Protocol: I5B-MC-JGDQ(c)

An Open-Label, Multicenter, Phase 1a/1b Study of Olaratumab (LY3012207) Plus Pembrolizumab (MK3475) in Patients with Unresectable Locally Advanced or Metastatic Soft Tissue Sarcoma Who Have Failed Standard Treatments

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Approval Date: 19 Sep 2018

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Confidential Information

Olaratumab (LY3012207)

This Phase 1 study is an open-label, multicenter, nonrandomized, dose-escalation study followed by cohort expansion of intravenous LY3012207 plus intravenous pembrolizumab (MK3475) in patients with unresectable locally advanced or metastatic soft tissue sarcoma who have failed standard treatments.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly on 07 October 2016
Amendment (a) Electronically Signed and Approved by Lilly on 07 February 2017.
Amendment (b) Electronically Signed and Approved by Lilly on 30 November 2017.
Amendment (c) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 19-Sep-2018 GMT

2. Synopsis

This Phase 1a/1b study is an open-label, multicenter, nonrandomized, dose-escalation study that includes a dose-expansion component to evaluate intravenous (IV) olaratumab (LY3012207) plus pembrolizumab (MK3475) in patients with unresectable locally advanced or metastatic soft tissue sarcoma (STS) who have failed standard treatments.

Clinical Protocol Synopsis: Study I5B-MC-JGDQ(b)

Name of Investigational Product: Olaratumab (LY3012207)	
Title of Study: An Open-Label, Multicenter, Phase 1a/1b Study of Olaratumab (LY3012207) Plus Pembrolizumab (MK3475) in Patients with Unresectable Locally Advanced or Metastatic Soft Tissue Sarcoma (STS) Who Have Failed Standard Treatments	
Number of Planned Patients: Approximately 37 Phase 1a: Entered: 14 Enrolled: 12 Phase 1b: Entered: 28 Enrolled: 25	**Phase of Development:** 1a/1b
Length of Study: 2 years **Planned first patient visit:** June 2017 **Planned last patient visit:** June 2019 **Phase 1a planned interim analysis:** Data will be reviewed on a cohort-by-cohort basis during dose escalation for evaluation of safety and determination of recommended Phase 2 dose. **Phase 1b planned interim analyses:** Two interim analyses may be planned. The first will occur once all patients enrolled in the cohort have completed approximately 3 months of treatment; the second will occur once all patients enrolled in the cohort have completed approximately 6 months of treatment. These interim analyses will evaluate preliminary antitumor activity and may be combined with ongoing trial-level or annual safety review.	
Objectives: **Phase 1a (dose escalation) primary objective:** • To confirm the safety and tolerability of the combination of olaratumab plus pembrolizumab in patients with unresectable locally advanced or metastatic STS who have failed standard treatments and determine the recommended dose of olaratumab in combination with pembrolizumab for evaluation in Phase 1b. **Phase 1a secondary objectives:** • To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of olaratumab when administered in combination with pembrolizumab • To determine the immunogenicity of olaratumab when administered in combination with pembrolizumab • To document any antitumor activity of olaratumab when administered in combination with pembrolizumab as assessed by: o Objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and immune-related RECIST (irRECIST) o Disease control rate (DCR) using RECIST v1.1 and irRECIST o Duration of response (DOR) using RECIST v1.1 and irRECIST o Progression-free survival (PFS) using RECIST v1.1 and irRECIST o Overall survival (OS) **Phase 1b (dose expansion) primary objective:** • The primary objective of the Phase 1b portion of the study is to confirm the safety and tolerability of olaratumab at the recommended dose in combination with pembrolizumab in patients with unresectable locally advanced or metastatic STS who have failed standard treatments. **Phase 1b secondary objectives:** • To document any antitumor activity of olaratumab at the recommended dose when administered in combination with pembrolizumab as assessed by: o ORR using RECIST v1.1 and irRECIST o DCR using RECIST v1.1 and irRECIST	

- DOR using RECIST v1.1 and irRECIST
- PFS using RECIST v1.1 and irRECIST
- OS

- To characterize the PK and PD of olaratumab at the recommended dose when administered in combination with pembrolizumab
- To determine the immunogenicity of olaratumab at the recommended dose when administered in combination with pembrolizumab

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Study Design: Study JGDQ is an open-label, multicenter, nonrandomized, Phase 1a/1b dose-escalation study followed by cohort expansion of IV olaratumab plus pembrolizumab in patients with unresectable locally advanced or metastatic STS who have failed standard treatments. In the Phase 1a dose-escalation portion of the study, eligible patients will receive olaratumab 15 mg/kg (starting dose) or 20 mg/kg on Day 1 and Day 8 plus pembrolizumab 200 mg IV (fixed dose) on Day 1 of a 21-day cycle. Patients will enroll in a 3+3 fashion until dose-limiting toxicity (DLT) is observed or the maximum tolerated dose is achieved. Patients in any cohort who do not complete Cycle 1 treatment for reasons other than a DLT will be replaced. A minimum of 6 patients will be enrolled to the highest tolerated dose in each cohort in Phase 1a. Upon determination of a recommended dose for olaratumab, an expansion cohort in the Phase 1b portion of the study will open. Eligible patients will receive the recommended doses of olaratumab plus pembrolizumab in a 21-day cycle.

Diagnosis and Main Criteria for Inclusion and Exclusions:

Inclusion:

[1] Have histologically confirmed diagnosis of unresectable locally advanced or metastatic STS, not amenable to curative treatment and after available standard therapies have failed to provide clinical benefit, or have been deemed inappropriate candidates for additional standard treatments by the investigator.

[2] Is ≥18 years of age.

[3] Are willing and able to perform written informed consent for the trial and are amenable to compliance with protocol schedules and testing.

[4] Have measurable or nonmeasurable but evaluable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).

[5] Have adequate organ function, with all screening labs performed within 14 days of first dose of study treatment.

[6] Have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at the time of enrollment.

[7] Have sufficient available material from archived formalin-fixed paraffin-embedded tumor tissue obtained within 6 months of study enrollment for CCI [redacted]

[8] Have resolution, except where otherwise stated in the inclusion criteria, of all clinically significant toxic effects of prior systemic cancer therapy, surgery, or radiotherapy to Grade ≤1 by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

[9a] If male, the patient is sterile (including vasectomy) or agrees to use an effective method of birth control and to not donate sperm during the study and for at least 120 days following the last dose of study treatment.

[9b] If female, is not of childbearing potential due to surgical sterilization confirmed by medical history or menopause. If female and of childbearing potential, has a negative serum or urine pregnancy test within 72 hours prior to the first dose of study medication, agrees to use a highly effective method of birth control during the study and for up to 120 days following the last dose of the study drugs, and is not breastfeeding.

[10] Have an anticipated life expectancy of ≥3 months.

[11] Inclusion Criterion [11] has been deleted.

Exclusion:

[12] Have disease that is suitable for local therapy administered with curative intent.

[13] Have received any previous systemic therapy (including investigational agents) targeting PD-1/PDL-1 or PD-1/PDL-2 signaling pathways (including previous participation in Merck MK-3475 trials). Prior treatment with olaratumab is allowed. Prior therapy with other immune checkpoint inhibitors, including but not limited to, anti-CD137 antibody or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody, is not permitted.

[14] Have had chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks and/or monoclonal antibody treatment within 4 weeks prior to study Day 1 or who have not recovered from the effects of previously administered agents.

[15]	Exclusion Criterion [15] has been deleted.
[16]	Have known active central nervous system (CNS) metastasis and/or carcinomatous meningitis. Patients with treated CNS metastases are eligible for this study if they have not received corticosteroids and/or anticonvulsants within 7 days of study treatment, and their disease is asymptomatic and radiographically stable for at least 60 days.
[17]	Have a history or current evidence of any serious medical condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or not be in the best interest of the patient to participate, in the opinion of the treating investigator.
[18]	Have received a live-virus vaccine within 30 days prior to planned treatment start.
[19]	Have received transfusion of blood products or administration of colony stimulating factors within 2 weeks prior to study Day 1.
[20]	Have histologically or cytologically confirmed Kaposi's sarcoma or gastrointestinal stromal tumor (GIST).
[21]	Have received treatment within 28 days of the initial dose of study drug with an investigational product or non-approved use of a drug (other than the study drug used in this study) or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
[22]	Have inflammatory bowel disease for which the patient has used immunosuppressive agents within the last 2 years.
[23]	Have had an allogenic tissue/solid organ transplant.

Test Product, Dosage, and Mode of Administration:
Olaratumab will be administered at 15 mg/kg or 20 mg/kg as an approximately 60 (± 5)-minute IV infusion on Day 1 and Day 8 of a 21-day cycle. Pembrolizumab will be administered as a 200-mg fixed dose IV over 30 minutes on Day 1 of a 21-day cycle.

Reference Therapy, Dose, and Mode of Administration:
Not applicable.

Planned Duration of Treatment: The planned duration of treatment with pembrolizumab is a maximum of 35 cycles (approximately 2 years). The planned duration of treatment for olaratumab is not fixed; all patients will remain on study until confirmed progressive disease, unacceptable toxicity, or they fulfill one of the other criteria for study treatment discontinuation

30-day and 90-day safety follow-up (postdiscontinuation): Upon discontinuation of study treatment, patients will receive short-term follow-up assessments approximately 30 and 90 days later.

Long-term follow-up (postdiscontinuation): Once the 90-day safety follow-up is complete, patients will enter the long-term follow-up period where they will continue to be followed every 6 weeks until progressive disease and approximately every 2 months thereafter (for survival) until death or overall study completion. Continued access: All patients remaining on study treatment without disease progression following study completion (at least 60 days after the last patient has discontinued treatment with pembrolizumab and after all study objectives are met) will be able to enter the continued access period of the study, where patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until disease progression, death, unacceptable toxicity, or start of new anticancer treatment.

Criteria for Evaluation

Efficacy: RECIST v1.1 and irRECIST

Safety: NCI-CTCAE v4.0

Immunogenicity: Validated assay internally developed by Lilly and designed to detect anti-drug antibodies (ADA) in the presence of olaratumab and by external assay for detection of anti-Galactose-alpha-1,3-galactose immunoglobulin (Ig)E antibodies.

Pharmacokinetics: Serum concentrations of olaratumab obtained at different time points will be summarized by descriptive statistics and noncompartmental analysis. Additional analysis utilizing the population PK approach may also be conducted.

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Statistical Methods:

Efficacy: Individual best overall response (BOR) using RECIST version 1.1 criteria, DOR, PFS, and OS will be listed and summarized. Rates including ORR and DCR will be computed and estimates reported with exact 95% confidence intervals (CIs). Time-to-event variables, including PFS, DOR, and OS will be analyzed using the Kaplan-Meier method. Survival curves will be used to summarize the data. If data are sufficiently mature, medians will be reported with the 95% CIs. In addition, for each time-to-event variable, survival rates at adequate time points will be reported. Individual changes in the tumor size over time will be presented graphically using line plots. The change in tumor size corresponding to the best response based on target lesions for each patient will be represented in waterfall plots by cohort.

Safety: All patients who receive at least 1 dose of any study therapy will be evaluated for safety and toxicity. The Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 (or higher) will be used when reporting AEs by MedDRA terms. MedDRA Lower Level Term will be used in the treatment-emergent computation. Treatment-emergent adverse events will be summarized by System Organ Class and by decreasing frequency of Preferred Terms) within System Organ Class (SOC). Safety analyses will include summaries of the following: DLTs at each dose level; adverse events (AEs), including severity and possible relationship to study drug; serious adverse events (SAEs), including possible relationship to study drug; AEs leading to dose adjustments; discontinuations from study treatment due to AEs or death; treatment-emergent abnormal changes in laboratory values; treatment-emergent abnormal changes in vital signs.

Immunogenicity: Immunogenicity data will be summarized by dose, drug concentrations, and time from dose. If warranted, evaluation of immunogenicity and AEs may be conducted. A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those patients with at least one positive ADA at any time point will be provided. The frequency of patients with at least one positive ADA assessment, and frequency of patients who develop ADA after a negative baseline assessment will be provided.

Pharmacokinetics: Serum olaratumab concentrations at different time points will be summarized by descriptive statistics. Additional analyses utilizing the population PK approach may also be conducted if deemed appropriate. PK and PD data will be analyzed with appropriate standard nonlinear analytic software. PK parameter estimates for olaratumab will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be maximum plasma concentration (C_{max}) and area under the concentration-time curve ($AUC_{[0\text{-}tlast]}$, $AUC_{[0\text{-}\infty]}$) of olaratumab. Other noncompartmental parameters, such as time of half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V/F) may be reported. Additional exploratory analyses will be performed if warranted by data and other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global PK management.

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4. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibody
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event(s) of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
$AUC_{(0\text{-}tlast)}$	area under the plasma concentration-time curve from time zero to last measurable plasma concentration
$AUC_{(0\text{-}\infty)}$	area under the plasma concentration-time curve from time zero to infinity
audit	A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BOR	best overall response
CI	confidence interval
CL/F (or CL)	apparent systemic clearance
C_{max}	maximum plasma concentration
CNS	central nervous system
collection database	A computer database where clinical trial data are entered and validated.
complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
continued access period	The period between study completion and end of trial during which patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met.
CR	complete response
CRF/eCRF	case report form/electronic case report form: Sometimes referred to as clinical report form, a printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician
CRS	clinical research scientist
CSF	colony-stimulating factor
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLET	dose-limiting equivalent toxicity
DLT	dose-limiting toxicity
DOR	duration of response
DP	drug product
DS	drug substance
ECG	electrocardiogram
ECI	event(s) of clinical interest
ECOG	Eastern Cooperative Oncology Group
end of trial	End of study (trial) is defined as the date of the last visit or last scheduled procedure at the last site shown in the Study Schedule for the last active patient in the study.
enroll	Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least one dose of study treatment.
enter	Patients who are entered in the trial are those who have signed the informed consent form directly or through their legally acceptable representatives.

ERB/IRB	ethical review board/institutional review board: A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
GCP	good clinical practice
GI	gastrointestinal
GIST	gastrointestinal stromal tumor
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for datalock.
investigational product (IP)	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial. Investigational product includes a product with a marketing authorization when: • used or assembled (formulated or packaged) in a way different from the authorized form • used for an unauthorized indication or • used to gain further information about the authorized form
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRR	infusion-related reaction
irRECIST	immune-related Response Evaluation Criteria In Solid Tumors
IV	intravenous

legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
monitor	A person responsible for ensuring the investigator site complies with the monitoring plan, applicable local SOPs (if any), and global Medical SOPs. Monitors are trained on the investigational product(s), the protocol, informed consent document, any other written information provided to subjects, relevant SOPs, International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP), and all applicable laws (for example, privacy and data protection) and regulations.
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participants are aware of the drug therapy received during the study.
ORR	objective response rate
OS	overall survival
patient	A subject with a defined disease.
PD	progressive disease
PDGF	platelet-derived growth factor
PFS	progression-free survival
PI	package insert
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
PR	partial response

PS	performance status
PSA	prostate-specific antigen
PVC	polyvinyl chloride
Q2W	every 2 weeks
Q3W	every 3 weeks
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
RP2D	recommended Phase 2 dose
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial.
screen failure	A patient who does not meet one or more criteria required for participation in a trial.
SmPC	Summary of Product Characteristics
sponsor	The party who takes responsibility for the initiation, management, and/or financing of a clinical study.
STS	soft tissue sarcoma
study completion	This study will be considered complete after the final analysis for overall survival is performed.
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life
t_{max}	time of maximal plasma concentration
TPO	third-party organization
ULN	upper limit of normal
UPS	undifferentiated pleomorphic sarcoma
US	United States
V/F (or V)	apparent volume of distribution

An Open-Label, Multicenter, Phase 1a/1b Study of Olaratumab (LY3012207) Plus Pembrolizumab (MK3475) in Patients with Unresectable Locally Advanced or Metastatic Soft Tissue Sarcoma Who Have Failed Standard Treatments

5. Introduction

5.1. Rationale and Justification for the Study

Sarcomas remain one of the most devastating solid tumors for children and adults. The rare nature of the disease and the heterogeneity within the tumor make it difficult to develop novel therapies. There are approximately 50 different histological tumor subtypes of soft tissue sarcomas (STS). STS is a rare type of cancer comprising approximately 1% of adult cancers, with an annual incidence of approximately 3300 and 12,000 newly diagnosed cases in the United Kingdom (UK) (Soft tissue sarcoma statistics page [WWW] 2010) and United States (US) (ACS 2016), respectively. Treatment of localized disease is usually with curative intent using surgical resection with or without radiotherapy and chemotherapy. STS recurs frequently as locally inoperable or metastatic disease and systemic therapy plays a prominent role. The mainstay therapy for treating advanced-stage STS has been cytotoxic chemotherapy. More recently, targeted agents have shown promising activity (that is, agents targeting platelet-derived growth factor [PDGF]).

