Statistical Analysis Plan I5B-MC-JGDM

A Phase 1b Trial to Assess the Modulation of Biological Markers in Patients With Potentially Resectable Soft Tissue Sarcoma Treated With Olaratumab Monotherapy Followed by Olaratumab Plus Doxorubicin Combination Therapy

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1. Statistical Analysis Plan for Clinical Studies: I5B-MC-JGDM: A Phase 1b Trial to Assess the Modulation of Biological Markers in Patients with Potentially Resectable Soft Tissue Sarcoma Treated with Olaratumab Monotherapy Followed by Olaratumab plus Doxorubicin Combination Therapy

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Olaratumab (LY3012207) Soft Tissue Sarcoma

Study I5B-MC-JGDM is an open-label, single-arm, multicenter, multicountry Phase 1b study to enumerate whole blood circulating tumor cells and to characterize platelet-derived growth factor receptor alpha, platelet-derived growth factor receptor beta and canonical ligands (PDGF-A, B, C and D) expression changes pre- and post-olaratumab monotherapy..

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Protocol I5B-MC-JGDM
Phase 1b

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

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3. Revision History

Statistical Analysis Version	Approval Date	Notes
1	26OCT2016	First version.
2		Administrative and format changes; Updated AE and CM imputation rule; Clarification of efficacy population. Update to include lung disease subgroup analyses. Clarification of evaluable population to correspond to protocol amendment C.

4. Study Objectives

4.1. Primary Objective

The primary objectives of this study are:

- to enumerate circulating tumor cells (CTCs) changes pre- and post-olaratumab monotherapy in wholeblood in patients with potentially resectable soft tissure sarcoma(STS).
- to characterize PDGFRα and platelet-derived growth factor receptor beta (PDGFRβ) and canonical ligands (*PDGF-A, B, C*, and *D*) expression changes pre- and post-olaratumab monotherapy in tumor tissue in patients with potentially resectable STS.

4.2. Secondary Objectives

The secondary objectives of this study are:

- to evaluate any antitumor activity observed with olaratumab:
  - progression-free survival (PFS) and 3-month PFS
  - ORR (complete response [CR] + partial response [PR])
  - disease control rate (DCR) (CR+ PR + stable disease [SD])
  - rate of resectability.
- to evaluate the safety of olaratumab as assessed by reported AEs, clinical laboratory tests, vital signs, physical examinations, electrocardiograms (ECGs), and echocardiograms (ECHOs) or multi-gated acquisition (MUGA) scans.
- to evaluate the pharmacokinetics (PK) of olaratumab and immunogenicity (IG) parameters of olaratumab.

4.3. Exploratory Objectives

The exploratory objectives of this study are:

- to evaluate blood, CTCs, and tumor tissue pre- and post-therapy for biomarkers related to pathways associated with STS, the mechanism of action (MOA) of olaratumab, cancer-related conditions, and/or immune cells/immune and tumor microenvironment functioning within the disease state and/or cancer-related conditions.
- to assess the relationship between biomarker expression at baseline, and change from baseline, and clinical outcomes.

5. A Priori Statistical Methods

5.1. Study Design and Sample Size Consideration

Study JGDM is an open-label, single-arm, multicenter, multicountry Phase 1b study to enumerate whole blood CTCs and to characterize PDGFRα and PDGFRβ and canonical ligands (*PDGF-A, B, C* and *D*) expression changes pre- and post-olaratumab monotherapy in tumor tissue in patients with potentially resectable STS.

Patients are to be treated with 20 mg/kg of olaratumab on Day 1 and Day 8 of Cycle 1, followed by up to 6 cycles (Cycle 2 – Cycle 7) of combination therapy with olaratumab plus doxorubicin. For Cycle 2, olaratumab is to be dosed at 20 mg/kg on Day 1 and Day 8 and doxorubicin is to be dosed at 75 mg/m2 on Day 1. For Cycle 3 – Cycle 7, olaratumab is to be dosed at 15 mg/kg on Day 1 and Day 8 and doxorubicin is to be dosed at 75 mg/m2 on Day 1. Each cycle of treatment is defined as an interval of 21 days. Approximately 35 patients are to be enrolled.

