I5B-MC-JGDN Statistical Analysis Plan Version 3

I5B-MC-JGDN: A Phase 1, Open-Label, Dose-Escalation Study of Olaratumab as a Single Agent and in Combination with Doxorubicin, Vincristine/Irinotecan, or High-Dose Ifosfamide in Pediatric Patients with Relapsed or Refractory Solid Tumors

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1. Statistical Analysis Plan: I5B-MC-JGDN: A Phase 1, Open-Label, Dose-Escalation Study of Olaratumab as a Single Agent and in Combination with Doxorubicin, Vincristine/Irinotecan, or High-Dose Ifosfamide in Pediatric Patients with Relapsed or Refractory Solid Tumors

LY3012207

This Phase I study is a multicenter, nonrandomized, open-label, dose-escalation study in pediatric patients with relapsed or refractory solid tumors.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol I5B-MC-JGDN
Phase 1

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly on date provided below

Approval Date: 26-NOV-2016 GMT

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3. Revision History

Statistical Analysis Plan Version	Approval Date	Notes
1	28-Apr-2016 GMT	Approval was prior to the first patient visit.
2	21-Nov- 2016 GMT	Version 2 was approved after protocol amendment a. Updates include updates to annual report analyses as well as clarification of sections text such as PK, interim, and study plan figure etc.
3	26-Nov- 2018 GMT	Version 3 includes updates related to the addition of Part C and Infusion Related Reaction definition update.

4. Study Objectives

4.1. Primary Objective

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

4.2. Secondary Objectives

The secondary objectives of this study are:

- to investigate the pharmacokinetic (PK) of olaratumab as monotherapy and in combination with either doxorubicin, vincristine/irinotecan, or high-dose ifosfamide in pediatric patients;
- to assess immunogenicity in pediatric patients;
- to document any antitumor activity observed with olaratumab in combination with either doxorubicin, vincristine/irinotecan, or high-dose ifosfamide in pediatric patients.

4.3. Exploratory Objectives

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

5. A Priori Statistical Methods

5.1. Study Design and Sample Size Consideration

Study I5B-MC-JGDN (JGDN) is a multicenter, dose-escalation, open-label Phase 1 pediatric safety clinical trial with 3 distinct components, Part A, B and C.

Part A will consist of at least 12 evaluable pediatric patients. Given the expected diversity of age and body weight in the study population, this sample size is expected to provide the necessary amount of PK information in order to characterize the disposition of olaratumab in the pediatric population. During Cycle 1 monotherapy, if the DLT rate is >1/3 (for example, greater than 4 out of 12 patients), then the dose of olaratumab will be reduced to 10 mg/kg. If the DLT rate is >1/3 in the first cycle (Cycle 2) of any of the combination therapy arms, then appropriate dose de-escalation of olaratumab for that combination will occur. Another cohort with at least 3 patients will be studied for that combination with olaratumab at 10 mg/kg.

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

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

Part B will consist of at least 12 evaluable pediatric patients. These patients will be treated for 1 cycle (21 days) of olaratumab monotherapy at 20 mg/kg on Day 1 and Day 8. If the patient does not experience a DLT in the first cycle of monotherapy, or meet any other criteria for discontinuation, the patient will then receive olaratumab (20 mg/kg) in combination with any of the 3 chemotherapy regimens in Part A that have successfully passed the DLT criteria described above for Part A (doxorubicin or vincristine/irinotecan or high-dose ifosfamide per investigator discretion). During Cycle 1 monotherapy, if the DLT rate is >1/3 (for example,greater than 4 out of 12 patients), then the dose of olaratumab will be reduced to 15 mg/kg for patients subsequently enrolled. If the DLT rate is >1/3 in any of combination therapy arms, then appropriate dose de-escalation of olaratumab for that combination will occur.

