999; McMillan et al. 2000; Shi et al. 2009). Moreover, a study by Stone et al. (2004) suggested that patients' tendency to focus on the most severe level of pain

during a recall period may bias average recalled pain. Therefore, the focus of the analysis will be on the "worst pain".

Analgesic use will be recorded on the eCRF. Data on each individual prescription and over-the-counter analgesic medication will be recorded on the Concomitant Medications eCRF, including but not limited to drug name and mode of administration. The use of analgesics should be reviewed with the patient during each visit. Any changes to analgesic use (new or stopped analgesics) will be recorded on the eCRF. Analgesics will be classified into 1 of 6 categories, using an analgesic ladder approach with medication category based on a World Health Organization Pain scale outlined in Table JGDP.12. A therapy category will be assigned according to the maximum category of therapy routinely administered based on analgesic data for that cycle.

For the mBPI-sf, 2 baseline assessments will be collected, the first one within 7 days of the first cycle (not on Cycle 1 Day 1) and the second one at Day 1 of the first cycle prior to study treatment administration. The baseline mBPI-sf score will be calculated as the average of the 2 baseline assessments.

The mBPI-sf population will include all patients who completed the baseline assessment (2 assessments within 7 days of Cycle 1 Day 1) followed by at least 1 mBPI-sf "worst pain" assessment after 1 cycle of study drug (Cycle 2 Day 1 or later).

Table JGDP.12. World Health Organization Pain Scale

Code	Description
0	No analgesia
1	Aspirin (for pain, not cardiovascular prophylaxis), acetaminophen, nonsteroidal anti-inflammatory drugs
2	Codeine, hydrocodone, pentazocine, oxycodone
3	Oral morphine, hydromorphone, methadone, transdermal fentanyl
4	Parenteral opiates
5	Neurosurgical procedures (blocks)

9.9.1.2. EORTC QLQ-30

Broadly used in cancer trials, validated, and available in over 80 different languages, the EORTC QLQ-C30 is a reliable and validated tool. The EORTC QLQ-C30 v3.0 is a self-administered, cancer-specific questionnaire with multidimensional scales. The EORTC QLQ-C30 self-reported general cancer instrument consists of 30 items covered by 1 of 3 dimensions:

- global health status/quality of life (2 items)
- functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning)
- symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact)

The EORTC QLQ-C30 questionnaire is administered per the Schedule of Activities (Section 2). The recall period is the past week, completion time is typically 5 to 7 minutes, and the questionnaire will be scored as described by the EORTC scoring manual (Fayers 2001). The QLQ-C30 population will include all patients who completed the baseline assessment (Cycle 1

Day 1) followed by at least 1 QLQ-C30 assessment after 1 dose of study drug (Cycle 2 Day 1 or later).

9.9.1.3. EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of self-reported health status (Herdman et al. 2011). Specifically, this questionnaire is included in this trial to evaluate health-state utilities associated with metastatic pancreatic cancer. These utility measures are an important input for economic evaluations concerning the value of treatment interventions.

The EQ-5D-5L is designed to be used in conjunction with other patient-reported measures. Patients will complete the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), 5-level (no problem, slight, moderate, severe, or extreme problem) assessment according to the Schedule of Activities (Section 2). A unique EQ-5D health state is defined by combining 1 level from each of the 5 dimensions. Additionally, patients will indicate their current health status by marking on a visual analogue scale ranging from 100 (best imaginable health state) to 0 (worst imaginable health state).

The recall period is "today." The EQ-5D-5L is designed for self-completion taking only a few minutes to complete.

The EQ-5D-5L population will include all patients who completed the baseline assessment (Cycle 1 Day 1) followed by at least 1 EQ-5D-5L assessment after 1 dose of study drug (Cycle 2 Day 1 or later).

EQ-5D-5L responses may be incorporated into cost utility analyses, but will not be included in the clinical study report.

9.9.2. Resource Utilization

Investigators will be asked to document the use of best supportive care (BSC) measures, concomitant medications, transfusions, and treatment-related hospitalization days. Such assessments are to be taken throughout the study through the 30-day short-term postdiscontinuation follow-up visit.

10. Statistical Considerations

10.1. Sample Size Determination

The Phase 1b portion of the study will sequentially evaluate two alternative dosing schedules using a "3 + 3" dose-escalation design. Based upon the design, the Phase 1b portion may enroll up to approximately 24 patients to determine the dose and regimen for olaratumab in combination with nab-paclitaxel and gemcitabine recommended for use in the Phase 2 portion of the study.

The Phase 2 portion of the study will enroll approximately 162 additional patients, randomized in a 1:1 fashion between study arms. The primary analysis of OS will be performed when a minimum of 113 OS events have been observed.