Starting with the first cycle of combination therapy (Cycle 2), the use of dexrazoxane (in a 10:1 ratio vs. doxorubicin dose) to mitigate cardiotoxicity during treatment with doxorubicin is allowed at the investigator's discretion and is recommended for all patients receiving 5 or more cycles of doxorubicin.

Tissue biopsies are required pre- and posttreatment with olaratumab monotherapy. The pretreatment tissue biopsy is to be performed within the screening period. The posttreatment tissue biopsy is to be performed after completion of the lead-in cycle of olaratumab monotherapy and prior to the initiation of combination therapy in Cycle 2. An optional third tissue biopsy (or tissue from a posttherapy surgical resection specimen) may be performed at the end of the patient's study treatment. If clinically feasible, the tissue biopsies should be taken from the same primary tumor lesion. If the patient has an additional surgical resection, tissue from this procedure is requested. Refer to Protocol Section 8.2.3.2 for details on tissue biopsies.

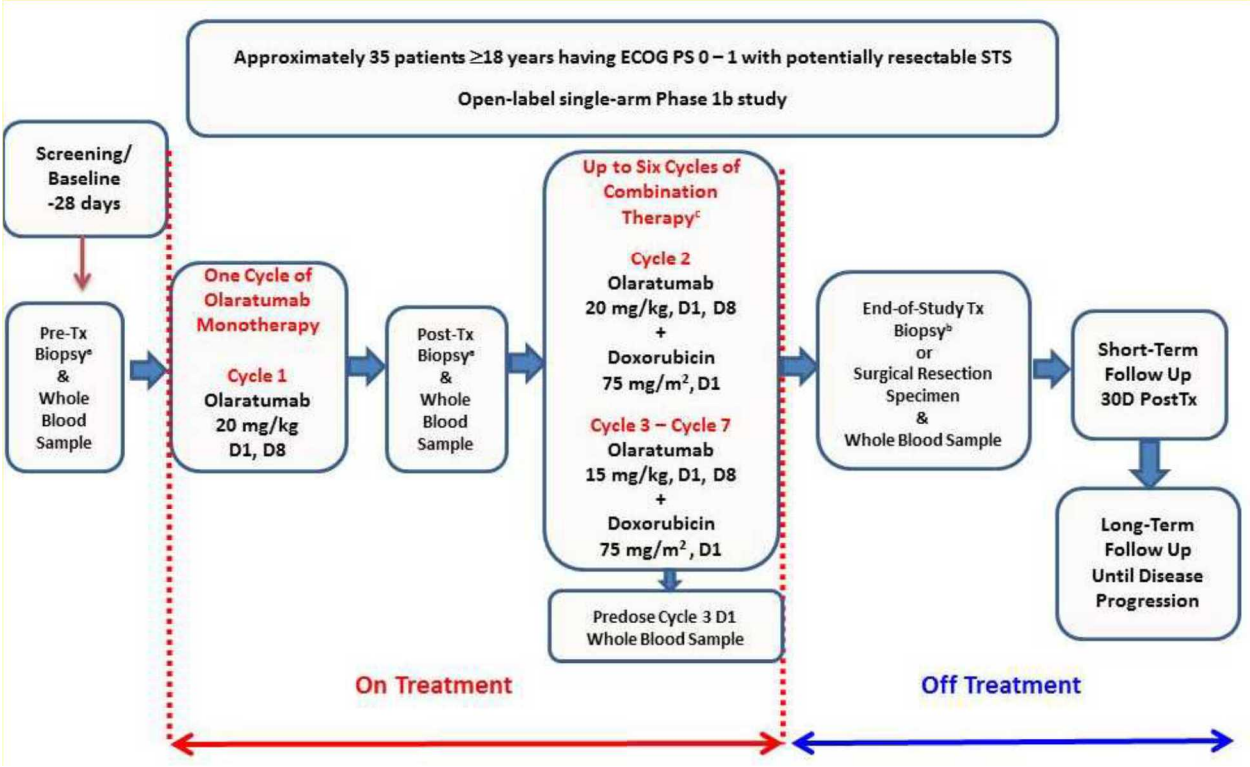
Whole blood samples for CTC analyses are to be collected predose at Cycle 1 Day 1 (C1D1), at Cycle 1 Day 8 (C1D8), at Cycle 2 Day 1 (C2D1), at Cycle 2 Day 8 (C2D8), at Cycle 3 Day 1 (C3D1), and at the end of the patient's study treatment or at the time of surgical resection. Refer to Protocol Section 8.2.3.1 for details on blood samples.