Olaratumab (LY3012207; hereafter, olaratumab), is a recombinant human immunoglobulin G subclass 1 (IgG1)-type monoclonal antibody (mAb) that binds to PDGFRα. This antibody possesses high affinity binding for PDGFRα and blocks PDGF-AA, -BB, and -CC from binding to the receptor. Recently, the randomized Phase 2 portion of Study I5B-IE-JGDG ([JGDG; [IMCL CP15-0806]; olaratumab plus doxorubicin versus doxorubicin alone in patients with advanced STS) met its primary progression-free survival (PFS) endpoint. Olaratumab plus doxorubicin resulted in a significant improvement in overall survival (OS) relative to the control arm (doxorubicin alone) (Tap et al. 2016).

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 and up to a dose of 15 mg/kg administered on Days 1 and 8 of a 21-day cycle. In randomized studies of olaratumab plus chemotherapies, a generally well-tolerated safety profile was observed for olaratumab. There were modest increases in known toxicities of the chemotherapy agent(s) when combined with olaratumab relative to chemotherapy alone. In Study JGDG in patients with STS, although there was a higher incidence of some known doxorubicin toxicities such as mucositis, nausea/vomiting, and diarrhea, these were monitorable, predominantly Grade ≤2, and did not lead to a higher incidence of treatment discontinuation. Overall, these toxicities were consistent with the toxicity profile of the combination agents used and are considered monitorable and acceptable for the patient populations studied. As with other monoclonal antibodies, hypersensitivity reactions (including fatal reactions) have been reported with olaratumab administration. Most infusion-related reactions (IRRs) were mild in severity. The common

signs and symptoms of IRRs were chills, flushing, pyrexia, dyspnea, and urticaria. More severe IRRs (Grade ≥3) can present within minutes of olaratumab infusion as severe hypersensitivity reactions or anaphylaxis, which may necessitate immediate treatment.

Immune checkpoint inhibition with antibodies has made a significant therapeutic impact in a variety of tumors. Pembrolizumab (MK-3475, Keytruda®) is a potent humanized immunoglobulin G4 (IgG4) mAb with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator Brochure.

Information on the most common adverse events observed with pembrolizumab can be found in the most current version of the pembrolizumab Investigator's Brochure or the Keytruda™ package insert.

Although there is limited clinical data with PD-L1 inhibitors in sarcoma, sarcomas have been linked to the immune system as early as the 1800s when William Coley noted a relationship between infection and regression of sarcoma (McCarthy 2006).

This study, I5B-MC-JGDQ (Study JGDQ) will evaluate the safety and efficacy of the combination of olaratumab with pembrolizumab in patients with unresectable locally advanced or metastatic STS who have failed standard treatments.

Immunotherapies, and particularly immune checkpoint inhibitors such as agents targeting the PD-1/PD-L1 signaling pathway, have been an area of interest and have shown activity in a variety of tumor types to date. Though these therapies are providing new treatment options, recent trial results are showing that the use of checkpoint inhibitors in combination with other therapies may be able to improve the efficacy observed for single agent checkpoint inhibitor use (Dammeijer et al. 2017).

Soft tissue sarcomas (STS) are a heterogeneous group of cancers originating from mesenchymal-derived soft tissues. Treatment beyond first line chemotherapy based regimens in metastatic STS has been characterized by relatively low response rates and limited improvements in OS to date (Comandone et al. 2017).

To date, there has been limited success with the use of immune checkpoint inhibitors in STS. Recently, data from several early studies of immune checkpoint inhibitors in STS have shown limited benefit to patients: A recent Phase 2 study of nivolumab in uterine leiomyosarcoma had no responses among the initial 12 patients (Ben-Ami et al. 2017); a retrospective review of nivolumab use in patients with metastatic STS or bone sarcomas showed 3 partial responses among 28 patients (Paoluzzi et al. 2016); and a study of pembrolizumab in prespecified histologic subtypes of STS showed responses varied between subtypes (Tawbi et al. 2017). In

this trial (SARC-028) pembrolizumab was studied in patients with bone sarcomas or STS evaluated patients with 4 types of STS (leiomyosarcoma, poorly differentiated/de-differentiated liposarcomas, undifferentiated pleomorphic sarcomas [UPS], and synovial sarcomas; approximately 10 patients per group). Objective response rate (ORR) of 40% (1 CR and 3 PR in 10 patients) was observed in the undifferentiated pleomorphic sarcoma subtype. In the poorly differentiated/dedifferentiated liposarcoma and synovial sarcoma groups, 2 and 1 PRs, respectively, were observed (N=10 for both groups). In the leiomyosarcoma group, 0 of 10 patients achieved a PR or better (Tawbi et al. 2017). .

There is a growing understanding of the tumor microenvironment and the interplay of immune components and the microenvironment. A recent report by Pollack et al. (2017) suggests that the highly mutated (UPS) subtype elicits a more clonal T-cell population and greater tumor infiltrating lymphocytes, which may explain the higher response rate observed in the previously mentioned study for UPS. However, Pollack et al. also showed that other subtypes present immunogenic antigens but may be limited in antigen presentation and/or T-cell infiltration.

The recent results for olaratumab plus doxorubicin in STS demonstrated improvement in median overall survival (26.5 vs 14.7 months for doxorubicin alone) (Tap et al. 2016). In this study, median PFS also favored the olaratumab plus doxorubicin treatment arm (6.6 vs 4.1 months). The magnitude of improvement reported in median OS was greater than the observed improvement in median PFS suggesting that the inhibitory effects of olaratumab on PDGFRα have a persisting effect that extends beyond the immediate treatment period. The ability of olaratumab to inhibit PDGFRα signaling, which can contribute to the stromal tumor microenvironment in STS, as well as the recent results in Study JGDG for olaratumab in STS, suggest a longer lasting effect whereby one possible mechanism is the disruption of some of the stroma and/or stromal signaling of the tumor microenvironment. As noted above, among STS subtypes that have shown responses to checkpoint inhibitors, there are subtypes with potentially immunogenic antigen presentation that may have limited response. Olaratumab may alter the tumor microenvironment in a manner which allows checkpoint blockade via pembrolizumab to elicit more robust immune response to tumor cells in STS than previously demonstrated in studies of monotherapy checkpoint inhibitors. Combining olaratumab, shown to work in combination with doxorubicin in STS, with pembrolizumab in STS may enhance anti-tumor activity of checkpoint inhibitors.

The sponsor, monitor, and investigators will perform this study in compliance with the protocol, good clinical practice (GCP) and International Conference on Harmonisation (ICH) guidelines, and applicable regulatory requirements.

5.1.1. Rationale for Amendment (a)

The original JGDQ study protocol, together with an Investigational New Drug application (IND) was submitted to the US Food and Drug Administration (FDA) in October of 2016. Following review, the FDA requested the following changes to the protocol, to which Lilly agreed and has implemented in this amendment:

- Addition of a 3-hour monitoring period for IRRs following pembrolizumab administration in Cycles 1 and 2.
- Delay in the start of the study Continued Access Period from 1 year after the last patient entered treatment to until after all patients have discontinued pembrolizumab treatment.
- Extension of the adverse event (AE) collection period following the end of study treatment (or initiation of a new anticancer therapy) from 30 days to 90 days.
- Elaboration on the safety data to be considered by Lilly in determining whether or not to enroll further patients to a cohort or to advance to the Phase 1b portion of the study.
- Elaboration on the criteria for continuing treatment after initial radiographic evidence of progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Removal of a statement that electrocardiograms (ECGs) would be evaluated in the determination of study eligibility.
- Wording changes regarding the number of patients to be enrolled at the highest tolerated dose.
- Inclusion of wording that addresses expected adverse reactions for olaratumab and pembrolizumab.

Concurrent with these FDA-requested changes, Lilly made a business decision to remove a parallel treatment arm investigating the combination of the Lilly Notch inhibitor compound (LY3039478) plus pembrolizumab from the study. Amendment (a) reflects the removal of this arm from the study.

Lastly, Lilly elected to make the following additional changes to the protocol:

- In collaboration with Merck & Co, updates to Section 5.1 to reflect the most current language regarding pembrolizumab mechanism of action and the approved indications for pembrolizumab.
- Correction of the minimum olaratumab concentration for infusion solutions.
- Addition of a requirement to permanently discontinue pembrolizumab in the event of recurrent Grade 2 pneumonitis based on a French Health Authority request to Merck & Co.
- Revisions to the olaratumab dose-escalation rules to clarify the conduct/progression of the study.
- Addition of a note on the Study Schedule to clarify that radiologic images are to be sent to and stored at a central vendor.

- Removal of the requirements for mean platelet volume and hemoglobin A1c testing from Attachment 2 (Clinical Laboratory Tests) and a change in the coagulation testing from central collection to performance at the local laboratory.
- Addition of a Cycle 4 Day 1 olaratumab pharmacokinetic (PK) sample to Attachment 4, as well as minor edits for clarity.
- Minor editorial revisions for clarity throughout the protocol.

The amended JGDQ(a) protocol will be the first version of the protocol operationalized at investigative sites.

5.1.2. Rationale for Amendment (b)

As of 21 September 2017, 2 of 4 patients enrolled in Cohort 1 had asymptomatic lipase increases (Grade 4) without any clinical or radiographic signs of pancreatitis. Asymptomatic lipase and amylase increases have been reported in patients treated with immuno-oncology agents (Postow 2015; Villadolid and Amin 2015; Bender et al. 2016). A 2015 review showed Grade ≥3 lipase increases were reported in multiple studies of immuno-oncology agents, ranging from an incidence of 1% to up to 13% (Naidoo et al. 2015). This review included a total of 16 patients with Grade ≥3 lipase increases, while other studies not included in this review provide further reports of lipase increases (Bender et al. 2016; Hamid et al. 2017). Based on observations of patients with ≥ Grade 3 asymptomatic lipase and amylase elevations, recently published recommendations suggest that no modification to treatment is indicated in such patients and that these laboratory parameters should not even be routinely tested due to lack of clinical consequence (Postow 2015; Fay et al. 2016; Hofmann et al. 2016).

However, per Study JGDQ protocol version (a), these Grade 4 lipase elevations qualified as DLTs, resulting in 2 patients with DLTs out of 4 enrolled and enrollment was, therefore, stopped.

Following discussions with the investigators and with Merck, this amendment revises the treatment modification guidelines to allow patients with clinically non-significant, treatable, or reversible lipase or amylase elevations to continue to receive study treatment. In addition, the DLT criteria have been updated to reflect the most current wording for pembrolizumab protocols including that non-hematologic laboratory elevations that are deemed clinically non-significant or are treatable/reversible would not be considered a DLT, nor in certain situations Grade 3 rash and Grade 3 fatigue are not considered DLTs. The rationale for this change regarding non-hematologic laboratory abnormalities is discussed above in this section; the revised DLT criteria are described in Section 7.2.2.2 and the revised dose modifications are described in Section 7.2.4. Based upon these protocol revisions, Lilly intends to enroll 1 to 3 additional patients at the first dose level to adequately determine the safety of the combination at this dose level.

In addition, minor editorial changes have been made throughout the protocol to improve clarity and practicability of the protocol, secure alignment with the intended study design, and update information available for study drugs.

5.1.3. Rationale For Amendment (c)

Protocol Amendment (c) for Study JGDQ adds the ability for pembrolizumab to be supplied for the study as an aqueous solution in addition to the lyophilized powder formulation.

The amendment also adds an exclusion criterion for patients that have had an allogenic tissue or solid organ transplant, consistent with other pembrolizumab clinical trials. Moreover, it clarifies data collection requirements intended for the follow-up period.

Amendment (c) also includes an update to the olaratumab premedication instructions.

Minor editorial changes have been made throughout the protocol to improve clarity and practicability of the protocol, secure alignment with the intended study design, and update information available for study drugs.

5.2. Objectives

5.2.1. Phase 1a: Dose Escalation

5.2.1.1. Primary Objective

The primary objective of the Phase 1a portion of the study is to confirm the safety and tolerability of the combination of olaratumab plus pembrolizumab in patients with unresectable locally advanced or metastatic STS who have failed standard treatments and determine the recommended dose of olaratumab in combination with pembrolizumab for evaluation in Phase 1b.

5.2.1.2. Secondary Objectives

The secondary objectives of the Phase 1a portion of the study are:

- To characterize the PK and pharmacodynamics (PD) of olaratumab when administered in combination with pembrolizumab
- To determine the immunogenicity of olaratumab when administered in combination with pembrolizumab
- To document any antitumor activity of olaratumab when administered in combination with pembrolizumab as assessed by:
    - Objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and immune-related RECIST (irRECIST)
    - Disease control rate (DCR) using RECIST v1.1 and irRECIST
    - Duration of response (DOR) using RECIST v1.1 and irRECIST
    - Progression-free survival (PFS) using RECIST v1.1 and irRECIST
    - Overall survival (OS)

5.2.2. Phase 1b: Dose Expansion

5.2.2.1. Primary Objective

The primary objective of the Phase 1b portion of the study is to confirm the safety and tolerability of olaratumab at the recommended dose in combination with pembrolizumab in patients with unresectable locally advanced or metastatic STS who have failed standard treatments.

5.2.2.2. Secondary Objectives

The secondary objectives of the Phase 1b portion of the study are:

- To document any antitumor activity of olaratumab at the recommended dose when administered in combination with pembrolizumab as assessed by:
  - ORR using RECIST v1.1 and irRECIST
  - DCR using RECIST v1.1 and irRECIST
  - DOR using RECIST v1.1 and irRECIST
  - PFS using RECIST v1.1 and irRECIST
  - OS
- To characterize the PK and PD of olaratumab at the recommended dose when administered in combination with pembrolizumab
- To determine the immunogenicity of olaratumab at the recommended dose when administered in combination with pembrolizumab

5.3. General Introduction to Olaratumab and Pembrolizumab

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

More detailed information about the known and expected benefits and risks of pembrolizumab may be found in the Keytruda Package Insert (PI) and Summary of Product Characteristics (SmPC).

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

5.3.1.1. Olaratumab

Olaratumab is a recombinant human immunoglobulin G subclass 1 (IgG1)-type mAb 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 (MAPK). Preclinical studies conducted with olaratumab have demonstrated antimitotic activity in cell lines and antitumor growth activity in human CCI [redacted] Olaratumab does not cross-react with PDGFRβ or with murine PDGFRα. Therefore, in vivo experiments in mice bearing human tumor xenografts treated with olaratumab may underestimate the potential anticancer activity of olaratumab because olaratumab cannot react with mouse stroma, or regulate cancer-associated vasculature in these models (Shah et al. 2010).

5.3.1.2. Pembrolizumab

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a mAb that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth (Merck 2016).

5.3.2. Nonclinical and Clinical Pharmacokinetics

5.3.2.1. Olaratumab

A pharmacokinetic (PK) profile of olaratumab consistent with that expected for a mAb was observed in both mice and monkeys based on assessments of half-life ($t_{½}$), clearance, and volume of distribution. In mice, the half-life was 7.4 days after intraperitoneal administration, which supported the twice weekly dosing strategy that was employed to evaluate olaratumab activity in xenograft models. Systemic exposure to olaratumab increased with increasing dose in both mice and monkeys. No consistent sex-related differences in exposure were observed in monkeys over 39 weeks and olaratumab accumulated by a factor of 1.4 to 2.4 between the first and last dose in the 39-week toxicity study. Olaratumab antidrug antibodies (ADA) were detected in several serum samples in repeat-dose toxicity studies; however, assessment of ADA was often

confounded by high circulating concentrations of olaratumab. A direct correlation between immunogenicity response and the rapid drug clearance exhibited by some animals was clearly demonstrated in the 39-week toxicity study.