An overall study-wise, two-sided alpha level of 0.20 will be applied to the primary endpoint of OS. One interim safety and efficacy analysis and one final efficacy analysis will be performed. The interim efficacy analysis will occur after 70 OS events, with OS compared between study arms. There will be no formal hypothesis testing or alpha-spending at the interim analysis with respect to efficacy in this study. The purpose of this interim analysis is solely to inform decision-making regarding whether or not to initiate early development of a separate Phase 3 trial.

Assuming the true OS HR is 0.67, there is at least 80% statistical power at a 1-sided significance level of 0.10 (or equivalently a 2-sided significance level of 0.20) to show a statistically significant difference in OS between study arms.

Researchers have reported a median OS of 8.5 months in pancreatic cancer patients receiving gemcitabine plus nab-paclitaxel versus 6.7 months with gemcitabine alone (Von Hoff et al. 2013). If the control arm in the current study performs similarly, the median OS for the experimental arm would be approximately 12 to 13 months, consistent with an HR of 0.67.

Efficacy analysis will be based on intent-to-treat analyses. In addition, the safety analysis requires only 1 dose of study drug to be included, thus patients excluded should be minimal.

10.2. Populations for Analyses

Phase 1b

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.

Safety population: All enrolled patients who receive any quantity of study treatment, regardless of their eligibility for the study, will be included in the safety analysis. Safety evaluation will be performed based on the actual initial therapy a patient has received, regardless of any other cohort to which he or she was assigned.

Biomarker population: will include the subset of patients from the ITT population from whom a valid assay result has been obtained. Samples for biomarker research will be collected at times specified in Appendix 4, where local regulations allow.

Phase 2

Intention-to-Treat (ITT) population: will include all randomized patients who received at least one dose of assigned treatment. The ITT analysis of efficacy data will consider allocation of patients to treatment groups as randomized and not by actual treatment received. This population will be used for all baseline, efficacy, and health economics analyses.

Per-protocol population: will include all randomized patients who receive at least 1 dose of study treatment and do not have any major protocol violations that could potentially affect the efficacy conclusions of the study. This population will be defined in detail in the SAP prior to database lock.

Safety population: will include all randomized patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the first dose of study treatment a patient actually received, regardless of the arm to which he or she was randomized. The safety population will be used for all dosing/exposure, safety, and resource utilization analyses.

Pharmacokinetic population: will include all treated patients who received at least 1 full dose of study treatment and have baseline and at least 1 postbaseline evaluable PK sample.

Biomarker population: will include the subset of patients from the ITT population from whom a valid assay result has been obtained. Samples for biomarker research will be collected at times specified in Appendix 4, where local regulations allow.

10.3. Statistical Analyses

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

Unless otherwise stated, all confidence intervals (CIs) will be reported using a 2-sided 95% level.

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 SAP and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1. Efficacy Analyses

10.3.1.1. Primary Endpoint

Overall Survival

Overall survival is defined as the time from the date of randomization to the date of death from any cause. For each patient, prior to each data analysis, a reasonable effort will be made to obtain the most up-to-date status of the patient (date of death or last date known to be alive). If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive. For any patient who has withdrawn consent for

further follow-up of survival data, OS will be censored at the last date for which the patient consented to be followed for the study.

Overall survival will be compared between treatment arms using a stratified log-rank test, stratified by the randomization strata. The corresponding hazard ratio between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata. Overall survival curves, the median and survival rates at various time points with 95% CI, for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). Sensitivity analyses for OS will be described in the SAP.

10.3.1.2. Secondary Endpoints

Progression-Free Survival

Progression-free survival is defined as the time from randomization until the first radiographic documentation of progression as defined by RECIST (Version 1.1) or death from any cause in the absence of PD. Patients who die without a reported prior progression will be considered to have progressed on the day of their death. Patients who did not progress or are lost to follow-up will be censored at the day of their last radiographic tumor assessment. If no baseline or postbaseline radiologic assessment is available, the patient will be censored at the date of randomization. If death or PD occurs after 2 or more consecutive missing radiographic visits, censoring will occur at the date of the last radiographic visit prior to the missed visits. The use of a new anticancer therapy prior to the occurrence of PD will result in censoring at the date of last radiographic assessment prior to initiation of new therapy.

Progression-free survival will be compared between treatment arms using a stratified log-rank test, stratified by the randomization strata. The corresponding HR between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by randomization strata. Progression-free survival curves, median PFS, and PFS rates at various time points with 95% CI for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). Sensitivity analyses for PFS will be described in the SAP.