After 1 cycle of monotherapy, patients will receive combination therapy for up to 6 cycles or until evidence of progressive disease (PD), unacceptable toxicity, surgical resection, death, or other withdrawal criteria are met. Patients who discontinue study treatment for reasons other than progression or surgical resection will be followed every 6 weeks (±7 days) until PD.
Refer to Protocol Attachment 1 for the Study Schedule.
Figure JGDM.1 illustrates the study design.

To investigate the primary objective, approximately 35 evaluable patients have to have completed the pre-treatment tissue biopsy, the predose C1D1 whole blood draw, 1 cycle of olaratumab monotherapy, the post-olaratumab monotherapy biopsy, and the predose C2D1 whole blood draw.
If the patient is noncompliant during olaratumab monotherapy (Cycle 1) and does not undergo

the pre-treatment tissue biopsy, the post-olaratumab monotherapy biopsy, or the predose C2D1 whole blood draw, he or she will be considered nonevaluable and may be replaced.
It is hypothesized that 49% (17 out of 35) or more patients will have a reduction of at least 30% in PDGFRα level change in tissue from baseline to post-olaratumab monotherapy. The sample size of 35 patients provides a 95% CI that the hit rate (proportion of patients with at least 30% reduction in PDGFRα level change from baseline) will be between 31% and 66%, which excludes a 30% or lower hit rate.

Figure JGDM.5.1 Illustration of study design



Abbreviations: C1D1 = Cycle 1 Day 1; C2D1 = Cycle 2 Day 1; C3D1 = Cycle 3 Day 1; CTC = circulating tumor cell; D = day(s); ECOG PS = Eastern Cooperative Oncology Group performance status; STS = soft tissue sarcoma, tx = treatment.
a The pre- and post-olaratumab monotherapy tissue biopsies and the whole blood sample collections pre-dose at C1D1, C1D8, C2D1, and C2D8 for CTC analyses are mandatory. The pre-olaratumab monotherapy biopsy is to be collected within the screening period. The post-olaratumab monotherapy biopsy is to be collected after completion of Cycle 1 and prior to initiation of Cycle 2 combination therapy. If clinically feasible, the biopsies should be taken from the same primary tumor lesion.
b An optional third tumor tissue biopsy is to be collected at the end of the patient's study treatment or when the patient undergoes a surgical resection through which a posttherapy tissue specimen can be collected. If clinically feasible, the biopsies should be taken from the same primary tumor lesion. Additionally, a whole blood sample for CTC analysis is to be collected at C3D1 and at the end of the patient's study treatment or at the time of surgical resection.c See text in protocol Section 6.2, Summary of Study Design.
Note: Each cycle of treatment is defined as an interval of 21 days.

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 cycle (cycle 1 versus cycle 2 onward) for specified analyses 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 5.3.5, 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. It 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. Circulating Tumor Cells (CTC) enumeration in blood

For all samples collected for each patient, circulating tumor cells identified by a combination of morphology and/or diagnostic staining characteristics will be enumerated as a simple count of circulating tumor cells per milliliter of peripheral blood.

5.3.2. PDGFRα and PDGFRβ protein expression in tumor tissue

PDGFRα and PDGFRβ protein expression will be assessed by immunohistochemical staining interpreted by a pathologist experienced in interpreting these assays. Separate assays will be used for each receptor. Results of both assays will be reported as qualitatively positive or negative based on analytically validated criteria for interpretation of each assay's protein expression score.

