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.

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).

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.

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

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.

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

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.

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.

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.

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.

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

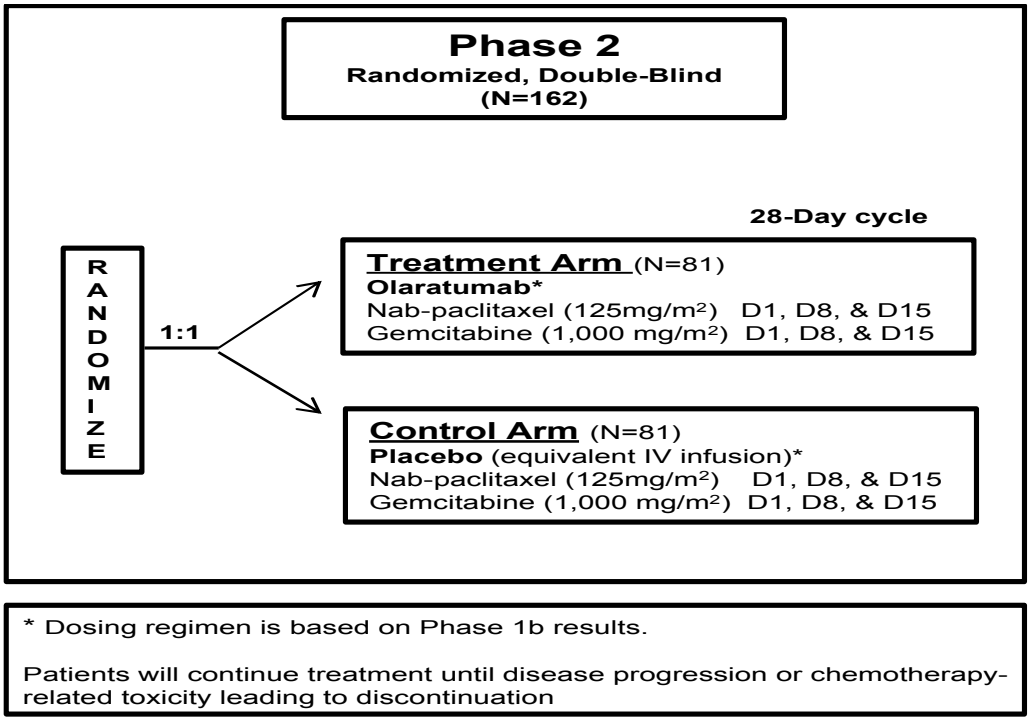
Phase 2:

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

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

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

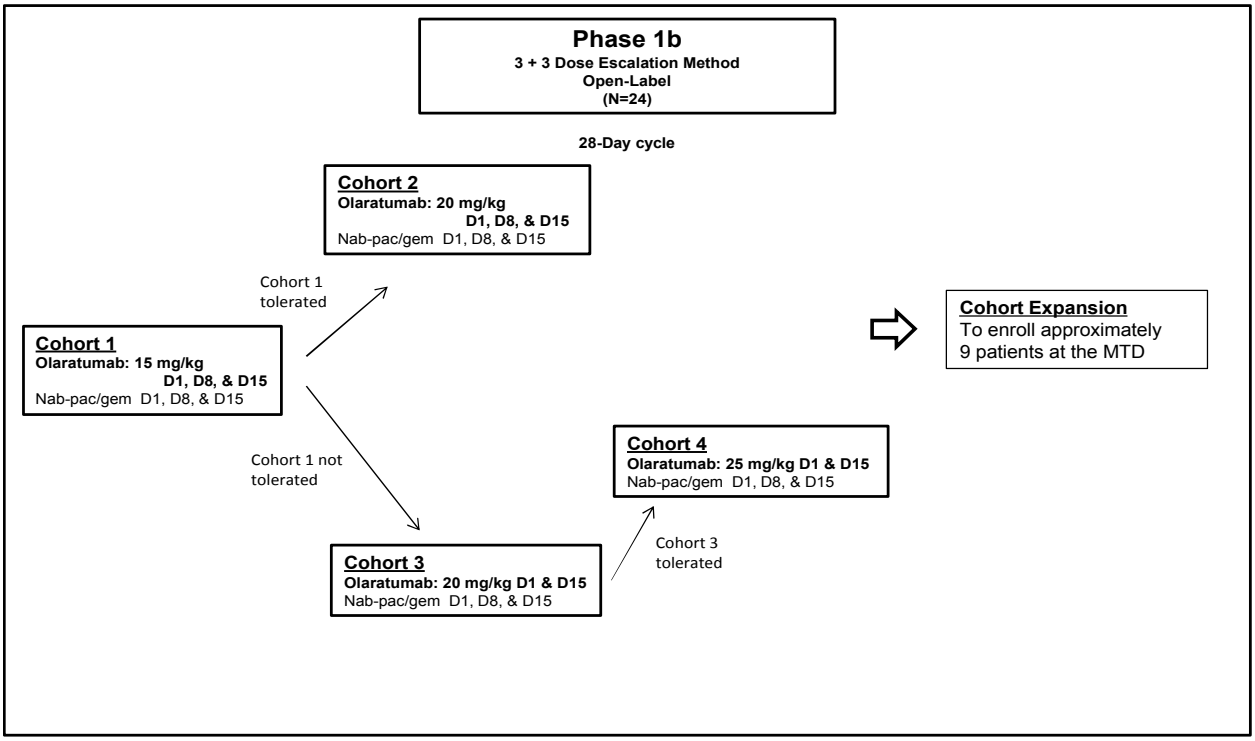
2. Schedule of Activities

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.

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).



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.

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.

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.

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.

10.3.3.4. 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

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.

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

[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.

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

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

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.