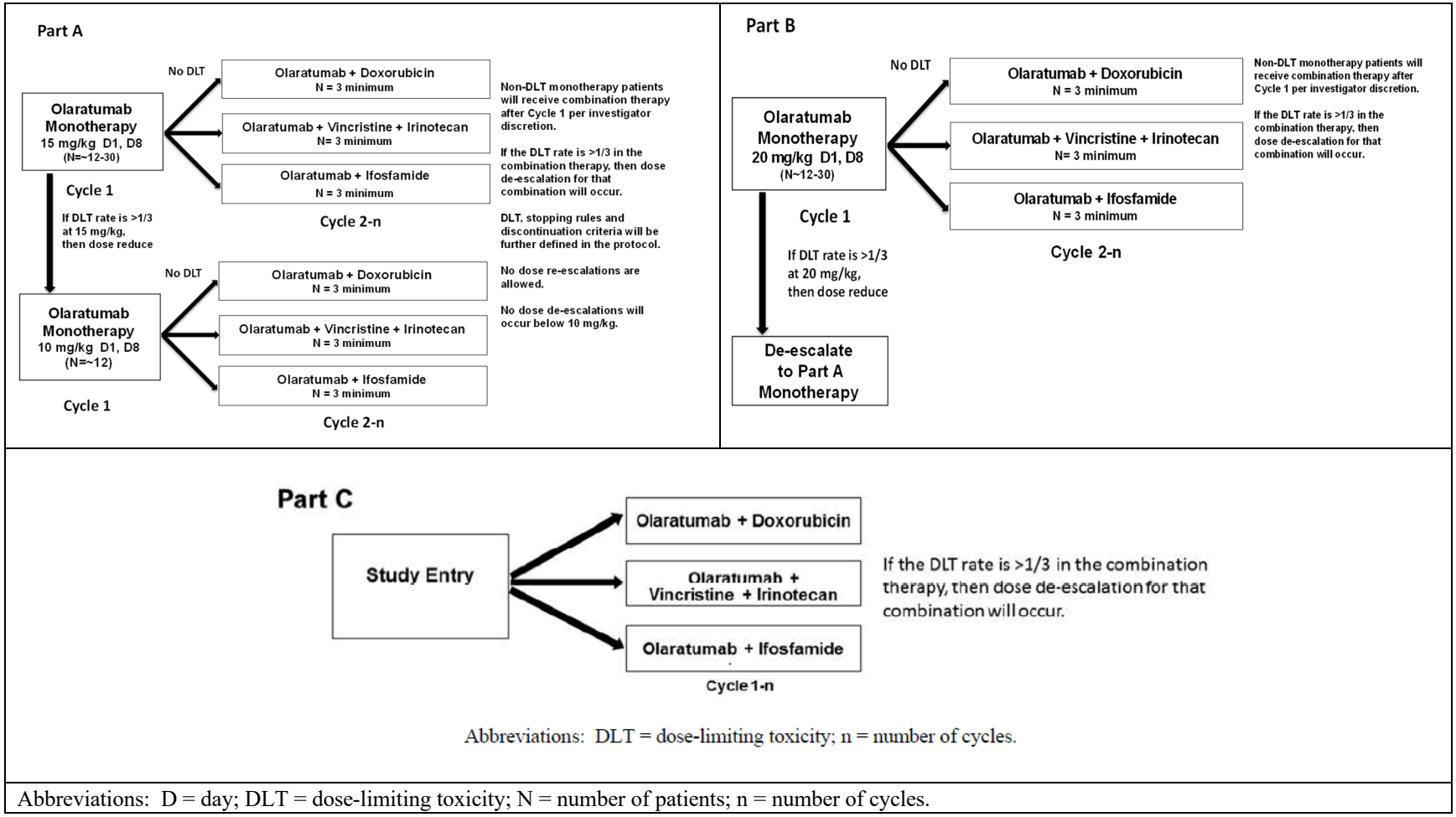
Part C patients will receive olaratumab (20 mg/kg) in combination with any of the 3 chemotherapy regimens (per investigator discretion) from Cycle 1onward (i.e no olaratumab monotherapy in Cycle 1 of Part C). Parts B and C together will enroll up to 45 patients (approximately 15 per chemotherapy arm). Treatment will continue until disease progression or other discontinuation criteria are met.The planned duration of treatment is not fixed; patients will remain on study until they fulfill one of the criteria for study discontinuation as specified in the protocol.

This study will enroll a minimum of 24 (maximum of 79) pediatric patients, including a minimum of approximately 10 osteosarcoma patients and 10 rhabdomyosarcoma patients across all treatment arms, if possible. The goal will be to enroll approximately 20 evaluable patients in

each combination arm across Parts A, B and C to characterize the safety and PK profile of olaratumab and the respective chemotherapeutic agents, and to inform dose choice for potential later-phase studies.

Figure JGDN.1 provides an illustration of the study design (Part A, B and Part C). Figure JGDN.2 provides an Olaratumab dosing plan for Part A, B and Part C of the study.

Figure JGDN.1 Illustration of study design



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

Figure JGDN.2 Illustration of Olartumab Dosing Plan[b]

Part A Cycle 1		**Combination Cycle 2 [a]**		**Combination Cycle 3 [a] onward**		**Initiate Part B if:**
15 mg/kg (~12 pts)	Acceptable DLT level	15 mg/kg	Acceptable DLT level	15mg/kg		Acceptable safety results, which must include a minimum of 6 evaluable patients, and the PK profile from Part A monotherapy
> 1/3 DLT			> 1/3 DLT Of any combination arm	10mg/kg (at least 3 pts)	No part B	At least one of the 15 mg/kg combination arms has met the following DLT criteria: less than one-third (that is, approximately ~33.3% [minimum of 3 patients]) DLT rate
10 mg/kg (~12 pts)		10mg/kg		10mg/kg	No part B	
Part B Cycle 1*		**Part B - Combination Cycle 2[a] / Part C Cycle 1[a]**		**Part B - Combination Cycle 3[a] onward / Part C – Combination Cycle 2[a] onward**		
20 mg/kg (~12 pts)	Acceptable DLT level	20 mg/kg	Acceptable DLT level	20 mg/kg		
> 1/3 DLT			> 1/3 DLT	15mg/kg		
15 mg/kg (~12 pts)	Acceptable DLT level	15 mg/kg	Acceptable DLT level	15 mg/kg		
> 1/3 DLT		> 1/3 DLT		10mg/kg		
		10mg/kg	Acceptable DLT level	10mg/kg		
		> 1/3 DLT	Study stop/reassess			
10 mg/kg (~12 pts)	Acceptable DLT level	10 mg/kg	Acceptable DLT level	10 mg/kg		
> 1/3 DLT (i.e. >4 of 12)		> 1/3 DLT				
Study stop/ reassess		Study stop or reassess				