5.3.3. PDGF-A, B, C, and D canonical ligand expression in tumor tissue

PDGF-A, B, C and D ligand expression will be assayed by real-time RT-PCR with relative quantification to housekeeping genes MRPL19, SF3A1 and PPIA. Normalized relative expression data will be reported using the Ct value of the gene of interest (GOI) and average Ct of the reference genes for that sample (RG) transformed with the following formula: 2^(20-GOI+RG)/1000. Additional approaches for normalizing and reporting relative gene expressions may be explored as deemed appropriate.

5.3.4. 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.

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)

  AESI for combination of olaratumab and doxorubicin:

  - Cardiac arrhythmias and cardiac dysfunction

  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).
- **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

5.3.5. Efficacy Variables

The study was not designed to make an efficacy assessment. However, any tumor response data will be tabulated according to assigned treatment.

Circulating tumor cells (CTC) will be assessed at pre-olaratumab and post-olaratumab in whole blood.

Secondary efficacy analysis will be performed to investigate antitumor activity by assigned treatment. 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.

Overall Response Rate (ORR) is defined as the percentage of patients achieving a best overall response of either Complete Response (CR), complete responses unconfirmed (CRus) or Partial Response (PR), as determined by RECIST 1.1. 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, CRu, PR, or SD as determined by RECIST 1.1. 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.

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 JGDM.5.1 defines the rules of censoring to be applied to PFS.

3-month Progression-free survival (PFS) is defined as the 3-month PFS rate as estimated using Kaplan-Meier methods. PFS is as defined above.

Rate of Resection is defined to be the percentage of patients whose tumors are determined to be resectable divided by the total number of patients. The evaluation of resectability of a tumor is determined by the surgeon in consultation with the multi-disciplinary team, and depends on the tumor stage and the patient's co-morbidity. The primary aim of surgery is to completely excise the tumor with a margin of normal tissue.

Table JGDM.5.1. Censoring Rule of PFS Primary Analysis

Situation	Event / Censor[d]	Date of Event or Censor[e]
Tumor progression[a] 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[b] postbaseline radiological tumor assessment available and death reported after 2 scan intervals[c] following first study dose	Censored	Date of first study dose
New anticancer treatment (including surgery) 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.

5.4. Handling of Dropouts or Missing Data

Rules for handling dropouts or missing data are listed by type of analysis alphabetically. Unless otherwise specified, observed data will be used and missing data will not be imputed or carried forward.

In the event that the date of progression is reported only to the nearest month, the date will be imputed for analysis (assumed to have occurred on the 15th day of the reported month).

General rules for imputing dates related to AE or concomitant therapy:

- Onset date of an AE or start date of a concomitant therapy:
    - If only the day is missing, the date will be set to:
        - First day of the month that the event occurred, if the onset yyyy-mm is after the yyyy-mm of first study treatment.
        - The day of the first study treatment, if the onset yyyy-mm is the same as yyyy-mm of the first study treatment.
    - If month is missing, the month should be set to July.
- Resolution date of an AE or end date of a concomitant therapy:
    - If only the day is missing, the date will be set to the last day of the month of the occurrence, or to the date of death if the patient died in the same month.
    - If month is missing, the month should be set to July.

If an onset date for an AE is missing, then the AE will be considered treatment emergent with unknown onset date. For additional therapies, if the start date is missing then the therapy will be assumed concomitant.

General rule for imputing other dates: If a date variable is needed for an analysis, use the following general rule to impute incomplete date:

- If only the day is missing, then assign Day 15 to the day.
- If month is missing, the month should be set to July.

However, after imputation, check if the imputed date is logically consistent with other relevant date variable(s) and make appropriate correction if necessary. For example, if a visit start date was 16 May 2008 and a tumor assessment date was xx May 2008 (missing day) but it was known that it occurred on or after that visit, then after imputation, the tumor assessment date became 16 May 2008. In this case, the imputed tumor assessment date should be compared to the visit start date and then corrected to be the later of the 15th day of the month and the visit start date.