Objective Response Rate

Objective response rate is defined as the number of patients who achieve a best overall response of complete response (CR) or partial response (PR) from randomization until PD/recurrence divided by the total number of patients randomized to the corresponding treatment arm (ITT population). Patients who do not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the response rate. The ORR, with 95% CI, will be summarized for each treatment arm and compared between treatment arms using the Cochran-Mantel-Haenszel test adjusting for the randomization strata.

Duration of Response

Duration of response is defined as the time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or objective

progression is observed, per RECIST 1.1 criteria, or the date of death from any cause in the absence of objectively determined disease progression or recurrence.

10.3.2. Safety Analyses

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

The MedDRA Version 19.1 or later will be used when reporting AEs by MedDRA terms. The MedDRA Lower Level Term will be used in the treatment-emergent computation. Treatment-emergent adverse events will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term within SOC.

Phase 2

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- SAEs, including possible relationship to study drug
- AEs leading to dose adjustments
- AESI
- IRR
- discontinuations from study treatment due to AEs or death
- treatment-emergent abnormal changes in laboratory values
- treatment-emergent abnormal changes in vital signs and ECGs

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 entered into the study, enrolled in the study, and treated as well as 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

Demographic data are collected and reported to demonstrate that the study population represents the target patient population considered for regulatory approval.

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

10.3.3.3. Concomitant Therapy

A summary of prior and concomitant medications by treatment arm will be reported.

10.3.3.4. Poststudy-Treatment-Discontinuation Therapy

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

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 treatment arm.

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

10.3.3.6. Pharmacokinetic Analyses

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

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

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

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

10.3.3.7. Patient Reported Outcomes Analyses - Phase 2 only

Patient-reported outcomes are measured through the following:

- mBPI-sf
- EORTC QLQ-C30
- EQ-5D-5L

For each instrument (mBPI-sf, EORTC QLQ-C30, and EQ-5D-5L), percentage compliance will be calculated as the number of completed assessments divided by the number of expected assessments (that is, patients still on study and alive). Percentage compliance and reasons for non-compliance will be summarized by treatment arm and time point.

Data will be separately summarized by treatment and time point using descriptive statistics. The main efficacy measure for the pain endpoint will be the time to first worsening of the mBPI-sf "worst pain" score. Time to first worsening in pain will be described using the method of

Kaplan and Meier and analyzes will be made between the 2 arms by a log-rank test. "Worsening" will be defined as either a "worst pain" increase of ≥2 points postbaseline or an analgesic drug class increase of ≥1 level (Farrar et al. 2001; Rowbotham 2001). However, other approaches to defining clinically meaningful worsening in pain might be considered. Further details will be provided in the SAP.

Additionally, time to first worsening of QLQ-C30 scale scores (see Section 9.9.1.2) will be analyzed using Kaplan-Meier and Cox methods. Further statistical analysis to be performed for PROs will be defined and detailed in the SAP.

The EQ-5D-5L responses may be incorporated into a cost-utility analyses but will not be included in the clinical study report.

10.3.3.8. Biomarker Analyses

The markers in peripheral blood, plasma, serum, and tumor that may indicate pharmacodynamics/tailoring effect of olaratumab or the combination partners may be explored and characterized by appropriate statistics for the association to clinical outcomes or for the characterization by baseline markers.

See Section 9.8 for details regarding biomarker evaluation.

10.3.3.9. Healthcare Resource Utilization

Hospitalizations, transfusions, and concomitant medications during study treatment will be summarized descriptively by treatment arm.

Investigators will be asked to document the use of best supportive care measures, concomitant medications, transfusions, and treatment-related hospitalization days. Such assessments are to be taken throughout the study through the 30-day short-term postdiscontinuation follow-up visit.

10.3.4. Subgroup Analyses

A prespecified list of subgroups will be identified in the SAP. The treatment effect within each subgroup will be summarized. Other subgroup analyses not specified in the SAP may be performed as deemed appropriate. These subgroups will be based on important characteristics, for example, prognostic significance.

10.3.5. Interim Analyses

An interim analysis that includes both safety and efficacy will be conducted. The analysis will occur after at least 70 OS events have been observed among Phase 2 patients. The interim analysis will not be used for purposes of formally testing any efficacy hypotheses.

The results from the interim analyses will be examined by an independent Data Monitoring Committee (iDMC). The membership, roles, and responsibilities of the of the iDMC will be defined in the SAP or iDMC Charter. The iDMC will review unblinded data. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team members until the study has been unblinded.

iDMC safety reviews will be performed for all randomized patients approximately twice per year, with the first such review taking place appoximately 6-10 months after the first patient has randomized. Details as to the process and communication plan will be provided in the iDMC Charter.

Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document. Further interim analysis may be considered after the last patient has been enrolled if deemed appropriate by the Sponsor.

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Appendix 1. Abbreviations and Definitions

Term	Definition
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.
α-gal	galactose-α-1-3-galactose
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the serum concentration time curve
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.
BSA	body surface area
CI	confidence interval
C_{max}	maximum concentration
CIOMS	Council for International Organizations of Medical Sciences
CL	clearance
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, global safety physician, or other medical officer.

CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DMC	data monitoring committee
DoR	duration of response
ECG	electrocardiogram
$EC_{min1}50$	half-maximal effective concentration at the end of the first cycle
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
effective method of contraception	For all countries except Japan, effective method of contraception means male condom with spermicide, female condom with spermicide, diaphragm with spermicide, cervical sponge, or cervical cap with spermicide. For Japan, effective method of contraception means bilateral tubal ligation, male condom with spermicide, intrauterine device that has been in place for at least 3 months before the first dose of study treatment, or an oral contraceptive pill taken for at least 3 months before the first dose of study treatment. Also see the definition of highly effective method of contraception.
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.
EORTC	European Organisation for Research and Treatment of Cancer
ERB	ethical review board
FDA	Food and Drug Administration
GCP	good clinical practice
G-CSF	granulocyte-colony stimulating factor
GF	growth factor
GPS	Global Patient Safety

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 A highly effective method of contraception is defined as one that results in a low failure rate (that is, <1% incidence of pregnancy per year) when used consistently and correctly, such as contraceptive implants, injectables, combined oral estrogen or progestogen-only contraceptives associated with inhibition of ovulation, some intrauterine contraceptive devices (IUDs), total abstinence, or a vasectomized partner. For patients using a hormonal contraceptive method, information regarding the study drugs under evaluation and their potential effect on the contraceptive should be addressed. Abstinence as a method of birth control is acceptable if it is the established and preferred method of contraception for the patient. Also see the definition of effective method of contraception.
HR	hazard ratio
IAC	Internal Assessment Committee
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference for Harmonisation
IgE	Immunoglobulin E
IgG1	immunoglobulin G subclass 1
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
ITT	intention-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
I.V.	intravenous(ly)
IVRS/IWRS	interactive voice-response system/interactive web-response system

MedDRA	Medical Dictionary for Regulatory Activities
mBPI-sf	Brief Pain Inventory Short Form Modified
Menopause	include women with either: (1) 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, GnRH, antiestrogens, selective estrogen receptor modulators, or chemotherapy), or (2) spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone level >40mIU/mL.
MTD	maximum tolerated dose. MTD is the highest dose of a drug or treatment that does not cause unacceptable side effects.
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDGF	platelet-derived growth factor
PDGFRα	platelet-derived growth factor receptor alpha
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
Randomize	the process of assigning patients to an experimental group on a random basis
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
SAP	Statistical Analysis Plan

Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
screen failure	Patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SOC	system organ class
SRC	Safety Review Committee
STS	soft tissue sarcoma
SUSARs	Suspected unexpected serious adverse reactions
$t_{1/2}$	half-life
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.
US	United States
V_{ss}	steady-state volume of distribution

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, where permitted by local law or regulation 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 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, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

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

- the current IB or package labeling, Patient Information Leaflet, Package Insert, or Summary of Product Characteristics 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 (CIOMS) 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

Physicians with a specialty 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.

The Lilly 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 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.

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

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

Study and Site Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB 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

All laboratory screening evaluations are to be performed within 28 days prior to enrollment/randomization, unless otherwise specified. Eligibility for inclusion in this clinical trial will be based on local clinical laboratory results (not transcribed onto eCRFs); duplicate samples will be submitted to the central laboratory where indicated below. For patient and study site convenience and safety, treatment decisions may be based upon results of tests performed locally. Discrepancies between local and central laboratory that may have an impact on eligibility or treatment decisions will not be considered protocol deviations. On-study clinical laboratory tests assayed for patient safety (such as hematology, serum chemistry, coagulation, and pregnancy tests) are to be collected prior to study treatment.