a. In combination with any of the 3 chemotherapy regimens in Part A that have successfully passed the DLT criteria described above for Part A (doxorubicin or vincristine/irinotecan or high-dose ifosfamide per investigator discretion).

b. Part A and B includes monotherapy treatment of Olaratumab in cycle 1 with the remainder being combination treatment. Part C includes combination treatment starting from Cycle 1.

5.2. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly). The analyses for this study will be descriptive, except for possible exploratory analysis as deemed appropriate. Data analyses will be provided by dose groups and for all study patients combined wherever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, and percentages. Unless otherwise specified, missing data will not be imputed.

The interpretation of the study results will be the responsibility of the investigator with the Lilly Clinical Research Physician (CRP)/Clinical Research Scientist (CRS), pharmacokineticist, and statistician. The CRP or 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.

Exploratory analyses of the data not described below will be conducted as deemed appropriate.

5.3. Definitions of Analysis Variables

Definitions of safety and efficacy analysis variables are listed in Section 5.3.1 and Section 5.3.2, respectively.

The general analysis variables are listed below alphabetically.

- **Age (years)**: (Informed Consent Date - Date of Birth + 1)/365.25.

Note. Average days in a year = 365.25, reflecting the Julian Year of 3 years with 365 days each and 1 leap year of 366 days. Birth month and day are imputed to be 01 July because only birth year is collected through the case report form (CRF).

- **Baseline measurement:** The last non-missing measurement prior to or on the first dose date will serve as the baseline measurement.
- **Duration is calculated as:**
  - Duration (days): (End Date – Start Date + 1)
  - Duration (weeks): (End Date – Start Date + 1)/7
  - Duration (months): (End Date – Start Date + 1)/30.4375
  - Duration (years): (End Date – Start Date + 1)/365.25
- **Study Day**: Study day indicates the number of days relative to the date of first dose. The day is calculated as assessment date – first dose date + 1 day if the assessment is done on or after the first dose day. If the assessment is done prior to the first dose day, study day will be calculated as assessment date – first dose date. Date of first dose is defined as Study Day 1.

5.3.1. Safety Variables

Safety measures that will be used in the study include adverse events (AEs), DLT, clinical laboratory test results, vital signs, electrocardiograms (ECGs) and ECHO/MUGA scanning.

Dose Limiting Toxicity (DLT)

Dose-limiting toxicity is defined as an AE during Cycle 1 (Cycle 2 for combination treatment) for a patient enrolled in Part A and Part B that is possibly related to the study drug and fulfills any one of the following criterion using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0:

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

DLT-Equivalent Toxicity

A DLT-equivalent toxicity is defined as DLT event occurring in Cycle 3 or later.

Adverse event-related variables are listed below:

- **Adverse event (AE)** is defined as any untoward medical occurrence in a patient administered a pharmaceutical product, without regard to the possibility of a causal relationship.
- **AEs of special interest (AESIs)**

AESI for olaratumab:

- Infusion-related reactions (IRRs)

Notes: Categories of AESI may be modified as the understanding of the safety of the investigational drug increases. The final list of categories will be maintained at both compound and study level and reported in the clinical study report (CSR).

- Infusion Related Reactions (IRR) and delayed hypersensitivity reactions analysis uses the current standard Medical Dictionary for Regulatory Activities (MedDRA) Standardised Medical Queries (SMQs) to search for relevant events. Treatment-emergent adverse events are characterized as follows:
    - Anaphylactic reaction SMQ (narrow or algorithm per MedDRAra SMQ guide)
    - Hypersensitivity SMQ (narrow) excluding PTs specific to injection site reactions
    - Angioedema SMQ (narrow)
    - Event maps to Preferred Term (PT) of Infusion related reaction
    - Event maps to PT of Cytokine release syndrome.

  Medical review of each case identified by the algorithm above will be conducted prior to unblinding. Considerations for narratives and final designations include family history, pre-existing conditions, concomitant meds (e.g., was epinephrine used to treat), ruling out other confounding causes such as bee stings and food allergies, timing of the event, mechanism or biologic plausibility, and number of administrations. Such cases that clearly have a cause other than study drug will be excluded from the analyses.