Safety analysis: The following rule for missing data processing will apply for safety analysis:

- Missing classifications concerning study medication relationship will be considered as related to study medication (both components).
- If the AE onset date is missing or partial, the date will be compared as far as possible with the date of first dose of study medication when determining whether or not the AE is present at baseline. In this case, the AE will be assumed to be treatment emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first dose of study medication.

5.5. Study Patients

5.5.1. Analysis Population

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

Table JGDM.5.2. Analysis Populations

Population	Definition	Analysis Type / Variable	Note
All Entered Patients	All patients who signed Inform Consent		
Safety Population	All enrolled patients who receive any quantity of investigationalproduct (IP), regardless of their eligibility for the study, will be included in the safety analysis.	Baseline characteristics, concomitant medication, efficacy analyses, Safety, e.g. dosing/exposure, AE and resource utilization.	Safety evaluation will be performed based on the assigned therapy. Select analyses will be conducted by cycle 1 versus cycle 2 onward.
Efficacy Population	The efficacy analysis will be performed on the intent-to-treat (ITT) population, which includes all enrolled patients that have received any quantity of investigational product (IP), regardless of their eligibility for the study.	The ITT population will be included in overall patient listings, in summary tables of patient demographics and disease characteristics, in the list of treatment discontinuation after enrollment, and in the analysis of efficacy.	
Biomarkers Evaluable 1 Population (BE1)	The biomarker evaluable 1 (BE1) population will include all ITT patients with evaluable samples at both baseline and post-olaratumab monotherapy. If the patient is noncompliant during olaratumab monotherapy (Cycle 1) and does not undergo the post-olaratumab monotherapy biopsy or the C1D1 pre-dose and C2D1 predose whole blood sample collection due to reasons other than drug-related toxicity, he or she will be considered nonevaluable	The BE1 population will be used in the biomarker analyses for the primary objective and exploratory objectives.	
Biomarkers Evaluable 2 Population (BE2)	The biomarker evaluable 2 (BE2) population will include all ITT population with evaluable samples at both baseline and post-combination (olaratumab plus doxorubicin) therapy. If the	The BE2 population will be used in the biomarker analyses for the exploratory objectives.	

	patient is noncompliant during olaratumab monotherapy (Cycle 1) and does not undergo the post-olaratumab monotherapy biopsy or the C1D1 pre-dose and C2D1 predose whole blood sample collection due to reasons other than drug-related toxicity, he or she will be considered nonevaluable		

\Abbreviations: AE = adverse event; BE = Biomarker Evaluable; IP = Investigator Product; ITT = Intent-to-Treat.

5.5.2. 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, assigned treatment and 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 assigned treatment and overall. The discontinuation reasons collected in CRF (eg. AE, PD, death, and etc) will be presented.
- Listing of patient discontinuation.

5.5.3. 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), ECOG performance status
- baseline disease characteristics:
  - at study entry only: current disease stage, grade, duration of disease (months), lung disease (yes, no)
- 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.

5.6. 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.

5.7. Concomitant Medications

The following concomitant medications used during study treatment period or up to the 30-day (± 7 days) 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.

5.8. 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.

5.9. Biomarker Analyses

The primary endpoints of the study are

- CTC enumeration changes pre- and post-olaratumab monotherapy in whole blood
- PDGFRα and PDGFRβ and canonical ligands (PDGF-A, B, C, and D) expression changes pre- and post-olaratumab monotherapy in tumor tissue

The percent change from baseline for post-olaratumab monotherapy in biomarker expressions will be provided for each patient and summarized for all qualified patients in the BE1 population. For patients with an observed value of 0 for baseline expression or both baseline and post-olaratumab monotherapy expressions, a value of 0.1 will be used. In particular, summary of number and frequency of patients with at least 30% reduction in change from baseline PDGFRα expression will be provided.

Exploratory biomarker analyses may be described in a separate biomarker statistical analysis plan, if deemed necessary.