The pharmacokinetics of olaratumab were studied in 171 patients who received doses of either 15 mg/kg on Days 1 and 8 of a 21-day cycle, or 20 mg/kg on Day 1 of a 14-day cycle. Based on population pharmacokinetic analysis, the mean clearance for olaratumab is 0.56 L/day and the volume of distribution at steady state is 7.7 L. This corresponds to a terminal half-life of approximately 11 days, and a time to steady state of approximately 7 weeks.

5.3.2.2. Pembrolizumab

The pharmacokinetics of intravenously administered pembrolizumab have been extensively studied in Cynomolgus monkeys through single-dose and repeat-dose studies across a wide range of dose levels and different dosing regimens. The single-dose study investigated 0.3, 3.0, and 30-mg/kg doses. The repeat-dose studies investigated 6-, 40-, and 200-mg/kg doses, as well as weekly and bi-weekly dosing regimens. The PK profile of pembrolizumab exhibited multiphasic kinetics, with greater than dose-proportionality exposure at the lower single doses (0.3 and 3.0 mg/kg) and dose-proportional exposure at the higher repeat-dose levels (6 to 200 mg/kg). In repeat-dose studies, neutralizing anti-pembrolizumab antibodies were detected in the lower dose groups (6 and 40 mg/kg), but no neutralizing ADA were detected in the highest dose group (200 mg/kg). Detection of neutralizing ADA corresponded with significantly lower pembrolizumab concentrations in the test animals. The terminal half-life of pembrolizumab in ADA-negative animals ranged from approximately 16 to 22 days in the repeat-dose studies. Repeat dosing resulted in accumulation of pembrolizumab that was dependent on dose and dosing frequency as expected. Steady-state of pembrolizumab was achieved by Day 71, which is consistent with approximately 3.5 terminal half-lives of the drug. In all the repeat-dose studies, systemic exposure of pembrolizumab was independent of sex.

The pharmacokinetics of pembrolizumab was studied in 2195 patients with various cancers who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on population pharmacokinetic analyses in patients with solid tumors, the geometric mean [% coefficient of variation (CV%)] for clearance (CL), steady-state volume of distribution, and terminal half-life were 202 mL/day (38%), 7.38 L (19%) and 27 days (38%), respectively.

Steady-state concentrations of pembrolizumab were reached by 19 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.2-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{ss}) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

5.3.3. Nonclinical Toxicology

Combination toxicology studies with olaratumab and pembrolizumab have not been conducted, as these studies are not warranted to support combination clinical trials intended to treat patients with advanced cancer (Nonclinical Evaluation for Anticancer Pharmaceuticals, ICH S9). The toxicity of olaratumab and pembrolizumab have been characterized individually in both clinical

and nonclinical studies and have a clinically manageable safety profile. The target organs identified in single-agent studies of each agent do not appear to overlap (see below). Based on this nonclinical data and the intended testing strategy, the combination of olaratumab and pembrolizumab is expected to have increased effectiveness when combined, without any potential additive toxicity.

5.3.3.1. Olaratumab

In repeat-dose monkey toxicity studies, the no-observable-adverse-effects levels (NOAEL) were established as the highest test doses: 50 mg/kg in the 5-week study and 75 mg/kg (Human Equivalent Dose of 24 mg/kg) in the 13- and 39-week studies. There were no olaratumab-related findings on the reproductive system in either gender or on the cardiovascular, respiratory, central nervous system (CNS), immune system, or effects on the gastrointestinal (GI) or hematopoietic systems. The exposure (area under the plasma or serum concentration-time curve [AUC]) following the last infusion of 75 mg/kg in the 39-week monkey study (284976 hr•µg/mL) was approximately 4-fold greater than exposures (AUC) of olaratumab that are needed for antitumor activity in humans (Study JGDG, 15 mg/kg).

5.3.3.2. Pembrolizumab

Pembrolizumab was evaluated in repeat-dose toxicology studies of one- and six-months duration in the monkey. In the one-month study, animals received a total of 5 IV doses of pembrolizumab at dose levels of 0, 6, 40 and 200 mg/kg/week. There were no effects on survival, clinical signs, body weight, food consumption, cardiovascular measurements, or clinical pathology endpoints. Histopathology data obtained in the 1-month study indicated a tendency toward increased monocytic and/or lymphocytic infiltration of tissues, many of which are known autoimmune target organs in humans; however, the severity scores were generally low in magnitude.

In the 6-month study, animals received a total of 12 biweekly IV doses of pembrolizumab at dose levels of 0-, 6-, 40-, and 200-mg/kg dose. Histological changes in this study were similar in character to those observed in the 1-month study, and included an increased incidence of monocytic and/or lymphocytic tissue infiltration; however, the magnitude and/or severity was similar across studies and did not exhibit a tendency toward increasing severity with increasing duration of exposure. These changes are consistent with the pharmacologic activity of the antibody: blocking signaling through the immunoinhibitory PD-1 pathway. In addition, in both monkey studies, exposure of pembrolizumab at all dose levels tested exceeded that measured in humans at the intended clinical dose and schedule of 2 mg/kg once every 3 weeks.

Please see the pembrolizumab IB for additional information.

5.4. Rationale for Selection of Dose

5.4.1. Rationale for Selection of Olaratumab Dose

The olaratumab dose-selection strategy for this study is based on the integrated safety, efficacy, and PK data for olaratumab across previous Phase 1 and Phase 2 studies. In 2 Phase 1 dose-escalation trials in patients with solid tumors (Studies I5B-IE-JGDC and I5B-IE-JGDF) and in the 2 Phase 2 monotherapy studies (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 and up to a dose of 15 mg/kg administered on Days 1 and 8 of a 21-day cycle. When used in combination with liposomal doxorubicin in Study I5B-IE-JGDA (olaratumab dose of 20 mg/kg every 2 weeks), and with paclitaxel plus carboplatin in Study I5B-IE-JGDB (olaratumab dose of 15 mg/kg Days 1 and 8 every 3 weeks), a higher rate of toxicities such as neutropenia and infections was observed versus the comparator agents. In Study JGDG, although there was a higher incidence of some known doxorubicin toxicities such as mucositis, nausea/vomiting, and diarrhea, these were monitorable, predominantly Grade ≤2, and did not lead to a higher incidence of treatment discontinuation. Overall, these toxicities were consistent with the toxicity profile of the combination agents used and are considered monitorable and acceptable for the patient populations studied.

The starting dose of olaratumab in the dose-escalation portion of this study (15 mg/kg given on Days 1 and 8 of a 21-day cycle) is the dose of olaratumab used in combination with doxorubicin in Study JGDG, where olaratumab plus doxorubicin met the primary study endpoint for PFS and demonstrated a significant improvement in OS above doxorubicin alone.

As above, in studies of olaratumab plus cytotoxic chemotherapy, some additional myelosuppression was observed upon the addition of olaratumab to the chemotherapy. As the addition of pembrolizumab is unlikely to result in significant myelosuppression, exploration of a higher dose of 20 mg/kg given on Day 1 and Day 8 of a 21-day cycle is warranted. The AE profile of olaratumab to date suggests there is no significant overlap in toxicities with the known AE profile of pembrolizumab. A loading dose of 20 mg/kg in Cycle 1 has been safely administered in several ongoing studies (Studies JGDJ, JGDI, and JGDK) in combination with doxorubicin. Exposure-response modeling from the recently completed Phase 2 Study JGDG indicated patients in the lowest quartile of exposure in Cycle 1 were below the identified target therapeutic concentrations and may benefit from higher exposures (Table JGDQ.1). The loading dose was intended to increase the proportion of patients above the therapeutic threshold in Cycle 1, thus providing rationale for the exploration of a 20-mg/kg dose in this study.

Table JGDQ.1. Olaratumab Phase 2 Dosing Exposure-Response Modeling and Phase 3 Dosing Projections

	Phase 2 Study JGDG (15-mg/kg dose for all doses)		Predicted exposures with loading dose in Phase 3 Study JGDJ	
	Cycle 1	Steady State	Cycle 1	Steady State
Percentage of patients below $EC_{min1}50$	45	23	24	22

Abbreviations: $EC_{min1}50$ = trough concentration (C_{min}) in Cycle 1 that induces 50% of the maximum effect; kg = kilogram; mg = milligrams.

5.4.2. Rationale for Selection of Pembrolizumab Dose

The dose of pembrolizumab planned to be studied in this trial is 200 mg every 3 weeks (Q3W). The dose recently approved in the US and several other countries for treatment of patients with

melanoma and NSCLC is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

In KEYNOTE-001, an open-label Phase 1 clinical trial, conducted to evaluate the safety, tolerability, PK and PD, and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose-escalation portion of this trial evaluated 3 dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) and dose-expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in patients with advanced solid tumors. All dose levels were well tolerated and no DLTs were observed. This first-inhuman study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No MTD has been identified. In addition, 2 randomized cohort evaluations of melanoma patients receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in patients with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2-mg/kg Q3W dose.

A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200-mg fixed dose are predicted to considerably overlap those obtained with the 2-mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. Pharmacokinetic properties of pembrolizumab, and specifically the weight dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in patients with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus the 200-mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed-dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed-dosing scheme will also reduce complexity in the

logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.

6. Investigational Plan

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once. Repeating 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. If a repeat laboratory value meets eligibility, it is recommended that the test is rechecked to confirm stability.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Study Population

6.1.1. Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria during screening prior to the first dose of study drug.

[1] Have histologically confirmed diagnosis of unresectable locally advanced or metastatic STS, not amenable to curative treatment and after available standard therapies (per local guidelines) have failed to provide clinical benefit, or been deemed inappropriate candidates for additional standard treatments by the investigator.

Patients with a diagnosis of Grade 1 liposarcoma (atypical lipomatous neoplasms) are eligible if there is histological or radiographic evidence of evolution to more aggressive disease.

[2] Is ≥18 years of age.

[3] Are willing and able to perform written informed consent for the trial and are amenable to compliance with protocol schedules and testing.

[4] Have measurable or nonmeasurable but evaluable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1 [v1.1]; Eisenhauer et al. 2009).

[5] Have adequate organ function, as defined in the table below, with all screening labs performed within 14 days of first dose of study treatment.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5 x 10^9/L
Platelets	≥100 x 10^9/L (platelet transfusions are not allowed within 2 weeks prior to Study Day 1, see Exclusion Criterion [20])
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L (packed red blood cell transfusions are not allowed within 2 weeks prior to Study Day 1, see Exclusion Criterion [20])
Renal	
Creatinine **or** Measured or calculated[a] creatinine clearance (CrCl) (GFR may be used in place of creatinine or CrCl) (Attachment 7)	≤1.5xULN **or** ≥60 mL/min
Hepatic	
Total bilirubin	≤1.5xULN
AST (SGOT) and ALT (SGPT)	≤2.5xULN **or** ≤5xULN for patients with liver metastases
Coagulation	
The patient has an adequate coagulation function as defined by International Normalized Ratio ≤1.5 x ULN or prothrombin time ≤1.5 x ULN, and partial thromboplastin time ≤1.5 x ULN if not receiving anticoagulation therapy. For patients receiving anticoagulants, exceptions to these coagulation parameters are allowed if they are within the intended or expected range for their therapeutic use. Patients must have no history of active bleeding (defined as within 14 days of first dose of study drug) or pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known esophageal varices).	

[a] Creatinine clearance should be calculated per institutional standard.

[6] Have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at the time of enrollment (refer to Attachment 6).

[7] Have sufficient available material from archived formalin-fixed paraffin-embedded tumor tissue obtained within 6 months of study enrollment CCI

[redacted]

[8] Have resolution, except where otherwise stated in the inclusion criteria, of all clinically significant toxic effects of prior systemic cancer therapy, surgery, or radiotherapy to Grade ≤1 by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (v 4.0).

[9a] If male, the patient is sterile (including vasectomy) or agrees to use an effective method of birth control (for example, male condom with spermicide) and to not donate sperm during the study and for at least 120 days following the last dose of study treatment.

[9b] 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.

Menopausal women 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, gonadotropin-releasing hormone, antiestrogens, selective estrogen receptor modulators, or chemotherapy), or

2) spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone level >40 mIU/mL.

If female and of childbearing potential, has a negative serum or urine pregnancy test within 72 hours prior to the first dose of study medication, agrees to use a highly effective method of birth control during the study and for up to 120 days following the last dose of the study drugs, and is not breastfeeding. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

A highly effective method of birth control 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), sexual 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.

[10] Have an anticipated life expectancy of ≥3 months.

[11] Inclusion Criterion [11] has been deleted.

6.1.2. Exclusion Criteria

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

[12] Have disease that is suitable for local therapy administered with curative intent.

[13] Have received any previous systemic therapy (including investigational agents) targeting PD-1/PDL-1 or PD-1/PDL-2 signaling pathways (including previous participation in Merck MK-3475 trials). Prior treatment with olaratumab is allowed. Prior therapy with other immune checkpoint inhibitors, including but not limited to, anti-CD137 antibody or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody, is not permitted.

[14] Have had chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks and/or monoclonal antibody treatment within 4 weeks prior to study Day 1 or who have not recovered (that is, to ≤ Grade 1 or baseline) from the effects of previously administered agents.

- Neuropathy (≤ Grade 2) or nonserious and nonlife-threatening toxicities, such as alopecia, altered taste, or nail changes, are an exception to this criterion.

Note: If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

[15] Exclusion Criterion [15] has been deleted.

[16] Have known active CNS metastasis and/or carcinomatous meningitis (screening not required). Patients with treated CNS metastases are eligible for this study if they have not received corticosteroids and/or anticonvulsants within 7 days of study treatment, and their disease is asymptomatic and radiographically stable for at least 60 days. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

[17] Have a history or current evidence of any serious medical condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or not be in the best interest of the patient to participate, in the opinion of the treating investigator. Serious medical condition(s) include, but are not limited to, the following:

- Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.

- Active autoimmune disease that has required systemic treatment in past 2 years from first dose of study treatment (that is, with use of disease-modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (for example, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- History of (non-infectious) pneumonitis that required steroids or current pneumonitis.
- Known human immunodeficiency virus (HIV) infection (HIV 1/2 antibodies) or acquired immunodeficiency syndrome (AIDS)-related illness (screening not required).
- History of interstitial lung disease.
- Known active Hepatitis A, B (for example, HBsAg reactive) or C (for example, HCV RNA [qualitative] is detected) infection (screening not required).
- Liver cirrhosis at a level of Child-Pugh B (or worse).
- Liver cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.
- Active or uncontrolled clinically serious infection requiring systemic therapy.
- Known psychiatric or substance abuse disorders that, in the opinion of the investigator, may prevent the patient from participating in the clinical trial.
- Known allergy or hypersensitivity reaction to olaratumab or any of its components.
- Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
- History of prior or second concurrent primary malignancies that, in the judgment of the investigator and Lilly, may affect the interpretation of results. Patients with carcinoma in situ of any origin and patients with prior malignancies who are in remission and whose likelihood of recurrence is very low (such as basal cell carcinoma), as judged by the investigator in consultation with Lilly CRP/CRS, are eligible for this study.

[18] Have received a live-virus vaccine within 30 days prior to planned treatment start. Examples of live vaccines include, but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, Bacillus

Calmette-Guérin (BCG), and typhoid vaccine. Seasonal flu vaccines that do not contain live virus are permitted.

[19] Have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte colony stimulating factors [G-CSF], GM-CSF or recombinant erythropoietin) within 2 weeks prior to study Day 1.

[20] Have histologically or cytologically confirmed Kaposi's sarcoma or gastrointestinal stromal tumor (GIST).