  Time frame: a day of infusion will be considered for immediate IRRs (i.e. immediate hypersensitivity reactions). The 6 days after an infusion will be considered for delayed hypersensitivity reactions (i.e. if olaratumab is administered on Day 1 events occurred on Days 2 to 7 are considered; if olaratumab is administered on Day 8 events occurred on Days 9 to14 are considered).

- **Consolidated AEs** are composite AE terms consisting of synonymous Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) to allow meaningful interpretation of the AE data. Consolidated AE categories and PTs will be maintained at compound level and reported in the CSR.
- **Serious adverse event (SAE)** is any AE that results in one of the following outcomes:
    - death
    - a life-threatening experience (that is, immediate risk of dying)
    - persistent or significant disability/incapacity
    - initial or prolonged in-patient hospitalization
    - congenital anomaly/birth defect
    - considered significant by the investigator for any other reason
- **Treatment-emergent adverse event (TEAE)** is defined as an event that first occurred or worsened in severity after baseline and 30 days after the last dose of study treatment and

related SAEs reported beyond 30 days after the last dose of study treatment, where last dose stands for actual dose, that is, 0 dose is not counted as last dose.

Exposure-related variables are listed below:

- **Dose exposures**: As reported in the eCRF
- **Number of dose level reductions**: Sum of the number of dose level reductions as reported in the eCRF
- **Dose delays**: As reported in the eCRF
- **Dose withheld/skip (Not Administered)**: As reported in the eCRF
- **Dose interruption**: As reported in the eCRF

5.3.2. Efficacy Variables

The study was not designed to make an efficacy assessment. However, any tumor response data will be tabulated according to study part and patient cohort.

Exploratory efficacy analysis will be performed to investigate antitumor activity within each combination arm. Response and disease progression will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al. 2009) for all tumors with the exception of CNS tumors. RANO (Wen et al. 2010) or Macdonald (Macdonald et al. 1990) criteria should be used for CNS tumors.

Overall Response Rate (ORR) is defined as the percentage of patients achieving a best overall response of either Complete Response (CR) or Partial Response (PR), as determined by RECIST 1.1/RANO/Macdonald criteria. The best overall response is the best response from the start of the treatment until PD/recurrence.

Disease control rate (DCR) is defined as the percentage of patients achieving a best overall response of CR, PR, or SD. Patients who do not have any postbaseline tumor response assessments for any reason are considered non-responders and are included in the denominator when calculating the response rate.

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 the criteria is met for PD is objectively documented, or initiation of other/additional antitumor therapy is first reported, or death. Patients who do not relapse are censored at the day of their last tumor assessment.

Progression-free survival (PFS) is defined as the time from the date of first study dose to the first date of radiologic disease progression or death due to any cause. Table JGDN.5.1 defines the rules of censoring to be applied to PFS.

Table JGDN.5.1. Censoring Rule of PFS Primary Analysis

Situation	Event / Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate radiological assessment or date of first study dose
unless		
No baseline radiological tumor assessment available	Censored	Date of first study dose
No adequate postbaseline radiological tumor assessment available and death reported after 2 scan intervals following first study dose	Censored	Date of first study dose
New anticancer treatment started and no tumor progression or death within 14 days	Censored	Date of adequate radiological assessment prior to (start of new therapy +14 days) or date of first study dose (whichever is later)
Tumor progression or death documented immediately after 2 or more consecutive missing scan intervals following last adequate radiological tumor assessment or first study dose (whichever is later)	Censored	Date of last adequate radiological assessment prior to the missing assessment or date of first study dose

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression free survival; PR = partial response; SD = stable disease.

a Symptomatic deteriorations (that is, symptomatic progressions, which are not radiologically confirmed) will not be considered as disease progressions.

b Adequate radiological tumor assessment refers to an assessment with one of the following responses: CR, PR, SD, or PD.

c The 2-scan interval is counted from the date of last adequate tumor assessment to the date of next 2 scheduled tumor assessments plus 14 days (adjusted by tumor assessment window).

d Refer to flow chart in Appendix 1 if a patient meets multiple censoring criteria.

e If there are multiple dates associated with 1 assessment, the assessment date will be set to the first date when the overall response is PD and the last date otherwise.

Overall survival (OS) is defined as the time from the date of first study dose to death due to any cause. Patients will be censored at the date of last known alive.

5.4. Study Patients

5.4.1. Analysis Population

Table JGDN.5.2 lists analysis population definitions and associated data type for analysis.

Table JGDN.5.2. Analysis Populations

Population	Definition	Analysis Type / Variable	Note
All Entered Patients	All patients who signed Inform Consent		
Safety Population	All entered patients who received any quantity of study drug	Baseline characteristics, concomitant medication, efficacy analyses, Safety, e.g. dosing/exposure, AE and resource utilization.	For efficacy analysis, patients will be grouped according to the assigned dose level cohort. For safety analysis, patients will be grouped according to the actual dose level received.
DLT-evaluable Population	Patients who complete Cycle 1 (Part A/B Cycle 2 for combination treatment) or discontinue due to a DLT prior to completing Cycle 1 treatment (Part A/B Cycle 2 for combination treatment) .	DLT assessment/AE	Patients will be grouped according to the actual dose level received.