5.10. Efficacy Analyses

A secondary objective of the study is to document any antitumor activity. The efficacy analysis will be conducted on the intent-to-treat (ITT) population. Tumor response data will be tabulated according to assigned treatment. Best overall response will be also summarized by assigned treatment. A listing will also be provided. The objective response rate (ORR=CR+Cru+PR) and disease control rate (DCR=CR+Cru+PR+SD) along with the 95 exact confidence interval (CI) will be tabulated. For patients having CR/CRu/PR, the median duration of response, together with a 95% CI will be estimated using Kaplan-Meier method. The median PFS and OS will be estimated along with 95% CI using Kaplan-Meier method.

Any deaths observed during the study will be summarized descriptively for each patient observed to have died. See section 5.4 pertaining to missing data for additional details.

Similar efficacy analyses will be conducted for those with lung disease versus not.

5.11. Safety Analyses

All the safety analyses will be performed based on Safety Population. Most safety analyses will be conducted on entire treatment phase. However, a selection of safety analyses will be conducted on cycle 1 only and cycle 2 onward separately. See section 5.4 pertaining to missing data for additional details.

5.11.1. 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 assigned treatment. Details of study drug administration will be included in patient listings.

Dose modifications, delays and discontinuations 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
- Calculated dose level administered (mg/kg) = Actual total dose of olaratumab (mg) / Closest body weight prior to that administration (kg)Cumulative dose level (mg/kg) = Sum of all calculated infusion doses
- Dose intensity (mg/kg/week)=(Cumulative dose level)÷(Duration of treatment)
- Planned dose intensity (mg/kg/week)
  - Cycle 1 = 20 mg/kg/three weeks
  - Cycle 2= 20 mg/kg/three weeks
  - Cycle 3-7= 15mg/kg/three weeks

- Relative dose intensity (%) (Based on planned dose)= (Dose intensity) ÷ (Planned 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
- Dose intensity (mg/m^2/weeks) =(Cumulative dose level)÷(Duration of treatment)
- Planned dose intensity (mg/m^2/week) = 75 mg/m^2/ 3 weeks= 25 (Cycle 2-7)
- Relative dose intensity (%)=(Dose intensity)÷(Dose intensity) x 100

5.11.2. 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 5.3.4.

Study drug-related AEs are AEs that were considered to be at least possibly related to study drug by an investigator. See section 5.4 pertaining to missing data.

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.

An overall summary of AEs will be provided to summarize the following categories using frequency counts and percentages by assigned treatment:

- 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

5.11.3. 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.

5.11.4. 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.

5.12. Pharmacokinetic Analyses

Serum concentrations of olaratumab prior to infusion (minimum concentration) and immediately after the end of the olaratumab infusion (approximately maximum concentration) will be summarized by descriptive statistics or visually presented. Additionally, PK parameter estimates will be computed by standard noncompartmental methods of analysis for olaratumab PK samples collected during cycle 2. The maximum concentration (Cmax), time of Cmax (tmax), area under the concentration-time curve (AUC), half life (t1/2), volume of distribution (Vd), clearance (CL), and other relevant parameters that can be calculated from the data will be reported from these noncompartmental analyses. Additional analyses utilizing the population pharmacokinetic approach may also be conducted if deemed appropriate.

5.13. 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. Quantitative analysis will be conducted on total IgE and alpha-Gal. Analyses will include change from baseline, mean, median, range and standard deviation.

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)

Listing for alpha-Ga1 and igE (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.

Additional efficacy or safety analyses may be performed in the subgroup of patients and immunogenicity endpoints.

5.14. Interim Analysis

With limited prior experience with the performance of the biomarker assays (i.e, QC issues, dynamic range, data variability), an interim analysis will be done to evaluate the biomarker data once approximately half of the evaluable patients complete the second tumor tissue biopsy and C2D1 whole blood draw. The purpose of this interim analysis is to review the biomarker data in order to identify technical issues that may potentially impact the study's ability to meet its key objectives. If this interim look at the biomarker data warrants any changes in the study conduct, it will be implemented in an appropriate manner (that is, protocol amendment). At this interim analysis, a review of the safety data will also be conducted.