[21] Have received treatment within 28 days of the initial dose of study drug with an investigational product or non-approved use of a drug (other than the study drug used in this study) or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study. Patients participating in surveys or observational studies are eligible to participate in this study.

[22] Have inflammatory bowel disease for which the patient has used immunosuppressive agents within the last 2 years.

[23] Have had an allogenic tissue/solid organ transplant.

6.2. Summary of Study Design

Study JGDQ is an open-label, multicenter, nonrandomized, Phase 1a/1b dose-escalation study followed by cohort expansion of IV olaratumab plus pembrolizumab in patients with unresectable locally advanced or metastatic STS. Treatment cycles will be 21 days (± 3 days).

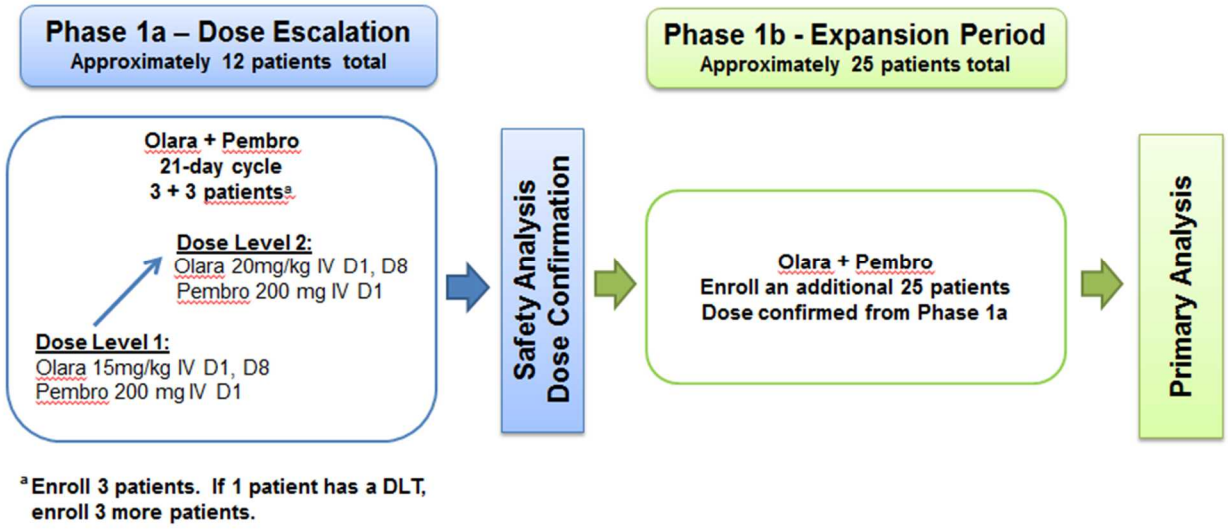
In the Phase 1a dose-escalation portion of the study, eligible patients will receive olaratumab 15 mg/kg (starting dose) or 20 mg/kg on Day 1 and Day 8 plus pembrolizumab 200 mg IV (fixed dose) on Day 1 of a 21-day cycle. Patients will enroll in a 3+3 fashion, according to the dose-escalation rules outlined in Section 7.2.2. No intrapatient dose escalation is permitted. Patients in any cohort who do not complete Cycle 1 treatment for reasons other than a DLT will be replaced. A minimum of 6 patients will be enrolled to the highest tolerated dose in Phase 1a. There will be a 2-week observation of the first patient at each dose level before additional patients in that cohort can be enrolled.

Upon determination of a recommended dose for olaratumab, a Phase 1b expansion cohort will open. Eligible patients will receive the recommended Phase 2 dose (RP2D) of olaratumab plus pembrolizumab in a 21-day cycle. In the Phase 1b portion, approximately 25 patients will be enrolled.

Figure JGDQ.1 illustrates the design of the trial.

The planned duration of treatment with pembrolizumab is a maximum of 35 cycles (approximately 2 years). The planned duration of treatment for olaratumab is not fixed; all patients will remain on study until confirmed progressive disease, unacceptable toxicity, or they fulfill one of the other criteria for study treatment discontinuation (Section 6.3).

The treatment period of the study includes a 30-day, 90-day, and a long-term follow-up period. The 30-day safety follow-up period begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment and lasts approximately 30 days. The 90-day safety follow-up period begins 1 day after the 30-day safety follow-up period ends and lasts approximately 60 days. Thereafter, patients will enter the long-term follow-up period as detailed in the Study Schedule (Attachment 1).



Abbreviations: D = day; DLT = dose-limiting toxicity; IV = intravenous; olara = olaratumab; pembro = pembrolizumab.

Figure JGDQ.1. Study design overview for Study I5B-MC-JGDQ.

6.2.1. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete) at a date determined by Lilly at least 60 days after the last patient has discontinued treatment with pembrolizumab and after all study objectives are met.

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

6.2.2. Continued Access Period

All patients remaining on study treatment (that is, with olaratumab only) without disease progression following study completion (at least 60 days after the last patient has discontinued treatment with pembrolizumab and after all study objectives are met) will be able to enter the continued access period of the study. The continued access period begins after study completion and ends at the end of trial. During the continued access period, patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until disease progression, death, unacceptable toxicity, or start of new anticancer treatment. The continued access period includes a follow-up visit. The follow-up visit 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. If it is deemed to be in the best interest of the patient to start a new anti-cancer treatment prior to the scheduled end of the follow-up visit, the follow-up visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

Lilly will notify investigators when the continued access period begins.

During the continued access period, all AEs, SAEs, and any study drug dose adjustments will be collected on the case report form (CRF).

Serious adverse events will also be reported to Lilly Global Patient Safety and collected in the pharmacovigilance system (Section 8.1.2.5). In the event that an SAE occurs, additional information (such as local laboratory results, concomitant medications, and hospitalizations) may be requested by Lilly in order to evaluate the reported SAE.

Investigators may perform other standard procedures and tests needed to treat and evaluate patients; however, Lilly will not routinely collect the results of these assessments.

6.3. Discontinuations

The reason for and date of treatment discontinuation will be collected for all patients. The date of discontinuation (for any reason) from study treatment is to be reported on the CRF.

If a patient withdraws informed consent, he or she must not be contacted unless he or she has explicitly provided permission and consent. Lilly may continue to use previously collected medical research data prior to the withdrawal, consistent with the original authorization.

6.3.1. Discontinuation of Patients Inadvertently Enrolled

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor CRP/CRS and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the Lilly CRP/CRS agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without investigational product if the Lilly CRP/CRS does not agree with the investigator's determination that it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

6.3.2. Discontinuation of Patients from Study or Study Drugs

In both the Phase 1a and 1b portions of the trial, patients for whom discontinuation of one study drug is necessary for safety reasons may continue to receive the other study drug at the discretion of the investigator. Patients who reach the maximum number of permitted cycles of

pembrolizumab (35) will be allowed to continue receiving olaratumab until discontinuation criteria is met.

Patients who are discontinued from all study drugs will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

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

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator/Physician Decision
    - the investigator/physician decides that the patient should be discontinued from the study or study drugs
    - the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from the study drugs should occur prior to introduction of the other agent
- Patient Decision
    - the patient requests to be discontinued from the study or study drugs
- Sponsor Decision
    - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- The patient has evidence of progressive disease.
    - If tumor imaging shows initial disease progression, patients may remain on study treatment with repeat imaging ≥4 weeks later to assess tumor response or confirmed progression per irRECIST.
- The patient experiences unacceptable toxicity.
- The patient is noncompliant with study procedures and/or treatment (Section 7.6).

6.3.2.1. Discontinuation of Study Therapy after Complete Response

Discontinuation of treatment may be considered for patients who have attained a confirmed complete response (CR). These patients must have been treated with pembrolizumab for at least 24 weeks and had at least 2 pembrolizumab treatments beyond the date when the initial CR was declared.

6.3.3. Patients Lost to Follow-Up

A patient would 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.

6.3.4. Discontinuation of Study Sites

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

6.3.5. Discontinuation of the Study

The study will be discontinued if Lilly, while considering the rights, safety, and well-being of the patient(s), judges discontinuation of the study necessary for any scientific, medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7. Treatment

7.1. Materials and Supplies

7.1.1. Olaratumab

Olaratumab will be supplied as a sterile preservative-free solution for IV infusion in single-use vials containing 500 mg/50 mL of olaratumab (10 mg/mL). Olaratumab is formulated in 10-mM histidine, 100-mM glycine, 50-mM sodium chloride, 75-mM mannitol, and 0.02% polysorbate-20, pH 5.5. All excipients used in the formulation of olaratumab drug product (DP) are of pharmacopeial grade.

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

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

CAUTION: IRRs may occur during or following olaratumab administration. See Section 7.5.1.1 for instructions on the management of olaratumab IRRs.

7.1.2. Pembrolizumab

Two DP dosage forms are available for pembrolizumab: a white to off white lyophilized powder, 50 mg/vial, and a liquid, 100 mg/vial, both in Type I glass vials intended for single use only.

- Pembrolizumab Powder for Solution for Infusion, 50 mg/vial is a lyophilized powder that is reconstituted with sterile water for injection prior to use. It is manufactured using either the fully formulated drug substance (DS) or the partially formulated DS. The fully formulated DS uses L histidine as a buffering agent, polysorbate 80 as surfactant, and sucrose as stabilizer/tonicity modifier. Pembrolizumab DP using the partially formulated DS is formulated with L histidine as a buffering agent, polysorbate 80 as a surfactant, and sucrose as a stabilizer/tonicity modifier and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (if necessary).
- Pembrolizumab Solution for Infusion 100 mg/vial is a liquid DP (manufactured using the fully formulated DS with L histidine as a buffering agent, polysorbate 80 as a surfactant, and sucrose as a stabilizer/tonicity modifier).

Both DP dosage forms are stored under refrigerated conditions (2°C to 8°C).

The lyophilized DP after reconstitution with sterile water for injection and the liquid DP are clear to opalescent solutions, essentially free of visible particles. The reconstituted lyophilized product and the liquid product are intended for IV administration. The reconstituted DP solution or the liquid DP can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in IV containers made of polyvinyl chloride (PVC) or non PVC material. Reconstituted vials should be used immediately to prepare the infusion solution in the IV bag,

and the infusion solution should be administered immediately. If the diluted pembrolizumab solution is not used immediately, it may be stored for no more than 24 hours at 2°C to 8°C. This 24 hour total hold from reconstitution may include up to 6 hours at room temperature (at or below 25°C). Any additional hold time must be at 2°C to 8°C. If refrigerated, the vials and/or IV bags must be allowed to come to room temperature prior to use.

The recommended dose of pembrolizumab in adults is 200 mg administered as an IV infusion over 30 minutes Q3W.

7.2. Study Drug Administration

The investigator or designee is responsible for:

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

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug(s) so that the situation can be assessed.

7.2.1. Dosing Schedule

Study drugs will be administered in both the Phase 1a and 1b portions of the trial as follows:

7.2.1.1. Olaratumab

Olaratumab will be administered as an approximately 60 minute IV infusion on Day 1 and Day 8 of a 21-day cycle at the doses shown in Table JGDQ.2. Exceptions to the 60-minute duration of the olaratumab infusion are permitted; see Pharmacy Manual for more information. On Day 1 of each cycle, olaratumab should be administered prior to pembrolizumab.

7.2.1.1.1. Olaratumab Premedication

Premedicate patients prior to administration of olaratumab as below:

- **Premedication in Cycle 1:**
  Premedication is **mandatory** for all patients during Cycle 1 prior to each dose of olaratumab. Premedicate all patients with the following (or equivalent) medications on Days 1 and 8 of Cycle 1:
  - Histamine H1 antagonist (for example, diphenhydramine)
  - Dexamethasone IV
- **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

Additional premedication may be provided at the investigator's discretion. Premedication must be provided in the setting of a prior Grade 1 or 2 olaratumab IRR, as detailed in Section 7.5.1.1.

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

Patients are required to be monitored for 1 hour after the olaratumab infusion in Cycles 1 and 2 for signs or symptoms of IRRs; see Section 7.5.1.1 for full description of required olaratumab monitoring period in Cycles 1 and 2. Patients should complete the required monitoring period prior to the start of pembrolizumab administration (when applicable). In addition, patients will be monitored for 3 hours following the end of the pembrolizumab infusion in Cycles 1 and 2 for signs and symptoms of IRRs (see Section 7.5.2.8).

7.2.1.2. Pembrolizumab

Pembrolizumab will be administered as a 200-mg fixed dose intravenously over 30 minutes on Day 1 of a 21-day cycle. Every effort should be made to ensure infusion timing is as close as possible to 30 minutes. However, a window of between -5 minutes and +10 minutes is permitted (that is, infusion time is 30 minutes -5 min/+10 min). Patients should be monitored in Cycles 1 and 2 for signs and symptoms of IRRs for 3 hours following the end of the pembrolizumab infusion.

Table JGDQ.2. Phase 1a and 1b Study Drug Administration

Drug	Dose Level	Dose	Route	Dosing Day of 21-Day Dosing Period
olaratumab	Level 1	15 mg/kg	IV	Day 1 and Day 8
	Level 2	20 mg/kg	IV	Day 1 and Day 8
pembrolizumab	Fixed dose	200 mg	IV	Day 1

Abbreviations: IV = intravenous.

7.2.2. Phase 1a Dose Escalation

A 3+3 dose-escalation design will be used to assess the safety of olaratumab given in combination with pembrolizumab. The DLT observation period will last for 1 cycle (approximately 21 days) for each patient in this portion of the study.

7.2.2.1. Olaratumab Dose-Escalation Rules

In the Phase 1a portion of the study, patients will begin olaratumab at Dose Level 1 (see Table JGDQ.2). The pembrolizumab dose will be fixed at 200 mg.

If none of the initial 3 DLT-evaluable patients (defined in Section 7.6.1) treated at Dose Level 1 develops a DLT, the study will proceed to enroll patients at the higher dose (Dose Level 2).

If 1 of the initial 3 DLT-evaluable patients treated at Dose Level 1 develops a DLT, 3 additional patients will be added to Dose Level 1. If ≤1 of 6 DLT-evaluable patients develops a DLT, the study will proceed to enroll patients at the higher dose (Dose Level 2).

If ≥2 DLT-evaluable patients develop a DLT at Dose Level 1, the regimen will be stopped.

If the study is enrolling patients at Dose Level 2 and 1 of the initial 3 DLT-evaluable patients develops a DLT, 3 additional patients will be added at Dose Level 2. If ≤1 of 6 DLT-evaluable patients develops a DLT, the Phase 1b (dose expansion) portion will start at Dose Level 2.

If the study is enrolling patients at Dose Level 2 and ≥2 of the initial 3 DLT-evaluable patients develops a DLT, Dose Level 2 will not be used in the Phase 1b (dose expansion) portion.

A minimum of 6 patients will be enrolled at the highest tolerated dose. All evaluable patients will be considered in deciding whether the dose is tolerated prior to expansion to Phase 1b.

No intra-patient dose escalation is allowed. Patients who withdraw from the study during the DLT observation period for reasons other than a treatment-related toxicity may be replaced within the same dose level.

Safety data, in particular AEs, will be the primary criteria for the dose escalation. No dose escalation can occur without prior discussion and agreement between the investigators and the Lilly CRP/CRS; the decision will be documented in writing.