Abbreviations: AE = adverse event; DLT = Dose-Limiting Toxicity.

5.4.2. Patient Disposition

A detailed description of patient disposition will include:

- Summary of the number of patients who entered into the study, and who received at least one dose of study treatment, by site, dose level, overall.
- The summary of the number (and percent) of patients with the primary reasons for discontinuation from study treatment and patients still receiving treatment by dose level and overall. The discontinuation reasons collected in CRF (eg. AE, PD, death, and etc) will be presented.
- Listing of patient discontinuation.

5.4.3. Demographic and Baseline Characteristics

The following patient demographic and other baseline characteristics will be summarized:

- patient demographics: age (years) and age group, gender, race (White, Black, Asian, All Other), ethnicity, height (cm), weight (kg), and BSA (m2), Karnofsky and Lansky performance status
- baseline disease characteristics:
  - at study entry only: current disease stage, grade, duration of disease (months)

- prior cancer therapies: type of therapy (surgery, radiotherapy, systemic therapy), type of prior surgery, type of prior radiotherapy, and type of prior systemic therapy
- Medical history by MedDRA PT, presented in decreasing frequency

  Note: Subjects reporting more than 1 condition/diagnosis within a PT will be counted only once for that PT.

Patient listings of demographic data and baseline characteristics will be provided. Patient listings of prior cancer therapies (surgery, radiotherapy, and systemic therapy) will also be provided.

Other patient characteristics will be summarized as deemed appropriate.

5.5. Important Protocol Deviations

Protocol deviations will be identified in Protocol Deviation Plan. Important protocol deviations (e.g. not meeting inclusion/exclusion criteria, noncompliance with protocol procedures, dosing errors, use of prohibited medication, continuing after meeting withdrawal criteria) will be listed by treatment group and by category of deviations.

5.6. Concomitant Medications

The following concomitant medications used during study treatment period or up to the 30-day postdiscontinuation follow-up period will be summarized by numbers and percentages by dose cohort, presented in decreasing frequency of the World Health Organisation drug term:

- all concomitant medications
- premedication for study drug

Patient listing of all concomitant therapies and premedications will be provided.

5.7. Treatment Compliance

The number of dose omissions, reductions, and delays, and the number of cycles received will be summarized by cohort.

A by-patient listing of treatment compliance data will be provided.

5.8. Efficacy Analyses

The study was not designed to make an efficacy assessment. Exploratory efficacy analysis will be performed to investigate antitumor activity within each combination arm. The efficacy analysis will include all treated patients (ie. Safety Population). Tumor response data will be tabulated according to dose cohort and combination arm. A listing of best overall response will be provided by cohort. Best overall response will be summarized by dose cohort and combination arm. The objective response rate (ORR=CR+PR) and disease control rate (DCR=CR+PR+SD) along with the 90% exact confidence interval (CI) will be tabulated for each cohort and combination arm. For patients having CR/PR, the median duration of response,

together with a 90% CI will be estimated using Kaplan-Meier method. The median PFS will be estimated along with 90% CI by dose cohort and combination arm, using Kaplan-Meier method.

Any deaths observed during the study will be summarized descriptively and possibly interpreted in the context of study drug dose for each patient observed to have died. Dependent on the maturity of the data, overall survival may be analyzed using time-to-event methods, such as Kaplan-Meier.

5.9. Safety Analyses

All the safety analyses will be performed based on Safety Population.

5.9.1. Study Drug Exposure

Study drug exposure will be summarized based on Safety Population. The summary will include duration of treatment, number of infusions, the number of cycles received per patient, cumulative dose, cumulative dose level, weekly dose intensity, relative dose intensity, by dose cohort and combination arm. Details of study drug administration will be included in patient listings.

Dose modifications and delays will also be summarized.

The exposure formulas are defined below.

Olaratumab:

- Duration of treatment (weeks) = ([Date of last dose − date of first dose] + 21) ÷ 7
- Cumulative dose (mg) = Sum of all doses
- Cumulative dose level (mg/kg) = Sum of (dose administered at each infusion [mg] ÷ Last available weight [kg] prior to that infusion)
- Weekly dose intensity (mg/kg/week)=(Cumulative dose level) ÷ (Duration of Treatment)
- Planned weekly dose intensity (mg/kg/week) (depending on the cohort)
  - Part A = 10 mg/kg/week
  - Part B = (2 x 20 mg/kg) / 3 weeks =40/3 mg/kg/week
- Relative dose intensity (%) = (Weekly dose intensity) ÷ (Planned weekly dose intensity) x 100

Doxorubicin:

- Duration of treatment (weeks) = ([Date of last dose − date of first dose] + 21) ÷ 7
- Cumulative dose (mg) = Sum of all doses
- Cumulative dose level (mg/m^2) = Sum of (dose administered at each infusion [mg] ÷ Last available body surface area [BSA] [m^2] prior to that infusion)
- BSA (m^2) = 0.007184 * weight (kg) ^0.425 * height (cm) ^0.725

- Weekly dose intensity (mg/m^2/week) =(Cumulative dose level) ÷ (Duration of treatment)
- Planned weekly dose intensity (mg/m^2/week) = 2 x 37.5 mg/m^2/ 3 weeks=25
- Relative dose intensity (%)=(Weekly dose intensity) ÷ (Planned weekly dose intensity) x 100

Vincristine:

- Duration of treatment (weeks) = ([Date of last dose − date of first dose] + 21) ÷ 7
- Cumulative dose (mg) = Sum of all doses
- Cumulative dose level (mg/m^2) = Sum of (dose administered at each infusion [mg] ÷ Last available body surface area [BSA] [m^2] prior to that infusion)
- BSA (m^2) = 0.007184 * weight (kg) ^0.425 * height (cm) ^0.725
- Weekly dose intensity (mg/m^2/week) =(Cumulative dose level)÷(Duration of treatment)
- Planned weekly dose intensity (mg/m^2/week)
  - If patient baseline weight>10kg: = 2 x 1.5 mg/m2/ 3 weeks=1
  - If patient baseline weight <10kg: =2 x 0.05/3 weeks=1/30
- Relative dose intensity (%)=(Weekly dose intensity)÷(Planned weekly dose intensity) x 100

Irinotecan:

- Duration of treatment (weeks) = ([Date of last dose − date of first dose] + 21) ÷ 7
- Cumulative dose (mg) = Sum of all doses
- Cumulative dose level (mg/m2) = Sum of (dose administered at each infusion [mg] ÷ Last available body surface area [BSA] [m2] prior to that infusion)
- BSA (m2) = 0.007184 * weight (kg) ^0.425 * height (cm) ^0.725
- Weekly dose intensity (mg/m2/week) =(Cumulative dose level) ÷ (Duration of treatment)
- Planned weekly dose intensity (mg/m2/week) = 5 x 50 mg/m2/ 3 weeks=250/3
- Relative dose intensity (%)=(Weekly dose intensity) ÷ (Planned weekly dose intensity) x 100

Ifosfamide:

- Duration of treatment (weeks) = ([Date of last dose − date of first dose] + 21) ÷ 7
- Cumulative dose (g) = Sum of all doses
- Cumulative dose level (g/m2) = Sum of (dose administered at each infusion [g] ÷ Last available body surface area [BSA] [m2] prior to that infusion)

- BSA (m2) = 0.007184 * weight (kg) ^0.425 * height (cm) ^0.725
- Weekly dose intensity (g/m2/week) =(Cumulative dose level) ÷ (Duration of treatment)
- Planned weekly dose intensity (g/m2/week) = 5 x 2.8 g/m2/ 3 weeks=14/3
- Relative dose intensity (%)=(Weekly dose intensity) ÷ (Planned weekly dose intensity) x 100

5.9.2. Adverse Events

Adverse events will be coded using the MedDRA dictionary. Severity grades will be assigned by investigators using the NCI-CTCAE Version 4.0.

The AE analysis variables have been specified in Section 5.3.1.

Study drug-related AEs are AEs that were considered to be at least possibly related to study drug by an investigator. Missing relationship is considered related to all study drugs.

The most current version of MedDRA at time of analysis will be used when reporting AEs by MedDRA terms. Unless otherwise specified, when summarized by PT, AEs will be presented in descending frequency of PT across treatment arms; when summarized by system organ class (SOC) and PT, AEs will be presented in descending frequency of PT within SOC across treatment arms. If more than one AE is recorded for a patient within any SOC or PT term, the patient will only be counted once on the most severe grade and the closest relationship to treatment.

Dose-limiting toxicities and DLT-equivalent toxicities will be listed by cohorts.

An overall summary of AEs will be provided to summarize the following categories using frequency counts and percentages by dose cohorts and combination arms:

- patients with at least one treatment-emergent adverse event (TEAE), serious adverse event (SAE), or CTCAE Grade 3 or 4 TEAE
- patients with AEs that led to death (all, up to 30 days after last dose of study drug), or discontinuation of study drug regimen

The summary will be provided for regardless of study drug causality, and repeated for events deemed by the investigator to be related to study treatment.

Treatment-emergent adverse events (TEAEs) will be summarized/listed as follows:

- treatment-emergent AE by system organ class (SOC) and PT
- study drug related TEAE
- summary of TEAEs by worst CTCAE grade
- consolidated TEAEs by consolidated category and PT
- study drug related consolidated TEAE

- summary of TEAEs by PT and descending frequency
- listing of TEAE leading to death (on treatment and within 30 days of last dose of study drug)
- listing of TEAE leading to discontinuation of olaratumab, chemotherapy, or any study drug
- listing of TEAEs leading to dose modification of any study drug, olaratumab, or chemotherapy

A patient listing of all AEs will be provided.