This would be in addition to the safety data review that will be conducted after 5 patients have completed 2 cycles of treatment.

5.15. Annual Report Analyses

The following reports are needed as requested for annual reporting purposes

5.15.1. 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.

5.15.2. 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

5.16. Clinical Trial Registry Analyses

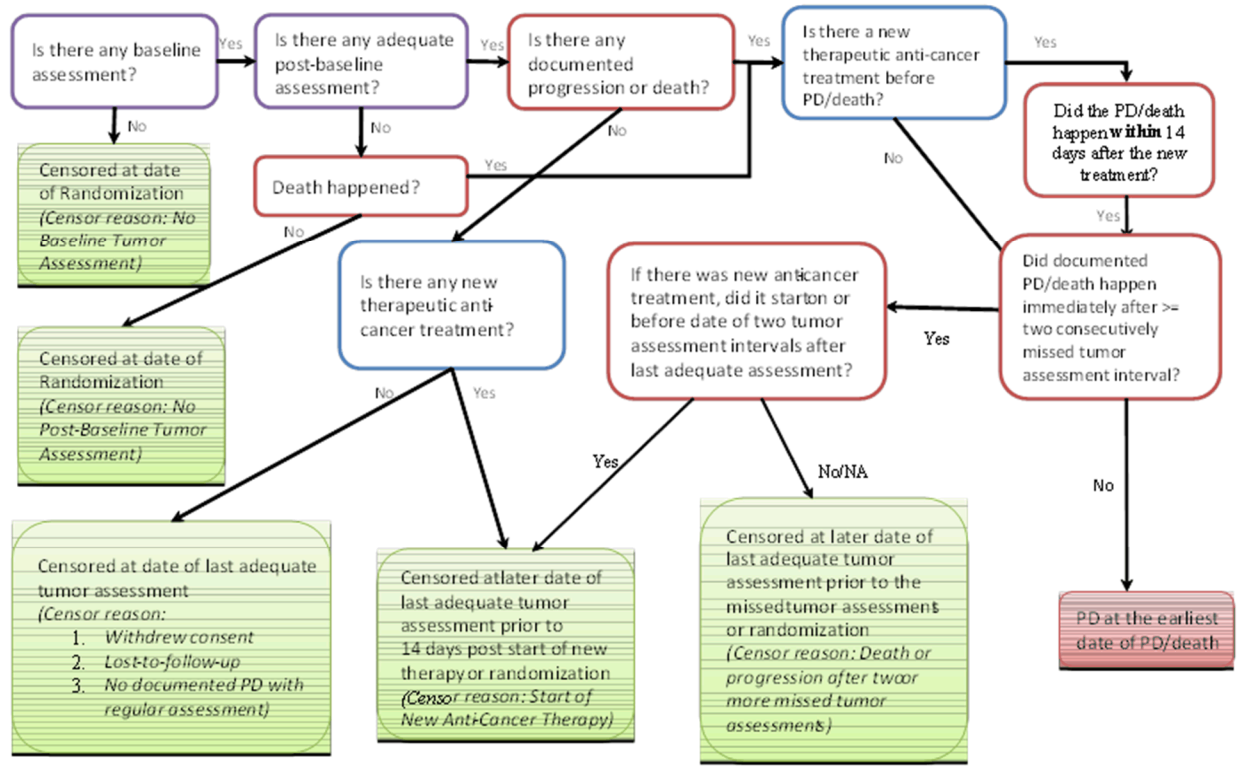
For the purpose of fulfilling the Clinical Trial Registry requirements, summaries of SAEs (whether treatment emergent or not) and 'Other' AEs (that is, non-serious TEAEs) by PT and treatment group will be performed. For each PT, the number of patients at risk, patients who experienced the event, and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

6. References

Eisenhauer, E., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., ... & Rubinstein, L. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer*, *45*(2), 228-247.

7. Appendices

Appendix 1. Flow Chart of PFS Censoring Rules



Abbreviation: PD = progressive disease