Clinical Laboratory Tests

Hematology[a]	
Leukocytes (WBC)	Erythrocytes (RBC)
Neutrophils, segmented and band forms	Hemoglobin
Lymphocytes	Hematocrit
Monocytes	Mean corpuscular volume (MCV)
Eosinophils	Mean corpuscular hemoglobin concentration (MCHC)
Basophils	Platelets
Coagulation[c]	
aPTT or PTT	
INR or PT	
Clinical Chemistry[a]	
Serum Concentrations of:	
Alanine aminotransferase (ALT)	Cholesterol
Albumin	Creatine kinase (CK)
Alkaline phosphatase	Creatinine
Aspartate aminotransferase (AST)	Glucose random, nonfasting
Bilirubin, direct	Magnesium
Bilirubin, total	Potassium
Blood urea nitrogen (BUN)	Sodium
Calcium	Uric acid
CA-19.9[c,e]	
Urinalysis[c]	
Blood	Protein
Glucose	Specific gravity
Ketones	Urine leukocyte esterase
pH	
Pregnancy Test[c]	
Serum pregnancy test (females only)[b]	
Urine pregnancy test[c,d]	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase ; BUN = blood urea nitrogen; CA19.9 = cancer antigen 19.9; INR = International normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cells; WBC = white blood cells.

[a] Tests performed at local laboratories for patient enrollment/management/safety must submit duplicate samples for testing at a Lilly-designated laboratory.

[b] Serum pregnancy test will be performed at screening on women of childbearing potential. If the baseline serum test is positive, a repeat serum and urine pregnancy test will be done; if those results are positive, the investigator is to consult with the Lilly clinical research physician or scientist regarding if dosing should occur and which follow-up laboratory tests are performed.

[c] Local or investigator-designated laboratory.

[d] While on-study, urine pregnancy test will be performed in females of childbearing potential only on Day 1 of every cycle or per local practice (whichever is of shorter duration) and at short-term follow-up visit. If the urine pregnancy test performed on Day 1 of each cycle is positive, confirm with a serum pregnancy test.

[e] CA-19.9 will be collected on Day 1 of each cycle.

Appendix 4. Pharmacokinetic, Immunogenicity, and Biomarker Research Sampling Schedule

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 pharmacokinetic blood samples not be withdrawn from the same site as the drug infusion.

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

Pharmacokinetic, Immunogenicity, and Biomarker Research Sampling Schedule – Phase 1b (Cohorts 1 and 2)

Cycle	Day	Dosing	Sampling Time	Olaratumab PK[a, c]	Plasma for Biomarkers	Whole Blood for PGx [e]	IG[b, c]
Screening	**0-28**						**X**
1	1		Prior to olaratumab[d]	X	X	X	
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab	X			
		Observation (1 hr)					
			60 ± 10 min post-olaratumab	X			
			4 ± 0.4 hr post-olaratumab	X			
	2		24 ± 3 hr post-olaratumab	X			
	5		Anytime	X			
	8		Prior to olaratumab[d]	X	X		
		Olaratumab (1 hr)					
			≤ 5 min post-infusion	X			
	15		Prior to olaratumab[d]	X	X		X
		Olaratumab (1 hr)					
			≤ 5 min post-infusion	X			
		Observation (1 hr)					
			60 ± 10 min post-olaratumab	X			
		nab-Paclitaxel (0.5 hr)					
			2 ± 0.25 hr post-nab-paclitaxel	X			
	16		24 ± 3 hr post-olaratumab	X			
	19		Anytime	X			
	22		Anytime	X			
2	1		Prior to olaratumab[d]	X	X		X
		Olaratumab (1 hr)					
	8		Prior to olaratumab[d]	X			
		Olaratumab (1 hr)					
	15		Prior to olaratumab[d]	X			
		Olaratumab (1 hr					
			≤ 5 min post-infusion	X			
3	1		Prior to olaratumab[d]	X	X		X
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab	X			
			60 ± 10 min post-olaratumab	X			
			4 ± 0.4 hr post-olaratumab	X			
	2		24 ± 3 hr post-olaratumab	X			
	5		Anytime	X			
	8		Prior to olaratumab[d]	X			
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab	X			
	15		Prior to olaratumab[d]	X			
		Olaratumab (1 hr)					
			≤ 5 min post-infusion	X			
			60 ± 10 min post-olaratumab	X			
			4 ± 0.4 hr post-olaratumab	X			
	16		24 ± 3 hr post-olaratumab	X			
	17		Anytime	X			
	19		Anytime	X			
4	1		Prior to olaratumab[d]	X			
5 and then every other cycle	1		Prior to olaratumab[d]	X			X
30-day follow-up visit			Anytime	X	X		X

Abbreviations: IG = immunogenicity; IRR = infusion-related reaction; PK = pharmacokinetic.

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

[b] For the immunogenicity assay for IgE anti-α-gal antibody screening, approx. 10 mL of whole blood will be drawn.

[c] If a patient experiences an IRR to olaratumab/placebo, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days (±3 days) after the IRR.

[d] 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.