The following treatment-emergent SAE summaries will be provided:

- summary of treatment-emergent SAE by SOC and PT
- summary of study drug-related treatment-emergent SAE by SOC and PT
- summary of consolidated treatment-emergent SAEs
- summary of study drug-related consolidated treatment-emergent SAEs

A listing of SAEs will be produced.

The following death reports will be provided:

- summary of deaths (all deaths and deaths within 30 days of last dose of study drug)

The following AE of special interest (AESIs) summary will be provided:

- summary of treatment-emergent AESIs by AESI group and PT (regardless of causality and study drug-related)
- listing of treatment-emergent AESIs

5.9.3. Clinical Laboratory Evaluation

The severity of laboratory results will be classified according to CTCAE Version 4.0. The shifts in CTCAE toxicity grading from baseline to worst postbaseline (first dose up to 30 days after the last dose of study treatment) grade will be produced.

A patient listing of all laboratory data will be provided with a flag for values outside of the laboratory normal range.

5.9.4. Vital Signs, Physical Findings, and Other Observations Related to Safety

Actual value and change from baseline for vital sign measurements will be summarized at each assessment time point using summary statistics. Electrocardiogram, Echocardiogram(ECHO)/MUGA measurements will also be summarized at each assessment time point using summary statistics. Listings of vital signs, ECG, ECHO/MUGA and data will be provided.

5.10. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of the study drug and have had samples collected. Serum concentrations of olaratumab prior to infusion (minimum concentration) and immediately after the infusion of olaratumab infusion (approximately maximum concentration) will be summarized by descriptive statistics or visually presented. Pharmacokinetic data collected for doxorubicin and doxorubicinol, vincristine, irinotecan, and ifosfamide will be analyzed using descriptive statistics.

Additional analyses such as population PK analysis and/or exposure-response using appropriate efficacy or safety clinical endpoints may be performed, if warranted by the data. If conducted the results willb e reported as a separate salnd alone report.

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

5.11. Immunogenicity

The immunogenicity analyses will be conducted on all immunogenicity evaluable patients (evaluable population) within the defined safety population. The frequency and percentage (incidence) of evaluable patients with positive, negative, or missing anti-drug antibody (ADA) to olaratumab at baseline, and with positive, negative, or inconclusive ADA at post-baseline will be summarized by dose cohort and combination treatment arm. Patients who are TE (treatment-emergent)-ADA positive (persistent positive or transient positive), TE-ADA persistent positive, and TE-ADA transient positive will also be summarized. Positive neutralizing ADA, negative neutralizing ADA and inconclusive neutralizing ADA will also be reported for patients with TE positive ADA.

The following analyses will also be performed based on evaluable or safety population:

- Listing of Treatment-Emergent Adverse Events for evaluable patients with at least one sample of ADA positive antibody to olaratumab (evaluable population)
- Listing of antibody to olaratumab and drug concentration data for evaluable patients who have at least one ADA positive sample (evaluable population)
- Listing of anti-olaratumab antibody for patients with IRR (safety population)
- Listing of antibody to olaratumab and drug concentration data (safety population)

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

5.12. Biomarker Analyses

Exploratory biomarker analyses will be performed according to a separate analysis plan.

5.13. Interim Analysis

No interim analyses are planned for this study.

Since this is a dose-finding study, data will be reviewed on a cohort-by-cohort basis during the study, until a tolerated dose of Olaratumab monotherapy will be identified in cycle 1 of Part A and Part B. DLTs will also be assessed within the combination therapy (Cycle 2 onward of Part A and B; Cycle 1 onward of Part C). Dose escalation and de-escalation are planned where decisions are based on DLT rates (see Figure JGDN.1). The starting dose in Part A is 15mg/kg and could de-escalate to 10 mg/kg if DLTs are observed. The dose in Part B will start at 20mg/kg and could de-escalate to the Part A identified tolerable Olaratumab dose. Part C will receive olartumab (20mg/kg) in combination with any of the 3 chemotherapy regimens from Cycle 1 onward (i.e. no olaratumab monotherapy in Cycle 1). The purpose of these cohort-by-cohort reviews is to evaluate the safety data at each dose level and determine if a DLT has been observed that would suggest a tolerated treatment combination has been met or exceeded. The investigators and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data as described in the protocol.

5.14. Annual Report Analyses

The following reports are needed as requested for annual reporting purposes

5.14.1. Clinical Investigator Brochure

- Summary of SAE (patients on therapy).
- Summary of deaths reported (patients on therapy).
- Summary of Patient disposition.
- Summary of primary reason for treatment discontinuation.
- Listing and summary of treatment-emergent adverse events –by CTCAE category and term.