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

7.2.2.2. Dose-Limiting Toxicity Determination

A DLT is defined as an AE during Cycle 1 that is possibly related to the study drug and fulfills any 1 of the following criteria using the NCI CTCAE v4.0:

- CTCAE Grade ≥3 nonhematologic toxicity. Exceptions that will not be considered a DLT are:
    - Grade 3 nausea, vomiting, diarrhea, or constipation that lasts ≤72 hours and that can be controlled with appropriate treatment; Grade 3 fatigue that lasts ≤72 hours; Grade 3 rash without the use of corticosteroids or anti-inflammatory agents per standard of care
    - Clinically non-significant, treatable, or reversible laboratory abnormalities including liver function tests, pancreatic enzymes, uric acid, electrolytes, etc. Grade 4 electrolyte disturbance lasting more than 24 hours despite appropriate treatment will be considered a DLT.
    - Transient (<7 days) Grade 3 elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) that are not accompanied by a Grade 2 bilirubin increase are considered an exception to the DLT criteria, unless there is a clear alternative cause (for example, worsening biliary obstruction) if agreed by the study investigator and Lilly CRP/CRS.
    - Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic

  - Grade 3 inflammatory reaction attributed to a local antitumor response (for example, inflammatory reaction at sites of metastatic disease, lymph nodes, etc.)
  - Concurrent vitiligo or alopecia of any AE grade
  - Any infusion or hypersensitivity reactions occurring during the infusion of the drug are not considered dose-related and therefore will NOT be considered a DLT

- Grade 4 anemia
- Grade 4 neutropenia or leukopenia of >5 days duration
- Any febrile neutropenia
- Grade 3 thrombocytopenia with clinically significant bleeding or Grade 4 thrombocytopenia
- Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (for example, any toxicity that is possibly related to the study medication that requires the withdrawal of the patient from the study during Cycle 1)

Investigators, together with the Lilly CRP/CRS, can declare a DLT if a patient is experiencing increasing toxicity during further cycles of treatment and it becomes clear that it will not be possible to continue on treatment without exposing the patient to excessive risk.

A dose-limiting equivalent toxicity (DLET) is an AE that meets the DLT criteria as defined above and occurs in any cycle other than Cycle 1 for a patient enrolled in the Phase 1a portion of the study.

The MTD is defined as the highest tested dose that has <33% probability of causing a DLT during Cycle 1. At the time of safety assessments for each cohort, all available safety data, including DLTs and DLETs from later cycles of treatment, will be included. In addition to the DLT assessment period in Cycle 1, safety data beyond Cycle 1 available at the time of safety review will also be taken into consideration prior to determining dose escalation, whether to enroll additional patients, or whether to proceed to the Phase 1b portion of the study.

Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from the definition of DLTs.

7.2.3. Phase 1b Dose Expansion

Based on the safety profile observed during the Phase 1a portion of the trial, the sponsor will determine the dosing regimen to be investigated in the Phase 1b portion of the study and open enrollment in the Phase 1b portion to further evaluate the combination therapy in this patient population.

Patients enrolled to the Phase 1a portion of the study will not participate in the Phase 1b portion. Patients in Phase 1b portion will meet the same eligibility criteria as for Phase 1a portion of the study. The purpose of Phase 1b expansion is to gather additional safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD), and preliminary efficacy information regarding the combination.

7.2.4. Dose Adjustments and Delays

7.2.4.1. Olaratumab

Olaratumab dose adjustments within Cycle 1 should be avoided if possible. If a dose adjustment or delay is required during Cycle 1 in the dose-escalation phase of the study, the patient will be allowed to continue but may be replaced if deemed appropriate by the Lilly CRP/CRS and investigator.

If a patient treated at a given dose level experiences a DLT (as defined in Section 7.2.2.2), then treatment will be suspended for that patient. Dosing may restart after recovery from toxicity at a lower dose after consultation between the investigator and Lilly CRP/CRS. If a toxicity does not meet the criteria for a DLT in Cycle 1 (or a DLET) but nonetheless requires omission of dose(s) for tolerability, then dosing may resume at the same dose or reduced dose after the toxicity resolves to baseline; however, the dose(s) omitted for tolerability during a cycle will not be replaced. Treatment may be delayed for up to 14 days to allow a patient sufficient time for recovery from study drug-related toxicity. If Day 8 dosing is delayed for approximately 14 days, the patient should resume treatment with Day 1 treatment for the next cycle.

The olaratumab dose for a patient should be reduced for all subsequent cycles of therapy, if the investigator determines that it is in the best interest of the patient or if the patient experienced at a DLT. For such patients requiring a dose reduction, re-escalation to the original dose level is not permitted. Patients who require more than 2 dose reductions of olaratumab will be discontinued from olaratumab treatment. If a patient experiences a DLET at a reduced dose level, then the patient will be discontinued from study treatment.

7.2.4.1.1. Hematologic Toxicity

Treatment should not begin on Day 1 of any cycle until the absolute neutrophil count (ANC) is ≥1500 cells/µL and the platelet count is ≥100,000 cells/µl.

Olaratumab treatment on Day 8 of any cycle should be held until ANC is >500 cells/µL and platelet count is ≥75,000 cells/µL.

7.2.4.1.2. Nonhematologic Toxicity

Specific guidelines for dose adjustments in patients who experience olaratumab IRRs may be found in Section 7.5.1.1.

General guidelines for dose modification for other nonhematologic toxicities related to olaratumab are shown in Table JGDQ.3. If more than 2 toxicity-related olaratumab dose reductions are required, olaratumab will be permanently discontinued.

Table JGDQ.3. General Guidelines for Dose Modification Due to Nonhematologic Toxicities Related to Olaratumab

Reaction Grade	Required Dose Modification
Grade 1	No dose modification is required.
Grade 2	At the investigator's discretion, the patient may continue to receive olaratumab per protocol, provided that the event does not pose a serious health risk or is easily treated.
Grade 3	For a Grade 3 toxicity not adequately controlled with appropriate supportive care, the dose must be withheld until toxicity is ≤ Grade 1 or has returned to pretreatment baseline; then treatment may resume at a reduced dose of 12 mg/kg for the 15-mg/kg cohort (Phase 1a) and reduced dose of 15 mg/kg for the 20-mg/kg cohort. If toxicity recurs after therapy resumes, a second dose reduction (second dose reduction of 10 mg/kg for the 15-mg/kg cohort and 12 mg/kg for the 20-mg/kg cohort) is permitted.
Grade 4	The dose must be withheld until dose toxicity is ≤ Grade 1 or has returned to baseline. Permanent discontinuation should be considered for any patient experiencing Grade 4 nonhematologic toxicity assessed as related to olaratumab. However, if resumption of dosing is deemed appropriate by the investigator, treatment may resume only after consultation with the Lilly study physician, with the dose reduced to 10 mg/kg for the 15-mg/kg cohort or to 15 mg/kg for the 20-mg/kg cohort. If Grade 4 toxicity recurs after therapy resumes, all study treatment will be discontinued.

Note: for asymptomatic Grade 3/4 laboratory abnormalities that are clinically non-significant, treatable, or reversible, treatment with olaratumab may continue without dose modifications at the discretion of the investigator.

7.2.4.2. Pembrolizumab

Adverse events (both nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and/or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table JGDQ.4. See Section 7.5.2 for supportive care guidelines for pembrolizumab, including use of corticosteroids.

Table JGDQ.4. Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab

General instructions:
Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable

bilirubin	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of		

		event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

[1] Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; irAE = immune-related adverse event; IV = intravenous; T1DM = Type 1 diabetes mellitus.

Note: Patients who have asymptomatic or clinically non-significant Grade 3 or 4 lipase or amylase elevations (that is, not associated with clinical symptoms or radiological signs of pancreatitis) which are transient as demonstrated by a decrease of at least 1 CTCAE Grade within 7 days ±3 days of onset will not require pembrolizumab discontinuation or modification. If the elevation has not decreased at least 1 CTCAE Grade within this time window, pembrolizumab treatment may only continue after consultation and discussion with the Sponsor.

7.3. Method of Assignment to Treatment

Before a patient's enrollment into the study, an eligibility check must be conducted between the investigational site and Lilly clinical research personnel to confirm that the patient meets all eligibility criteria. Upon confirmation of eligibility, the sponsor will confirm the dose and identification number assignment for the patient. No dose escalations (that is, to the next cohort) can occur without prior discussion and agreement with the responsible Lilly CRP/CRS.

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

7.4. Blinding

This is an open-label study.

7.5. Concomitant Therapy

No other chemotherapy, radiotherapy, immunotherapy, cancer-related hormone therapy, or experimental drugs will be permitted while the patients are on this study. The need for any form of radiotherapy will be cause for early discontinuation from study treatment (palliative radiotherapy is permitted if clinically indicated, after discussion with the Lilly CRP/CRS). In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate discontinuation from study treatment. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the eCRF. Replacement hormonal therapy initiated before study entry will be allowed.

Patients should receive full supportive care with the exception that the routine use of G-CSF is not permitted during this study. Patients should not receive G-CSF prophylactically in any cycle. G-CSFs may only be used for patients who have ANC$<0.5 \times 10^9$, neutropenic fever, or documented infections while neutropenic. G-CSFs must be discontinued at least 24 hours before the start of the next cycle of treatment. Should the use of hematopoietic colony-stimulating factors (CSFs) be necessary, follow the American Society of Clinical Oncology (ASCO) recommendations for the use of CSFs (Smith et al. 2006). If clinically indicated at any time during the study, erythropoietin and packed red blood cell transfusions may be used according to ASCO guidelines (Rizzo et al. 2008).

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

7.5.1. Supportive Care Guidelines for Olaratumab

7.5.1.1. Infusion-Related Reactions

As with other monoclonal antibodies, hypersensitivity reactions may occur during or following olaratumab administration. Premedications to be given prior to olaratumab infusions are described in Section 7.2.1.

An approximate 1-hour observation period is required after the administration of olaratumab during the first and second cycles of olaratumab. Patients should complete the olaratumab observation period prior to starting pembrolizumab (when applicable). If there is no evidence of an IRR during the initial 2 cycles of olaratumab, then no observation period is required for subsequent treatment cycles. In the event an IRR occurs thereafter, the 1-hour observation should be reinstituted. During the observation period, patients treated with olaratumab should be closely monitored for signs and symptoms indicative of an infusion reaction by the medical staff from the start of the infusion until at least 1 hour after the end of the infusion in an area where emergency medical resuscitation equipment and other agents (epinephrine, prednisolone equivalents, etc.) are available.

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

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

Treatment guidelines for olaratumab IRRs as well as premedications for subsequent infusions are described in Table JGDQ.5.

Table JGDQ.5. Olaratumab Infusion-Related Reaction Treatment Guidelines

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

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

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

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

7.5.2. Supportive Care Guidelines for Pembrolizumab

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary, as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes, such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 7.2.4 for dose modification guidelines.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

7.5.2.1. Pneumonitis

Grade 2 immune-mediated pneumonitis events should be treated with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Pembrolizumab should be permanently discontinued in patients who experience recurrent Grade 2 pneumonitis.

Grade 3 or 4 events should be immediately treated with IV steroids. Administer additional anti-inflammatory measures, as needed.

Prophylactic antibiotics for opportunistic infections should be added in the case of prolonged steroid administration.

7.5.2.2. Diarrhea/Colitis

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

For **Grade 2 diarrhea/colitis**, administer oral corticosteroids.

For **Grade 3 or 4 diarrhea/colitis**, treat with IV steroids followed by high-dose oral steroids.

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

7.5.2.3. Type 1 Diabetes Mellitus or Hyperglycemia

The following are recommendations for management of Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or Grade ≥3 hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA):

- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3 or 4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Grade 2 events should be treated with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Grade 3 or 4 events should be treated with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over at least 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

7.5.2.4. Hypophysitis

For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

For Grade 3 to 4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

7.5.2.5. Hyperthyroidism or Hypothyroidism

Thyroid disorders can occur at any time during treatment. Patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Grade 2 hyperthyroidism events (and **Grade 2 to 4** hypothyroidism):

- In hyperthyroidism, non-selective beta-blockers (for example, propranolol) are suggested as initial therapy.
- In hypothyroidism, thyroid hormone replacement therapy with levothyroxine or liothyronine is indicated per standard of care.

Grade 3 or 4 hyperthyroidism:

- Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

7.5.2.6. Hepatic Injury

For **Grade 2** immune-mediated hepatitis, monitor liver function tests more frequently until returned to baseline values (consider weekly). Treatment with IV or oral corticosteroids should be considered.

For **Grade 3 or 4** immune-mediated hepatitis, treat with IV corticosteroids for 24 to 48 hours.

When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

7.5.2.7. Renal Failure or Nephritis

In the case of **Grade 2** events, treatment with corticosteroids is recommended.

Patients that experience **Grade 3 or 4** events should be treated with systemic corticosteroids.

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

7.5.2.8. Pembrolizumab Infusion-Related Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

A 3-hour observation period is required after the administration of pembrolizumab during the first and second cycles. During the observation period, patients treated with pembrolizumab should be closely monitored for signs and symptoms indicative of an infusion reaction by the medical staff from the start of the infusion until at least 3 hours after the end of the infusion.

Table JGDQ.6 shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab.

Table JGDQ.6. Pembrolizumab Infusion-Related Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (for example, from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Patient may be premedicated 1.5 hr (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

Pembrolizumab Infusion-Related Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (that is, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (for example, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Abbreviations: IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs = non-steroidal anti-inflammatory drugs; po = by mouth.

7.6. Treatment Compliance

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

7.6.1. Evaluable Patients

Patients who withdraw from the study before receiving study drug(s) will be replaced and will not be included in the safety or efficacy assessments. Safety analyses will be conducted on all patients who have received at least 1 dose of study drug, regardless of whether they are deemed evaluable for the assessment of a dose level.

In the Phase 1a portion of the study, any patient who is discontinued from study treatment before completing 1 cycle of treatment will be deemed non-evaluable for assessment of a dose level, unless they experience a DLT prior to withdrawal.

Non-evaluable patients may be replaced to ensure that enough patients complete 1 cycle of therapy at each dose level, unless accrual to that cohort has stopped due to a DLT.

Patients who are not evaluable for pharmacokinetics, but who complete 1 cycle of therapy, may be replaced upon consultation with the investigator(s) and the Lilly CRP/CRS to ensure adequate PK data, unless accrual to that cohort has stopped due to a DLT.

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

8.1. Safety Evaluations

The safety and tolerability of olaratumab have been assessed in nonclinical toxicology studies, and the results from these studies are detailed in the olaratumab IB (Lilly 2016). The safety and tolerability of pembrolizumab has been assessed in nonclinical and clinical studies; the results from these studies are detailed in the Keytruda PI and SmPC. This Phase 1 study contains detailed safety monitoring that will permit initial characterization of the safety profile of olaratumab in combination with pembrolizumab in patients. Study procedures and their timing, including collection of blood, urine, and tumor tissue samples, are described in the Study Schedule (Attachment 1).

Standard laboratory tests, including chemistry, hematology, coagulation, and urinalysis panels, will be performed. All standard laboratory tests will be analyzed centrally, with the exception of urinalyses and pregnancy tests. Central or local laboratory results will be used to determine patient eligibility at baseline and local laboratory results may be used for on-study dosing decisions; if so, testing must still be performed by the central laboratory. These central laboratory results will be used for subsequent safety analyses. In the event of minor discrepancies between local and central laboratory results, the investigator may use the local results for treatment decisions, and the central laboratory results will remain part of the safety database. Other clinical laboratory tests will also be collected. Attachment 2 lists the specific tests that will be performed for this study.

8.1.1. Safety Data Collection and Review

Investigators are responsible for monitoring the safety of patients who have entered into this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of the patient during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1).

Table JGDQ.7 presents a summary of AE and SAE reporting guidelines. Table JGDQ.7 also shows which database or system is used to store AE and SAE data.

8.1.2. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any clinically significant findings from labs, vital sign measurements, and so on that occur should also be reported to Lilly or its designee as an AE.

Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect. Progression of the cancer under study is not considered an AE.

The investigator, monitor, and sponsor will review the collected data regularly for evidence of AEs. All patients will be assessed routinely for AEs as outlined in the study schedule. All AEs observed will be graded using CTCAE v 4.0.

The NCI-CTCAE v 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. All AEs observed will be graded using CTCAE v 4.0. Any minor version of CTCAE v 4.0 (for example, version 4.0) may be used for this study. Minor CTCAE v 4.0 updates from the NCI will not necessitate a protocol amendment. For AEs without matching terminology within the NCI-CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the CRF. This collection is in addition to verbatim text used to describe the AE.