Pharmacokinetic, Immunogenicity, and Biomarker Research Sampling Schedule – Phase 2

Cycle	Day	Dosing	Sampling Time	Olaratumab PK[a, c]	Plasma for Biomarkers	Whole Blood for PGx [e]	IG[b, c]
Screening	**0-28** [f]						**X**
1	1		Prior to olaratumab/placebo[d]	X	X	X	
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
	8		Prior to olaratumab/placebo[d]	X	X		
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
	15		Prior to olaratumab dose/placebo[d]	X	X		X
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
		nab-Paclitaxel (1 hr)					
			≤ 5 min. post-nab-paclitaxel	X			
2	1		Prior to olaratumab/placebo[d]	X	X		X
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
	8		Prior to olaratumab/placebo[d]	X			
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
	15		Prior to olaratumab/placebo[d]	X			
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
3	1		Prior to olaratumab/placebo[d]	X	X		X
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
	8		Prior to olaratumab/placebo[d]	X			
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
	15		Prior to olaratumab/placebo[d]	X			
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
4	1		Prior to olaratumab/placebo[d]	X			
5 and then every other cycle	1		Prior to olaratumab/placebo[d]	X			X
30-day follow-up visit			Anytime	X	X		X

Abbreviations: IG = immunogenicity; IRR = Infusion-related reaction; PK = pharmacokinetic.

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

[b] For the immunogenicity assay for IgE anti-α-gal antibody screening, approx. 10 mL of whole blood will be drawn.

[c] If a patient experiences an IRR to olaratumab/placebo, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days (±3 days) after the IRR.

[d] 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.

[e] Sample collected predose Cycle 1 Day 1.

[f] For patients who are in screening and have not started treatment during the temporary hold, the screening window will be extended an additional 14-days.

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 clinical research physician.

Hepatic Monitoring Tests

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

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

[a] Assayed by Lilly-designated laboratory.

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

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

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:

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

For serum creatinine concentration in μmol/L:

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

Abbreviations: CrCl = creatinine clearance; wt = weight.

[a] Age in years, weight in kilograms.

Source: Cockcroft and Gault 1976.

Appendix 7. Protocol Amendment I5B-MC-JGDP(e) Summary: A Phase 1b (Open-Label) / Phase 2 (Randomized, Double-Blinded) Study Evaluating Nab-Paclitaxel and Gemcitabine With or Without Olaratumab in the Treatment of First-Line Metastatic Pancreatic Cancer

Overview

Protocol I5B-MC-JGDP: A Phase 1b (Open-Label) / Phase 2 (Randomized, Double-Blinded) Study Evaluating Nab-Paclitaxel and Gemcitabine With or Without Olaratumab in the Treatment of First-Line Metastatic Pancreatic Cancer) has been amended. The new protocol is indicated by amendment (e) and will be used to conduct the study in place of any preceding version of the protocol.

The protocol was amended to include screening criteria for IgE antibodies against α-gal and premedication requirements to mitigate the risk for an observed rate of Grade ≥3 IRRs on Study JGDP that was greater than the rate of 3.1% previously observed across the olaratumab program.

The changes made to this protocol are as follows:

Key/Clarifying Changes:

- Updated an exclusion criterion for patients who have levels of IgE antibodies against α-gal greater than the upper limit of normal (Section 6.2).
- Removed an exclusion criterion for patients receiving warfarin (Section 6.2).
- Updated Premedication Cycle 1 guidelines for olaratumab/placebo to include premedication 30-60 minutes prior to dosing and add Histamine H2 antagonist (Section 7.1.1.1).
- Updated tables for PK, Immunogenicity, and Biomarker Research Sampling Schedule to include IgE anti-α-gal antibody screening for Phase 1b and 2 and alter the screening window in Phase 2 (Appendix 4).

…

- **Revised Protocol Sections**

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

Protocol I5B-MC-JGDP(~~d~~e)
A Phase 1b (Open-Label) / Phase 2 (Randomized, Double-Blinded) Study Evaluating Nab-Paclitaxel and Gemcitabine With or Without Olaratumab in the Treatment of First-Line Metastatic Pancreatic Cancer

5. Study Design

…

5.4.5. Rationale for Amendment (e)

Amendment (e) updates the protocol to include screening criteria for Immunoglobulin E (IgE) antibodies against galactose-α-1-3-galactose (α-gal) and premedication requirements to mitigate the risk for an observed rate of Grade ≥3 infusion-related reactions (IRRs) on Study JGDP that was greater than the rate of 3.1% previously observed across the olaratumab program. Based on data from the Phase 1 and Phase 2 portion of Study JGDP, Grade ≥3 IRRs were observed at an approximate rate between 5% and 10% of olaratumab-treated patients.