5.14.2. Development Saftey Update Report

- Cumulative Subject Exposure by Age Group and Sex
- Cumulative Subject Exposure by Racial Group
- Estimated Cumulative Subject Exposure
- Subject Exposure by Gender
- Listing of Patients Who Discontinued Due to Adverse Event

- Listing of Deaths

5.15. Clinical Trial Registry Analyses

For the purpose of fulfilling the Clinical Trial Registry requirements, summaries of SAEs (whether treatment emergent or not) and 'Other' AEs (that is, non-serious TEAEs) by PT and treatment group will be performed. For each PT, the number of patients at risk, patients who experienced the event, and events will be presented. In addition, the summary will be provided as a dataset in XML format.

6. References

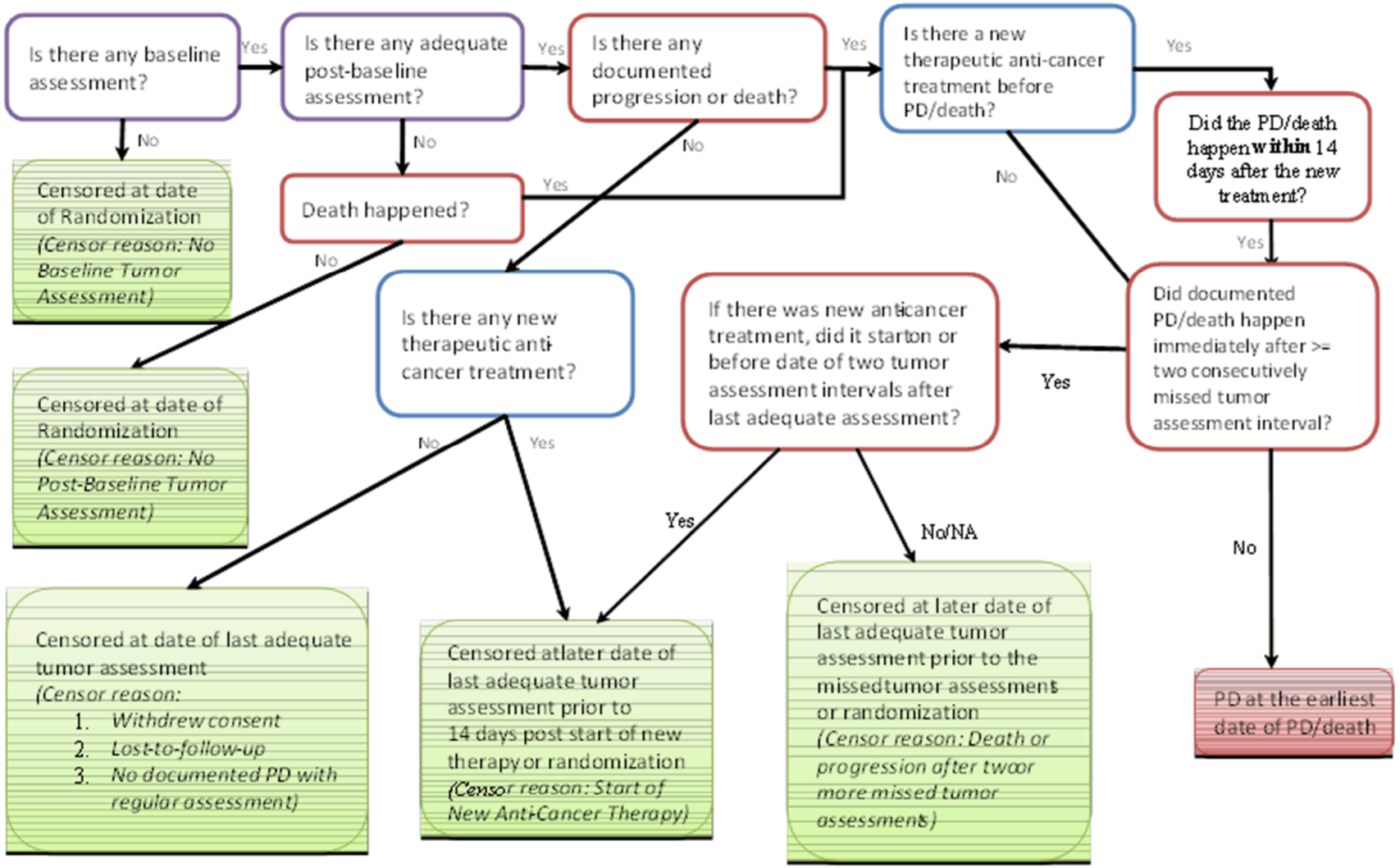
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Frod R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J.New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2) 228-247.

Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol*. 1990;8(7):1277-1280.

Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, DeGroot J, Wick W, Gilbert MR, Lassman AB, Tsie C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Lamborn KR, Voglebaum MA, van den Bent MJ, Chang SM. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology Working Group. *J Clin Oncol*. 2010;28(11):1963-1972.

7. Appendix

Appendix 1. Flow Chart of PFS Censoring Rules



Abbreviation: PD = progressive disease