In addition to collecting the AE verbatim, the CTCAE term, and the CTCAE severity grade, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Data on fetal outcome and breastfeeding should be collected, if feasible, for regulatory reporting and drug safety evaluation. Upon documentation of pregnancy, the patient must be removed from study treatment immediately.

For all enrolled patients, study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. While the patient is on study, site personnel will record any change in these preexisting condition(s) and the occurrence and nature of any AEs. In addition, all AEs related to protocol procedures are reported to Lilly or designee.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure or study drug via eCRF.

The investigator decides whether he or she interprets the observed AEs as either related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terminologies are defined:

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

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

8.1.2.1. Serious Adverse Events

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

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

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

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

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

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the sponsor in the same timeframe as SAEs to meet certain local requirements.

Therefore, these events are considered serious by the sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

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

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

If an investigator becomes aware of SAEs occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure or study drug, the investigator should report the SAEs to the sponsor and the SAEs will be entered in the Lilly Safety System.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

8.1.2.2. Notable Adverse Events

Adverse events that have been identified as safety signals during preclinical or early clinical trials or based on class effects of similar drugs are known as adverse events of special interest (AESI) for olaratumab and as events of clinical interest (ECI) for pembrolizumab. These events will be monitored prospectively in the clinical development program.

8.1.2.2.1. Adverse Events of Special Interest for Olaratumab

IRRs are an AESI for olaratumab. AESIs are defined by a careful assessment and grouping of individual related MedDRA preferred terms. Section 7.5.1.1 describes supportive care measures for olaratumab IRRs.

8.1.2.2.2. Events of Clinical Interest for Pembrolizumab

Selected non-serious and serious AEs are ECIs for pembrolizumab and must be reported to the sponsor.

ECIs for pembrolizumab are:

1) an overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory values. An overdose will be defined as ≥1000 mg (5 times the protocol-specified dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

2) an elevated AST or ALT laboratory value that is greater than or equal to 3X the upper limit of normal (ULN) and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN, and at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, as determined by way of protocol-specific laboratory testing or unscheduled laboratory testing.

For the time period beginning when the consent form is signed until treatment allocation, any ECI, or follow-up to an ECI, that occurs to any patient must be reported within 24 hours to the sponsor if it causes the patient to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or procedure.

For the time period beginning at treatment assignment through 30 days following cessation of treatment, any ECI or follow-up to an ECI, whether or not related to the sponsor's product, must be reported to the sponsor, either by electronic media or paper. ECIs that fulfill SAE criteria must be reported within 24 hours.

8.1.2.3. Adverse Event and Serious Adverse Event Reporting

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.

8.1.2.3.1. Prior to Administration of Study Drug(s)

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

8.1.2.3.2. On-Study Treatment

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring while the patient is receiving study drug must be reported to Lilly or its designee. A patient is considered to be receiving study drug from the time he/she receives the first dose of study drug to when he/she receives the last dose of study drug.

8.1.2.3.3. Follow-Up Visits

The study includes a 30-day and 90-day safety follow-up period. The initial follow-up visit (Visit 801) begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (±7 days). The 90-day safety follow-up period (Visit 802) begins 1 day after the 30-day safety follow-up period ends and lasts approximately 60 days. At the end of the follow-up visit, the patient will be required to have safety assessments as outlined in Attachment 1. All AEs and SAEs, regardless of relatedness to study drugs or protocol procedures, occurring during the safety follow-up visits (Visits 801 and 802) must be reported to Lilly or its designee.

Following the safety assessments, which mark the end of the safety follow-up visit (Visits 801 and 802), if there is an ongoing AE or SAE that is possibly related to study drug, that AE or SAE should be followed in subsequent follow-up visits (Visit 803-8XX) until the event is resolved,

the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, the patient dies or is lost to follow-up.

After the safety follow-up visit (Visit 802), AEs are not required to be reported unless the investigator feels the AEs were related to either study drug or a protocol procedure. If an investigator becomes aware of an SAE believed to be related to protocol procedures or study drug, the investigator should report the SAE to the sponsor, and the SAE will be entered in the in the Lilly Safety System.

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

8.1.2.4. Suspected Unexpected Serious Adverse Reactions

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

8.1.2.5. Summary of AE/SAE Reporting Guidelines

The AE and SAE reporting guidelines are summarized in Table JGDQ.7.

Table JGDQ.7. Adverse Event and Serious Adverse Reporting Guidelines for Study JGDQ

Timing	Types of AEs/SAEs Reported	Collection Database	Lilly Safety System
Prestudy (baseline assessments) (Starts at the signing of informed consent and ends just before the first dose of study drug)	Preexisting conditions	x	
	All AEs	x	
	All SAEs regardless of relatedness	x	x
On therapy [Starts at first dose of study drug(s) and ends at last dose of study drug(s)]	All AEs	x	
	All SAEs regardless of relatedness	x	x
30-day follow-up (Visit 801) (Starts 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).	All AEs	x	
	All SAEs regardless of relatedness	x	x
90-day follow-up (Visit 802) (Starts 1 day after the 30-day safety follow-up period ends and lasts approximately 60 days, at which time end-of-study safety assessments are completed)	All AEs	x	
	All SAEs regardless of relatedness	x	x
Subsequent follow-up visits, if necessary for patient monitoring	Ongoing AEs possibly related to study drug(s) or protocol procedures	x	
	All SAEs related to protocol procedures or study drug	x	x
Long-term follow-up (Visit 803-8XX) (Starts the day after the 90-day safety follow-up is completed and ends at death or entry into continued access period)	AEs related to study drug or protocol procedure	x	
	SAEs related to study drug or protocol procedure	x	x
Continued access period	All AEs	x	
	All SAEs regardless of relatedness	x	x
Continued access period follow-up (30 days; or sooner if patient begins new anticancer therapy)	All AEs	x	
	All SAEs regardless of relatedness	x	x
Patient no longer on study	All SAEs related to protocol procedures or study drug that the investigator becomes aware of		x

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

8.1.3. Other Safety Measures

8.1.3.1. Electrocardiograms

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

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 (ideally while the patient is still present) to identify any clinically relevant findings.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) to determine whether the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation. 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.

8.1.4. Safety Monitoring

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

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

- trends in safety data,
- laboratory analytes,
- AEs including monitoring of olaratumab AESI and pembrolizumab ECI (see Section 8.1.2.2)
- If a study patient experiences elevated ALT $\geq$5X ULN and elevated total bilirubin $\geq$2X ULN, clinical and laboratory monitoring should be initiated by the investigator. For patients entering the study with ALT $\geq$3X ULN, monitoring should be triggered at ALT $\geq$2X baseline.

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

8.1.5. Complaint Handling

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

Complaints related to concomitant drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the complaint process in accordance with the instructions provided for this study:

- recording a complete description of the complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

8.2. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study.

Attachment 4 lists the schedule of pharmacokinetic, biomarker, pharmacogenetic, and immunogenicity samples to be collected in this study.

8.2.1. Samples for Drug Concentration Measurements Pharmacokinetics

Pharmacokinetics will be collected as specified in the Pharmacokinetic, Biomarker, and Immunogenicity Sampling Schedule (Attachment 4). Based on the time and dates specified in Attachment 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 the Pharmacokinetic Sampling Schedule (Attachment 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 Attachment 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 the sponsor. It is preferred that the blood samples be obtained from a peripheral access point. 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 the sponsor. Serum concentrations of olaratumab will be assayed using designated validated enzyme-linked immunosorbent assay (ELISA) methods.

The PK samples will be stored at a facility designated by the sponsor. The remaining plasma or serum from the samples collected for PK may be pooled and used for exploratory metabolism work as deemed appropriate.

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

8.2.2. Samples for Pharmacogenetics Research

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

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

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

8.2.3. Samples for Pharmacodynamics and Biomarkers

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

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

- CCI [redacted]
- CCI [redacted]

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

- CCI
  CCI

Sample collection including blood and tumor tissue will occur at specified time points as indicated in Attachment 4.

CCI

8.2.3.1. CCI

8.2.3.2. CCI

CCI

[redacted]

8.2.4. Samples for Immunogenicity Research

In the Phase 1a and Phase 1b portions of the trial, blood samples for immunogenicity testing will be collected to determine antibody production against olaratumab. To interpret the results of immunogenicity, blood samples will be collected at the same time points as the blood samples designated to measure the serum concentrations of olaratumab (as noted in Attachment 4).

In the event of an olaratumab IRR, unscheduled blood samples will be collected for additional immunogenicity and PK 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 30 days (± 3 days) after onset of the event (as noted in Section 7.5.1.1).

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

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

8.3. Efficacy Evaluations

A secondary objective of both the Phase 1a and 1b portions of the study is to assess the following efficacy endpoints:

- ORR
- DCR
- DOR
- PFS
- OS

ORR, DCR, DOR, and PFS will be assessed according to RECIST v1.1 (Eisenhauer et al. 2009).

PFS is defined as the time from the date of study enrollment until the date of the first observed radiographically documented PD or death due to any cause, whichever comes first. Overall survival, including 1- and 2-year survival rates, is determined from the date of first treatment until death due to any cause.

Patients may continue to be treated with the combination therapy until a confirmed progression is documented per irRECIST.

Following computerized axial tomography (CT) scan or magnetic resonance imaging (MRI) during the screening period, investigators will assess tumor response modified for confirmation of progression (irRECIST) every 6 weeks (± 5 working days) for up to 24 weeks. Confirmatory scans will be preferably obtained at the next routine scheduled imaging time point (that is, 6 weeks) and no earlier than 4 weeks later. After 24 weeks, tumor assessments will be conducted every 12 weeks. Additional radiologic assessments are permissible at the discretion of the investigator. The method of assessment used at baseline should be used consistently for a patient throughout the trial. Refer to Attachment 1 for details regarding the timing of specific efficacy measures.

Immune-Related RECIST (irRECIST)

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab (Wolchok et al. 2009). Therefore, RECIST 1.1 will be adapted to account for the unique tumor response characteristics known to occur with pembrolizumab treatment (irRECIST) and additionally assessed using these criteria. Adaptations for irRECIST are detailed in Attachment 8.

If radiologic imaging verifies initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing study treatment as described below while awaiting radiologic confirmation of progression.

If repeat imaging shows <20% increase in target lesion size compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued/resumed.

If repeat imaging confirms PD due to any of the scenarios listed below, patients will be discontinued from study treatment. In determining whether or not the tumor burden has increased or decreased, the site study team should consider all target lesions as well as non-target lesions.

Scenarios where PD is confirmed at repeat imaging:

- Tumor burden remains increased by ≥20% and at least a 5-mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is worse (qualitative)
- New lesion resulting in initial PD is worse (qualitative)
- Additional new lesion(s) since last evaluation

In patients who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a patient on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Patients may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- no decline in ECOG performance status
- absence of rapid progression of disease
- absence of progressive tumor at critical anatomical sites (for example, cord compression) requiring urgent alternative medical intervention

When feasible, patients should not be discontinued from study treatment until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some patients may have a transient tumor flare in the first few months after the start of immunotherapy, but subsequent disease response. Patients who are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

8.4. Procedure/Sampling Compliance

Every attempt will be made to enroll patients who have the ability to understand and comply with instructions. Noncompliant patients may be discontinued from study treatment.

The collection times of safety assessments, pharmacokinetic samples, pharmacodynamic samples, and efficacy measurements are given as targets, to be achieved within reasonable limits. The scheduled time points may be subject to minor alterations; however, the actual collection time must be correctly recorded on the lab requisition form.

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

9. Data Management Methods

9.1. Data Quality Assurance

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

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

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

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable IRB/ERBs with direct access to the original source documents.

9.2. Data Capture Systems

9.2.1. Case Report Form

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

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

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

9.2.2. Ancillary Data

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

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database.

Data will subsequently be transferred from the central vendor to the Lilly data warehouse. Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

10. Data Analyses

10.1. General Considerations

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

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

10.1.1. Sample Size Determination

In Phase 1a portion of the study, up to approximately 12 patients may be treated and evaluated in order to determine the recommended dose of olaratumab for the Phase 1b portion (RP2D). In the Phase 1b portion, approximately 25 patients will be enrolled.

The primary objective of this study is to confirm the feasibility of the RP2D and to further characterize the safety profile at the RP2D. The secondary objective is to evaluate any preliminary efficacy signal. With 6 patients treated at the RP2D in Phase 1a (dose escalation) and 25 patients treated at the RP2D in Phase 1b (dose confirmation), a total of 31 patients can provide adequate precision for the estimated incidence rate of the following quantities of interest:

(1) patients having a specified AE, or

(2) patients showing a response (PR/CR) to treatment

With a total sample size of N=31, the 95% confidence interval (CI) is approximately equal to the observed incidence rate (± 15 to 20%). Example point estimates of incidence rates and corresponding 2-sided 95% CIs are summarized in Table JGDQ.8. The values are provided as a reference for estimation rather than a basis of any decision criteria. The RP2D may be revised based on the safety data obtained in Phase 1b (Iasonos and O'Quigley 2013).

Table JGDQ.8. Estimated Incidence Rate and Its 2-Sided 95% CI

Number of Cases (N=31)	Est. Rate	95% CI[a]	
		Lower Limit	Upper Limit
0	0.0	0.0	0.11
5	0.16	0.05	0.34
10	0.32	0.17	0.51
15	0.48	0.30	0.67
20	0.65	0.45	0.81
25	0.81	0.63	0.93

Abbreviations: CI = confidence interval; Est = estimated; N = total number of patients.
[a] 95% Clopper-Pearson interval for binomial distribution with sample size of 3.

Patients who are enrolled during dose escalation but discontinue treatment during Cycle 1 for reasons other than treatment-related AEs may be replaced to ensure that enough patients are evaluable to determine the RP2D.

Study JGDQ requires (inclusion criterion [7]) the availability of sufficient material from archived tumor tissue obtained within 6 months of study enrollment (or, if such tissue is not available, a newly obtained biopsy). CCI

[redacted]

10.1.2. Populations for Analyses

The following populations will be defined for this study:

Safety population: will include all enrolled 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. The safety population will be used for all dosing/exposure, safety, and efficacy analyses.

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

CCI [redacted]

10.2. Patient Disposition

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

10.3. Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics (including age, sex, screening height and weight, and screening body mass index [BMI]) will be reported.
- Baseline disease characteristics
- Prior disease-related therapies
- Concomitant medications

Other patient characteristics will be summarized as deemed appropriate.

10.4. Safety Analyses

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

The Medical Dictionary for Regulatory Activities (MedDRA) Version 16.1 (or higher) will be used when reporting AEs by MedDRA terms. The MedDRA Lower Level Term (LLT) 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 Terms (PT) within SOC.

Safety analyses will include summaries of the following:

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

10.5. Pharmacokinetic Analyses

Serum olaratumab concentrations at different time points will be summarized by descriptive statistics. Additional analyses utilizing the population pharmacokinetic approach may also be conducted if deemed appropriate.

PK and PD data will be analyzed with appropriate standard nonlinear analytic software. Pharmacokinetic parameter estimates for olaratumab will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be maximum concentration (C_{max}) and area under the concentration-time curve ($AUC_{[0\text{-}tlast]}$, $AUC_{[0\text{-}\infty]}$) of olaratumab. Other noncompartmental parameters, such as time of half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V/F) may be reported. Additional exploratory analyses will be performed if warranted by data and other validated pharmacokinetic software programs (for example, NONMEM) may be used if appropriate and approved by Global Pharmacokinetic management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

10.6. CCI

[redacted]

10.7. Immunogenicity

Immunogenicity data will be summarized by dose, drug concentrations, and time from dose. If warranted, evaluation of immunogenicity and AEs may be conducted. A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those patients with at least one positive ADA at any time point will be provided. The frequency of patients with at least one positive ADA assessment, and frequency of patients who develop ADA after a negative baseline assessment will be provided.