Infusion related reactions are a known Adverse Drug Reaction for olaratumab, and the rate of IRR is 12.5% (all grades) and 3.1% (Grade ≥3). Grade ≥3 IRR occur within minutes of first infusion of olaratumab. The risk of anaphylactic reaction is associated with elevated IgE antibody levels. Across 8 studies with olaratumab (401 evaluable olaratumab-treated patients), IgE antibody levels greater than the manufacturer-specified ULN had a positive predictive value of 75% (34.9% - 96.8%) and a negative predictive value of 99% (98.2% - 99.9%) for Grade ≥3 IRRs, with sensitivity of 75% (34.9% - 96.8%) and specificity of 99% (98.2% - 99.9%). Two patients had Grade ≥3 IRR with an IgE antibody level ≤ ULN (0.28 kU/L and <0.10 kU/L, respectively). Prior to this amendment, patients in Study JGDP were tested for pre-existing IgE antibody against α-gal as pre-planned retrospective analysis. However, the results of these tests were not available prior to first dosing of olaratumab/placebo. Pre-testing for elevated IgE antibody levels against α-gal for all untreated patients as part of screening is being implemented as a risk mitigation strategy.

This amendment implements actions to mitigate the risk of increased Grade ≥3 IRRs observed in Study JGDP. Specifically, screening in the Phase 2 portion of the study was modified to include immunogenicity testing, and the inclusion/exclusion criteria were updated to clarify that patients

with IgE anti-α-gal antibody levels greater than the upper limit of normal will be excluded from this study. In addition, the required premedication regimen prior to Cycle 1 Day 1 of olaratumab/placebo was clarified to include: dexamethasone (or steroid equivalent); a histamine H1 antagonistist (for example, diphenhydramine); and a histamine H2 antagonist (for example, ranitidine).

6. Study Population

…

6.2. Exclusion Criteria

…

[25] have known allergy to nab-paclitaxel, gemcitabine, or olaratumab (levels of IgE antibodies against α-gal that are above the upper limit of normal) or any ingredient of olaratumab, nab-paclitaxel, or gemcitabine formulations.

~~[30] are currently receiving warfarin and are unable to be switched to low molecular weight heparin or oral Factor II or Xa inhibitor with half-life less than 24 hours and achieve stable coagulation prior to first dose of study treatment.~~

…

7. Treatments

…

7.1. Treatments Administered

…

7.1.1. Premedication

…

7.1.1.1. Olaratumab/Placebo

Infusion-related reactions ~~(IRRs)~~, including Grade ≥3 events, have been observed with olaratumab. To date, all Grade ≥3 IRR events have occurred during the first olaratumab infusion, most of them within 30 minutes from the start of infusion. Symptoms of IRRs have included flushing, shortness of breath, bronchospasm, fever/chills, and in severe cases have manifested as severe hypotension, anaphylactic shock, or cardiac arrest.

The following premedications need to be administered prior to olaratumab/placebo infusions in Study JGDP. Additional premedication may be provided at the investigator's discretion.

- **Premedication in Cycle 1:**
  Premedication is **mandatory** for all patients during Cycle 1 prior to each dose of olaratumab/placebo. Premedicate all patients with the following (or equivalent) medications 30-60 minutes prior to olaratumab/placebo dosing on Days 1, 8, and 15 of Cycle 1:
  - Histamine H1 antagonist (for example, diphenhydramine)
  - Dexamethasone intravenously
  - Histamine H2 antagonist (for example, ranitidine)

- **Premedication in Cycles 2-n:**
  For subsequent cycles, premedication with a histamine H1 antagonist (for example, diphenhydramine) is recommended prior to each dose of olaratumab/placebo.
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7.4.4. Dosing Discontinuation

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7.4.4.3. Olaratumab

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7.4.4.3.1. Olaratumab Infusion-Related Reactions

Olaratumab should be immediately and permanently discontinued for Grade 3 or 4 IRR. For olaratumab IRR treatment guidelines see Table JGDP.7.

Due the observed rate of Grade ≥3 IRRs in the Phase 1 and Phase 2 portions of Study JGDP that was greater than the rate of 3.1% previously observed across the olaratumab program, testing for IgE anti-α-gal antibodies must be performed as part of screening, and patient with antibody levels >ULN should be excluded.