10.8. Efficacy

The following endpoints will be listed and summarized: individual best overall response (BOR) using RECIST version 1.1 criteria, DOR, PFS, and OS. In addition, the following endpoints will be listed and summarized using irRECIST criteria: BOR, DOR, and PFS by irRECIST. Rates including ORR and DCR will be computed and the estimates will be reported with exact 95% CIs. Time-to-event variables including PFS, DOR, and OS will be analyzed using the Kaplan-Meier method (Kaplan and Meier 1958). Survival curves will be used to summarize the data. If data are sufficiently mature, medians will be reported with the 95% CIs. In addition, for each time-to-event variable, survival rates at adequate time points will be reported (for example, 3, 6, and 12 months).

Individual changes in the tumor size over time will be presented graphically using line plots. The change in tumor size corresponding to the best response based on target lesions for each patient will be represented in waterfall plots by cohort.

10.9. Interim Analyses

Because this is a dose-finding study, data will be reviewed on a cohort-by-cohort basis during the Phase 1a portion of the study. The purpose of these cohort-by-cohort reviews is to evaluate the safety data at each dose level and determine if a DLT has been observed. The investigators and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data as described in this protocol.

For the Phase 1b portion of the study, 2 interim analyses are planned. The first will occur once all patients enrolled in the cohort have completed or had the opportunity to complete approximately 3 months of treatment; the second will occur once all patients enrolled in the cohort have completed or had the opportunity to complete approximately 6 months of treatment. The intent of these interim analyses is to evaluate preliminary antitumor activity. The interim analyses may also be combined with ongoing trial-level safety review or annual safety review for annual safety update reporting. No independent data monitoring committee will be required for this study.

This study will be considered complete (that is, the scientific evaluation will be complete) at a date determined by Lilly at least 60 days after the last patient has discontinued treatment with pembrolizumab and after all study objectives have been met. Study objectives may be considered as met once all enrolled patients having had opportunity for approximately 1 year follow-up from date of study enrollment. It is expected that at that time, enough data will have been obtained to assess the primary objective and the secondary objectives and allow the creation of a clinical study report. For PFS and OS, in the event that that the data are not mature enough to characterize the entire survival curve, a landmark analysis at 12 months will be done for the purpose of the clinical study report. All data defined in the protocol will continue to be collected from patients who remain on treatment in the continued access period. These data may be reported separately and analyses on all patients with these data may not be performed.

11. Informed Consent, Ethical Review, and Regulatory Considerations

11.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study in a timely manner.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study and to document that the patient is satisfied with his or her understanding of the potential risks and benefits of participating in the study and desires to participate in the study.

The investigator is ultimately responsible for ensuring that informed consent is given by each patient or legal representative before the study is started. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

11.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites. All ICFs must be compliant with the ICH guideline on GCP. Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

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

- the current IB or package labeling (for example Patient Information Leaflet, Package Insert, or Summary of Product Characteristics) and updates during the course of the study
- ICF
- relevant curricula vitae

11.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

2) the ICH GCP Guideline (E6)

3) applicable laws and regulations.

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

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

An identification code assigned (by the investigator) to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other study-related data.

11.3.1. Investigator Information

Site-specific contact information may be provided in a separate document.

11.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

11.3.3. Final Report Signature

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

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

The sponsor's responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Study Schedule

I5B-MC-JGDQ(b) Baseline Assessments (Phase 1a and Phase 1b)

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤7
Informed consent			
Radiological tumor assessment	X		
Medical history		X	
Demography		X	
Prior treatment therapies		X	
Physical exam		X	
Weight / BSA		X	
Vital signs		X	
ECOG performance status		X	
Concomitant medications	X		
ECG	X		
Hematology		X	
Serum chemistry		X	
Thyroid function tests		X	
Coagulation profile		X	
Urinalysis		X	
Pregnancy test			X
Tumor measurement (palpable or visible)		X	
CTCAE v4.0 grading (Preexisting conditions)		X	

CCI

I5B-MC-JGDQ(b) Baseline Assessments (Phase 1a and Phase 1b)

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤7	Comments
CCI				

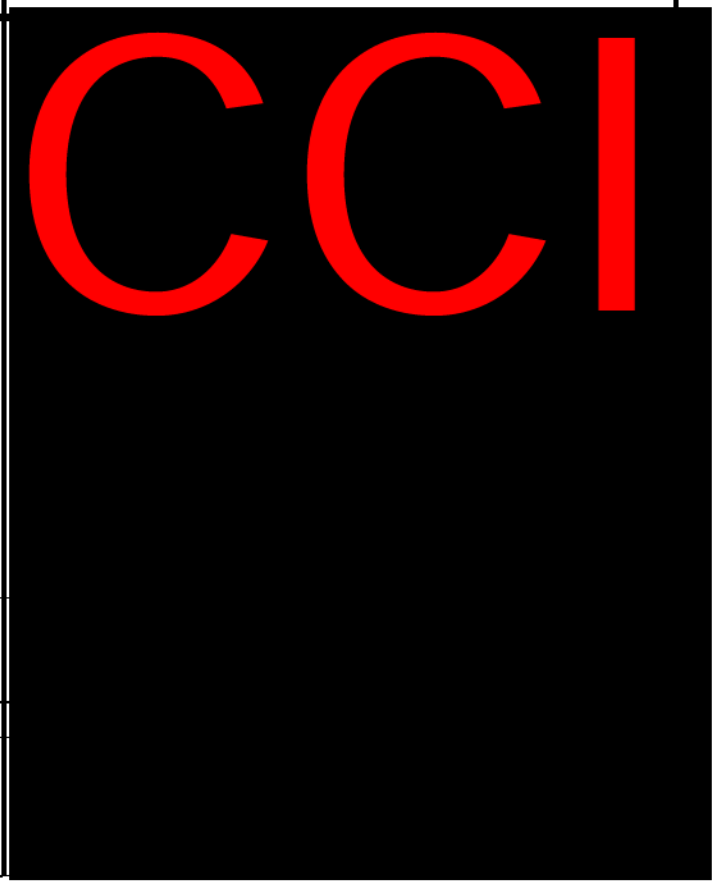
Abbreviations: BSA = body surface area; C1D1 = Cycle 1, Day 1; CRP = clinical research physician; CRS = clinical research scientist; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; STS = soft tissue sarcoma; v = version.

I5B-MC-JGDQ(b) Treatment Period and Poststudy Assessments: Phase 1a and 1b

	Cycle 1		Cycle 2		Cycle 3-n		Follow-Up[a]			Comments
	21-day cycle		21-day cycle		21-day cycle		30-day and 90-day Safety Follow-Up[b]		Long-Term[c]	
Relative Day Within a Cycle[d]	1	8	1	8	1	8	Visit 801	Visit 802	Visit 803-8XX	
Olaratumab	X	X	X	X	X	X				[redacted]
Pembrolizumab	X		X		X					
Physical exam	X	X	X	X	X	X	X	X		
Weight / BSA	X		X		X					

I5B-MC-JGDQ(b) Treatment Period and Poststudy Assessments: Phase 1a and 1b

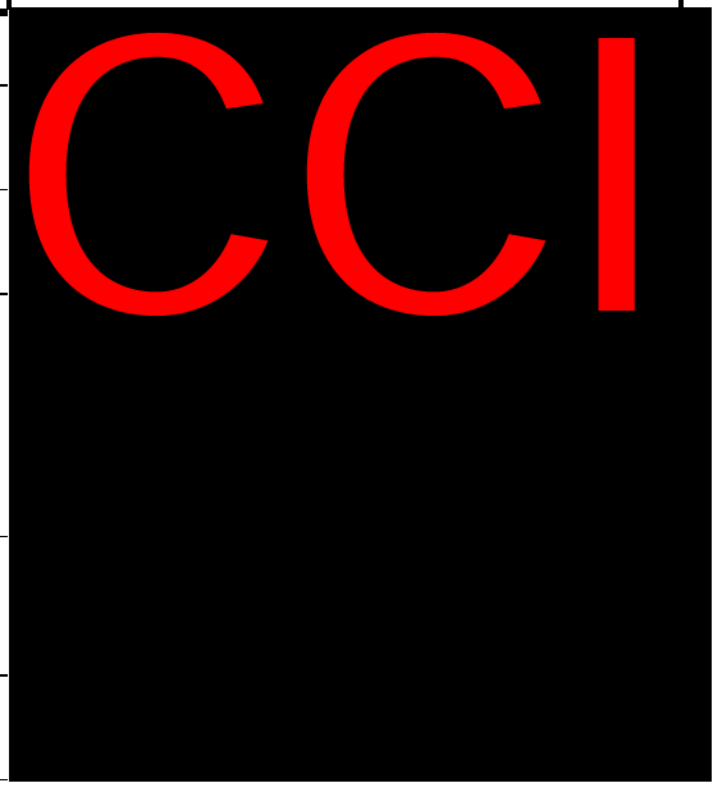
	Cycle 1		Cycle 2		Cycle 3-n		Follow-Up[a]			Comments
	21-day cycle		21-day cycle		21-day cycle		30-day and 90-day Safety Follow-Up[b]		Long-Term[c]	
Relative Day Within a Cycle[d]	1	8	1	8	1	8	Visit 801	Visit 802	Visit 803-8XX	
Vital signs	X	X	X	X	X	X	X	X		
ECOG performance status	X		X		X		X	X		
ECG	X						X	X		
Hematology	X	X	X	X	X	X	X	X		



Serum chemistry	X	X	X	X	X	X	X	X	

I5B-MC-JGDQ(b) Treatment Period and Poststudy Assessments: Phase 1a and 1b

	Cycle 1		Cycle 2		Cycle 3-n		Follow-Up[a]			Comments
	21-day cycle		21-day cycle		21-day cycle		30-day and 90-day Safety Follow-Up[b]		Long-Term[c]	
Relative Day Within a Cycle[d]	**1**	**8**	**1**	**8**	**1**	**8**	**Visit 801**	**Visit 802**	**Visit 803-8XX**	
Thyroid function tests	X				X		X	X		
Coagulation profile	X				X					
Urinalysis	X				X					
Pregnancy test	X		X		X		X	X		
CTCAE v4.0 grading	X		X		X		X	X	X	
Concomitant meds	X		X		X		X	X		



PK sampling	See Attachment 4 for specific time points	See Attachment 4 for specific time points	See Attachment 4 for specific time points	See Attachment 4 for specific time points			CCI

I5B-MC-JGDQ(b) Treatment Period and Poststudy Assessments: Phase 1a and 1b

	Cycle 1		Cycle 2		Cycle 3-n		Follow-Up[a]			Comments
	21-day cycle		21-day cycle		21-day cycle		30-day and 90-day Safety Follow-Up[b]		Long-Term[c]	
Relative Day Within a Cycle[d]	1	8	1	8	1	8	Visit 801	Visit 802	Visit 803-8XX	
CCI										
Immunogenicity	See Attachment 4 for specific time points		See Attachment 4 for specific time points				See Attachment 4 for specific time points			
Pharmacogenetics whole blood sample	X									
Tumor measurements (palpable or visible)			X		X				X	

CCI

I5B-MC-JGDQ(b) Treatment Period and Poststudy Assessments: Phase 1a and 1b

	Cycle 1		Cycle 2		Cycle 3-n		Follow-Up[a]			Comments
	21-day cycle		21-day cycle		21-day cycle		30-day and 90-day Safety Follow-Up[b]		Long-Term[c]	
Relative Day Within a Cycle[d]	1	8	1	8	1	8	Visit 801	Visit 802	Visit 803-8XX	
Radiological tumor assessment					X		X	X	X	CCI
Collection of survival information							X	X	X	
Collection of post-study-treatment anticancer therapy information							X	X	X	

Abbreviations: AE = adverse event; BP = blood pressure; BSA = body surface area; C = cycle; CRF/eCRF = case report form/electronic case report form; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; hrs = hours; IRR = infusion-related reaction; irRECIST = immune-related Response Evaluation Criteria In Solid Tumors; MRI = magnetic resonance imaging; olara = olaratumab; PD = progressive disease; pembro = pembrolizumab; PK = pharmacokinetic; RR= respiration rate; SAEs = serious adverse events.

I5B-MC-JGDQ(b) Treatment Period and Poststudy Assessments: Phase 1a and 1b

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

[b] **30-day and 90-day Safety follow-up** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 90 days (±7 days). The date of this agreement is to be reported on the CRF as the date of discontinuation from study treatment. Visit 801 should occur approximately 30 days (±7 days) after the decision to discontinue treatment. Visit 802 begins 1 day after the 30-day safety follow-up period ends and lasts approximately 60 days. If it is deemed to be in the best interest of the patient to start a new anti-cancer 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.

[c] **Long-term follow-up (Visits 803-8XX)** begins the day after 90-day safety follow-up is completed.

Follow-up for progression: Patients that discontinue study treatment for reasons other than progression will be followed every 6 weeks (±7 days) until PD or initiation of other anticancer therapy. Additional radiologic assessments are permissible at the discretion of the investigator.

Follow-up for survival: All patients will be followed every 2 months (±7 days) for the first 2 years, then every 6 months (±14 days) until the patient's death or overall study completion.

[d] A window of ±3 days will be permitted due to holidays, weekends, inclement weather or other unforeseen circumstances, including unexpected changes in patient schedules, and will not count as a protocol deviation. In later cycles, longer delays may be allowed in consultation with Lilly medical representative.

I5B-MC-JGDQ(b) Continued Access Period

	Continued Access Period[a]			
	Visit 501 - 5XX		Follow-Up Visit 901[b]	Comments
	21-day cycle			
Relative Day within a Cycle[c]	**1**	**8**		
Olaratumab	X	X		
Dosing information	X			
PK sampling / Immunogenicity				
CTCAE v4.0 grading	X		X	

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; IRR = infusion-related reaction; PK = pharmacokinetics; SAE = serious adverse event.

[a] The continued access period (Visits 501-5XX) begins after study completion and ends at the end of trial (see Section 6.2.1). Following study completion, patients without disease progression who continue to experience clinical benefit and no undue risks may continue to receive study treatment until disease progression, death, unacceptable toxicity, or start of new anticancer treatment. During this period, investigators may perform standard procedures and tests not shown here as needed to treat and evaluate patients; however, Lilly will not routinely collect the results of these assessments.

[b] The continued access follow-up visit (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 (±7 days). If it is deemed to be in the best interest of the patient to start a new anti-cancer treatment prior to the scheduled end of the follow-up visit, the visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

[c] Delays of up 7 days will be permitted due to holidays, weekends, inclement weather or other unforeseen circumstances and will not count as a protocol deviation.

Attachment 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a]
Hemoglobin	Sodium
Hematocrit	Magnesium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total bilirubin
Neutrophils	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase (ALT/SGPT)
Monocytes	Aspartate aminotransferase (AST/SGOT)
Eosinophils	Blood urea nitrogen
Basophils	Creatinine
Platelets	Uric acid
	Calcium
	Glucose, random
Coagulation[b]	Albumin
aPTT	Total protein
PT/INR	Chloride
	Bicarbonate
	Direct bilirubin
Urinalysis[b]	Creatinine clearance
Specific gravity	Phosphorus
pH	Lipase
Protein	
Glucose	**Thyroid Function Tests**[a]
Ketones	T3 (or FT3)
Blood	FT4
Urine leukocyte esterase	Thyroid Stimulating Hormone (TSH)
pH	
	Serum or Urine Pregnancy Test (females only)[b]

Abbreviations: aPTT = activated partial thromboplastin time; FT3 = free triiodothyronine; FT4 = free thyroxine; PT/INR = international normalized ratio of prothrombin time; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T3 = triiodothyronine; WBC = white blood cells.

[a] Assayed by Lilly-designated central laboratory.

[b] Local or investigator-designated laboratory.

Attachment 3. Hepatic Monitoring Tests for Treatment Emergent Abnormality

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

Hepatic Monitoring Tests

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

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

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

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

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


CCI


CCI

Attachment 5. Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events

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

Patient Demographics

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

Study Identification

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

Study Drug

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

Adverse Event

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

Relationship to Study Drug & Protocol Procedures

Concomitant Drug Therapy

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

In Case of Death

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

Attachment 6. ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out performance of a light or sedentary nature, for example, light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken et al. 1982.

Attachment 7. Creatinine Clearance Formula

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

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

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

Reference: Cockcroft and Gault 1976.