…

Appendix 1. Abbreviations and Definitions

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α-gal	galactose-α-1-3-galactose

…

IgE	Immunoglobulin E

…

Appendix 4. Pharmacokinetic, Immunogenicity, and Biomarker Research Sampling Schedule

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Pharmacokinetic, Immunogenicity, and Biomarker Research Sampling Schedule – Phase 1b (Cohorts 1 and 2)

Cycle	Day	Dosing	Sampling Time	Olaratumab PK[a, c]	Plasma for Biomarkers	Whole Blood for PGx [e]	IG[b, c]
Screening	0-28						X
1	1		Prior to olaratumab[d]	X	X	X	~~X~~
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab	X			
		Observation (1 hr)					
			60 ± 10 min post-olaratumab	X			
			4 ± 0.4 hr post-olaratumab	X			
	2		24 ± 3 hr post-olaratumab	X			
	5		Anytime	X			
	8		Prior to olaratumab[d]	X	X		
		Olaratumab (1 hr)					
			≤ 5 min post-infusion	X			
	15		Prior to olaratumab[d]	X	X		X
		Olaratumab (1 hr)					
			≤ 5 min post-infusion	X			
		Observation (1 hr)					
			60 ± 10 min post-olaratumab	X			
		nab-Paclitaxel (0.5 hr)					
			2 ± 0.25 hr post-nab-paclitaxel	X			
	16		24 ± 3 hr post-olaratumab	X			
	19		Anytime	X			
	22		Anytime	X			
2	1		Prior to olaratumab[d]	X	X		X
		Olaratumab (1 hr)					
	8		Prior to olaratumab[d]	X			
		Olaratumab (1 hr)					
	15		Prior to olaratumab[d]	X			
		Olaratumab (1 hr					
			≤ 5 min post-infusion	X			
3	1		Prior to olaratumab[d]	X	X		X
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab	X			
			60 ± 10 min post-olaratumab	X			
			4 ± 0.4 hr post-olaratumab	X			
	2		24 ± 3 hr post-olaratumab	X			
	5		Anytime	X			
	8		Prior to olaratumab[d]	X			
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab	X			
	15		Prior to olaratumab[d]	X			
		Olaratumab (1 hr)					
			≤ 5 min post-infusion	X			
			60 ± 10 min post-olaratumab	X			
			4 ± 0.4 hr post-olaratumab	X			
	16		24 ± 3 hr post-olaratumab	X			
	17		Anytime	X			
	19		Anytime	X			
4	1		Prior to olaratumab[d]	X			
5 and then every other cycle	1		Prior to olaratumab[d]	X			X
30-day follow-up visit			Anytime	X	X		X

Abbreviations: IG = immunogenicity; IRR = infusion-related reaction; PK = pharmacokinetic.

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

[b] For the immunogenicity assay for IgE anti-α-gal antibody screening, approx. 10 mL of whole blood will be drawn.

[c] If a patient experiences an IRR to olaratumab/placebo, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days (±3 days) after the IRR.

[d] 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.

. . .

Pharmacokinetic, Immunogenicity, and Biomarker Research Sampling Schedule – Phase 2

Cycle	Day	Dosing	Sampling Time	Olaratumab PK[a, c]	Plasma for Biomarkers	Whole Blood for PGx [e]	IG[b, c]
Screening	0-28 [f]						X
1	1		Prior to olaratumab/placebo[d]	X	X	X	~~X~~
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
	8		Prior to olaratumab/placebo[d]	X	X		
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
	15		Prior to olaratumab dose/placebo[d]	X	X		X
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
		nab-Paclitaxel (1 hr)					
			≤ 5 min. post-nab-paclitaxel	X			
2	1		Prior to olaratumab/placebo[d]	X	X		X
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
	8		Prior to olaratumab/placebo[d]	X			
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
	15		Prior to olaratumab/placebo[d]	X			
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
3	1		Prior to olaratumab/placebo[d]	X	X		X
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
	8		Prior to olaratumab/placebo[d]	X			
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
	15		Prior to olaratumab/placebo[d]	X			
		Olaratumab (1 hr)					
			≤ 5 min post-olaratumab/placebo	X			
4	1		Prior to olaratumab/placebo[d]	X			
5 and then every other cycle	1		Prior to olaratumab/placebo[d]	X			X
30-day follow-up visit			Anytime	X	X		X

Abbreviations: IG = immunogenicity; IRR = Infusion-related reaction; PK = pharmacokinetic.

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

[b] For the immunogenicity assay for IgE anti-α-gal antibody screening, approx. 10 mL of whole blood will be drawn.

[c] If a patient experiences an IRR to olaratumab/placebo, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days (±3 days) after the IRR.

[d] 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.

[e] Sample collected predose Cycle 1 Day 1.

[f] For patients who are in screening and have not started treatment during the temporary hold, the screening window will be extended an additional 14-days.

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