-OR-

$$GFR(mL/min/1.73m2) = 170 \times [PCr]^{-0.999} \times [age]^{-0.176}$$
$$\times [0.762\ \text{if patient is female}] \times [1.18\ \text{if patient is black}]$$
$$\times [SUN]^{-0.17} \times [Alb]^{+0.318}$$

PCr= Plasma Creatinine, mg/dL; SUN= Serum urea nitrogen, mg/dL; Alb= Serum albumin, g/dL

Source: Murray and Ratain 2003

Attachment 8. RECIST 1.1 and irRECIST

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

RECIST 1.1

Measurability of Tumor at Baseline

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

Measurable

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

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

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

Nonmeasurable

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

Special Considerations for Lesion Measurability

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with Prior Local Treatment:

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

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

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

Nontarget Lesions

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

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

Specifications by Methods of Measurement

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

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

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

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

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

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

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

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

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

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

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

Response Criteria

Evaluation of Target Lesions

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

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

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

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

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

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

Evaluation of Nontarget Lesions

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

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

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

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

Evaluation of Best Overall Response

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

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table ATT.8.1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table ATT.8.1. Time Point Response: Patients with Target (± Nontarget) Disease

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

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table ATT.8.2 is to be used when patients have *nonmeasurable* disease only.

Table ATT.8.2. Time Point Response: Patients with Nontarget Disease Only

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

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease.

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

Frequency of Tumor Re-Evaluation

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

Confirmatory Measurement/Duration of Response

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

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

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

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective

progression is observed (taking as reference for PD the smallest measurements recorded on study). For any patient who is not known to have died or to have had progression of disease as of the data inclusion cut-off date, duration of response will be censored at the date of last objective response assessment prior to the date of any subsequent systemic anticancer therapy. The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

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

Independent Review of Response and Progression

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

Immune-related RECIST (irRECIST) Assessment of Disease

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab (immune-related RECIST [irRECIST]). irRECIST will be applied as detailed below for treatment-related decisions, and the resulting data will be included in the clinical database.

If radiologic imaging verifies initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing study treatment per below while awaiting radiologic confirmation of progression.

If repeat imaging shows <20% increase in target lesion size compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued / resumed.

If repeat imaging confirms PD due to any of the scenarios listed below, patients will be discontinued from study treatment.

In determining whether or not the tumor burden has increased or decreased, site study team should consider all target lesions as well as non-target lesions.

Scenarios where PD is confirmed at repeat imaging:

- Tumor burden remains increased ≥ 20% and at least a 5-mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is worse (qualitative)
- New lesion resulting in initial PD is worse (qualitative)
- Additional new lesion(s) since last evaluation

In patients who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a patient on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Patients may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- no decline in ECOG performance status
- absence of rapid progression of disease

- absence of progressive tumor at critical anatomical sites (for example, cord compression) requiring urgent alternative medical intervention

When feasible, patients should not be discontinued from study treatment until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some patients can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Patients who are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

Table ATT.8.3 summarizes the guidance for imaging and treatment after the first radiologic evidence of PD.

Table ATT.8.3. Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
First radiologic evidence of PD by RECIST 1.1	Repeat imaging ≥4 weeks later at site to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan	Repeat imaging ≥4 weeks later to confirm PD, per investigator discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with sponsor)[a]	No additional imaging required[b]	N/A
Repeat tumor imaging shows SD, PR, or CR by irRECIST at the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

Abbreviations: CR = complete response; irRECIST = immune-related Response Evaluation Criteria In Solid Tumors; N/A = not applicable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] If a subject has confirmed radiographic progression (that is, 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals outlined in Section 8.3.

[b] Patients that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation.

Attachment 9. Protocol Amendment I5B-MC-JGDQ(c) Summary

Overview

Protocol I5B-MC-JGDQ, An Open-Label, Multicenter, Phase 1a/1b Study of Olaratumab (LY3012207) Plus Pembrolizumab (MK3475) in Patients with Unresectable Locally Advanced or Metastatic Soft Tissue Sarcoma Who Have Failed Standard Treatments, has been amended. The new protocol is indicated by Amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

Lilly has elected to make the following changes to this protocol; these changes are shown in the "Revised Protocol Sections" section below:

- Added an exclusion criterion for patients that have had an allogenic tissue or solid organ transplant, consistent with other pembrolizumab clinical trials (Section 6.1.2).
- Added the ability for pembrolizumab to be supplied for the study as an aqueous solution in addition to the lyophilized powder formulation (Section 7.1.2).
- Updates to the management of pembrolizumab related AEs were added consistent with other ongoing pembrolizumab protocols (Table JGDQ.4).
- Clarified data collection requirements intended for the follow-up period (Table JGDQ.6).
- Updated the olaratumab premedication instructions (Section 7.2.1.1.1).
- Other minor editorial changes were made to add clarity.

Revised Protocol Sections

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

1. Protocol I5B-MC-JGDQ(~~b~~c)

…

Protocol Electronically Signed and Approved by Lilly on 07 October 2016
Amendment (a) Electronically Signed and Approved by Lilly on 07 ~~Feburary~~February 2017.
-Amendment (b) Electronically Signed and Approved by Lilly on 30 November 2017.
Amendment (c) Electronically Signed and Approved by Lilly on date provided below.

2. Synopsis

…

Objectives:

…

Phase 1a secondary objectives:

- To characterize the pharmacokinetics (PK) and ~~(PK)~~ pharmacodynamics (PD) of olaratumab when administered in combination with pembrolizumab

…

CCI [redacted]

Diagnosis and Main Criteria for Inclusion and Exclusions:

…

Exclusion:

…

[23] Have had an allogenic tissue/solid organ transplant.

…

Criteria for Evaluation

…

Immunogenicity: Validated assay internally developed by Lilly and designed to detect anti-drug antibodies (ADA) in the presence of olaratumab and by external assay for detection of anti-Galactose-alpha-1,3-galactose immunoglobulin (Ig)E antibodies.

Pharmacokinetics: Serum concentrations of olaratumab obtained at different time points will be summarized by descriptive statistics and noncompartmental analysis. Additional analysis utilizing the population ~~pharmacokinetic~~ PK approach may also be conducted.

CCI [redacted]

…

…

4. Abbreviations and Definitions

Term	Definition
…	
DP	drug product
DS	drug substance
…	
PVC	polyvinyl chloride
…	

5. Introduction

5.1. Rationale and Justification for the Study

…

To date, there has been limited success with the use of immune checkpoint inhibitors in STS. Recently, data from several early studies of immune checkpoint inhibitors in STS have shown limited benefit to patients: A recent Phase 2 study of nivolumab in uterine leiomyosarcoma had no responses among the initial 12 patients (Ben-Ami et al. 2017); a retrospective review of nivolumab use in patients with metastatic STS or bone sarcomas showed 3 partial responses among 28 patients (Paoluzzi et al. 2016); and a study of pembrolizumab in prespecified histologic subtypes of STS showed responses varied between subtypes (Tawbi et al. 2017). In this trial (SARC-028) pembrolizumab was studied in patients with bone sarcomas or STS evaluated patients with 4 types of STS (leiomyosarcoma, poorly differentiated/de-differentiated liposarcomas, undifferentiated pleomorphic sarcomas [UPS], and synovial sarcomas; approximately 10 patients per group). Objective response rate (ORR) of 40% (1 CR and 3 PR in 10 patients) was observed in the undifferentiated pleomorphic sarcoma subtype. In the poorly differentiated/dedifferentiated liposarcoma and synovial sarcoma groups, 2 and 1 PRs, respectively, were observed (N=10 for both groups). In the leiomyosarcoma group, 0 of 10 patients achieved a PR or better (Tawbi et al. 2017). .

…

5.1.3. Rationale For Amendment (c)

Protocol Amendment (c) for Study JGDQ adds the ability for pembrolizumab to be supplied for the study as an aqueous solution in addition to the lyophilized powder formulation.

The amendment also adds an exclusion criterion for patients that have had an allogenic tissue or solid organ transplant, consistent with other pembrolizumab clinical trials. Moreover, it clarifies data collection requirements intended for the follow-up period.

Amendment (c) also includes an update to the olaratumab premedication instructions.

Minor editorial changes have been made throughout the protocol to improve clarity and practicability of the protocol, secure alignment with the intended study design, and update information available for study drugs.

…

5.2. Objectives

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…

6. Investigational Plan

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6.1. Study Population

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6.1.2. Exclusion Criteria

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[19] Have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte colony stimulating factors [G-CSF], GM-CSF or recombinant ~~erythropoetin~~erythropoietin) within 2 weeks prior to study Day 1.

…

[23] Ha~~s~~ve had an allogenic tissue/solid organ transplant.

…

7. Treatment

7.1. Materials and Supplies

7.1.1. Olaratumab

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

histidine, 100-mM glycine, 50-mM sodium chloride, 75-mM mannitol, and 0.02% polysorbate-20, pH 5.5. All excipients used in the formulation of olaratumab drug product (DP) are of pharmacopeial grade.

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

…

7.1.2. Pembrolizumab

~~The drug product pembrolizumab will be supplied~~ Two DP dosage forms are available for pembrolizumab: a white to off white lyophilized powder, 50 mg/vial, and a liquid, 100 mg/vial, both in Type I glass vials intended for single use only.

- Pembrolizumab Powder for Solution for Infusion, 50 mg/vial is a lyophilized powder that is reconstituted with sterile water for injection prior to use. It is manufactured using either the fully formulated drug substance (DS) or the partially formulated DS. The fully formulated DS uses L histidine as a buffering agent, polysorbate 80 as surfactant, and sucrose as stabilizer/tonicity modifier. Pembrolizumab DP using the partially formulated DS is formulated with L histidine as a buffering agent, polysorbate 80 as a surfactant, and sucrose as a stabilizer/tonicity modifier and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (if necessary).
- Pembrolizumab Solution for Infusion 100 mg/vial is a liquid DP (manufactured using the fully formulated DS with L histidine as a buffering agent, polysorbate 80 as a surfactant, and sucrose as a stabilizer/tonicity modifier).

Both DP dosage forms are stored under refrigerated conditions (2°C to 8°C).

The lyophilized DP after reconstitution with sterile water for injection and the liquid DP are clear to opalescent solutions, essentially free of visible particles. The reconstituted lyophilized product and the liquid product are intended for IV administration. The reconstituted DP solution or the liquid DP can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in IV containers made of polyvinyl chloride (PVC) or non PVC material. Reconstituted vials should be used immediately to prepare the infusion solution in the IV bag, and the infusion solution should be administered immediately. If the diluted pembrolizumab solution is not used immediately, it may be stored for no more than 24 hours at 2°C to 8°C. This 24 hour total hold from reconstitution may include up to 6 hours at room temperature (at or below 25°C). Any additional hold time must be at 2°C to 8°C. If refrigerated, the vials and/or IV bags must be allowed to come to room temperature prior to use.

The recommended dose of pembrolizumab in adults is 200 mg administered as an IV infusion over 30 minutes Q3W.~~as a~~A ~~sterile, non-pyrogenic lyophilized powder for IV infusion in single-use Type I glass vials containing 50 mg of pembrolizumab. The product is preservative-free, white to off-white powder and free from visible foreign matter. The pembrolizumab powder~~

~~should be reconstituted with 2.3-mL sterile water for injection (SWFI; injected along the walls of the vial and not directly on the powder) to yield a 2.4-mL solution containing 25 mg/mL of pembrolizumab.~~

~~The drug product must be stored under refrigerated condition 2°C to 8°C (36°F to 46°F). Prior to reconstitution, the vial of lyophilized powder can be out of refrigeration (temperatures at or below 25°C [77°F]) for up to 24 hours.~~ Aa -

~~Following reconstitution with SWFI, pembrolizumab infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) or regional equivalent and the final concentration of pembrolizumab in the infusion solution should be between 1 mg/mL and 10 mg/mL. If normal saline is not available, 5% Dextrose Injection, USP or regional equivalent (5% dextrose) is permissible. The preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.~~

~~Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted drug product solution in vials, room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, reconstituted vials and/or IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) for up to 20 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.~~

~~Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if discoloration or extraneous particulate matter (other than translucent to white proteinaceous particles) is observed.~~

~~Sites should follow their SOPs for drug transport and delivery, with all possible effort to minimize agitation of the reconstituted and diluted drug product between the pharmacy and the clinic~~

~~**Do not shake or freeze pembrolizumab vial(s). Do not administer the product as an IV bolus. Do not combine, dilute, or administer pembrolizumab as an infusion with other medicinal products. Do not coadminister other drugs through the same infusion line.**~~

7.2. Study Drug Administration

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7.2.1. Dosing Schedule

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7.2.1.1. Olaratumab

Olaratumab will be administered as an approximately 60 ~~(± 5)~~ minute IV infusion on Day 1 and Day 8 of a 21-day cycle at the doses shown in Table JGDQ.2. ~~Certain exceptions~~Exceptions to the 60-minute duration of the olaratumab infusion are permitted; see Pharmacy Manual for more information.

7.2.1.1.1. Olaratumab Premedication

On Day 1 of each cycle, olaratumab should be administered prior to pembrolizumab. ~~Premedicate all patients with the following (or equivalent) medications: a histamine H1 antagonist (for example, diphenhydramine) and dexamethasone intravenously 30 to 60 minutes prior to the olaratumab doses on Days 1 and 8 of Cycle 1. For subsequent cycles, premedicate all patients with a histamine H1 antagonist (for example, diphenhydramine) intravenously 30 to 60 minutes prior to each dose of olaratumab.~~

Premedicate patients prior to administration of olaratumab as below:

- **Premedication in Cycle 1:**
  Premedication is **mandatory** for all patients during Cycle 1 prior to each dose of olaratumab. Premedicate all patients with the following (or equivalent) medications on Days 1 and 8 of Cycle 1:
  - Histamine H1 antagonist (for example, diphenhydramine)
  - Dexamethasone IV

- **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

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7.2.1.2. Pembrolizumab

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7.2.4. Dose Adjustments and Delays

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7.2.4.2. Pembrolizumab

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Table JGDQ.4. Dose Modification and Toxicity Management Guidelines for Immune Related AEs Associated with Pembrolizumab

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Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
…				
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

[1] Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:
For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

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7.5. Concomitant Therapy

…

7.5.1. Supportive Care Guidelines for Olaratumab

7.5.1.1. Infusion-Related Reactions

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An approximately 1-hour observation period is required after the administration of olaratumab during the first and second cycles of olaratumab. Patients should complete the olaratumab observation period prior to starting pembrolizumab (when applicable). If there is no evidence of an IRR during the initial 2 cycles of olaratumab, then no observation period is required for subsequent treatment cycles. In the event an IRR occurs thereafter, the 1-hour observation should be reinstituted. During the observation period, patients treated with olaratumab should be closely monitored for signs and symptoms indicative of an infusion reaction by the medical staff from the start of the infusion until at least 1 hour after the end of the infusion in an area where emergency medical resuscitation equipment and other agents (epinephrine, prednisolone equivalents, etc.) are available.

…

7.5.2. Supportive Care Guidelines for Pembrolizumab

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7.5.2.8. Pembrolizumab Infusion-Related Reactions

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Table JGDQ.6. Pembrolizumab Infusion-Related Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as	Patient may be premedicated 1.5 hr (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (for example, from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

…

Attachment 1. Study Schedule

…

I5B-MC-JGDQ(b) Treatment Period and Poststudy Assessments: Phase 1a and 1b

…

[c] **Long-term follow-up (Visits 803-8XX)** begins the day after 90-day safety follow-up is completed.
Follow-up for progression: Patients that discontinue study treatment for reasons other than progression will be followed every 6 weeks (±7 days) until PD or initiation of other anticancer therapy. Additional radiologic assessments are permissible at the discretion of the investigator.
Follow-up for survival: All ~~Patients~~ patients will be followed every 2 months (±7 days) for the first 2 years, then every 6 months (±14 days) until the patient's death or overall study completion.

…

PPD

Approver: PPD
Approval Date & Time: 18-Sep-2018 18:24:30 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 19-Sep-2018 11:16:30 GMT
Signature meaning: Approved