Janssen Research & Development

Statistical Analysis Plan

A Phase 1b/2, Open-Label, Randomized Study of Daratumumab Administered in Combination with Atezolizumab Compared with Atezolizumab Alone in Subjects with Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer

Protocol 54767414LUC2001
Phase 1b/2

DARZALEX®

JNJ-54767414 daratumumab

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ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CBR	clinical benefit rate
BSC	best supportive care
CMH	Cochran–Mantel–Haenszel
COPD	chronic obstructive pulmonary disease
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
sCR	stringent complete response
CRF	case report form (electronic)
DLT	dose-limiting toxicity
DoR	duration of response
DPS	data presentation specifications
ECG	electrocardiogram
ECOG	eastern cooperative oncology group
FEV1	forced expiratory volume in the first second
FFPE	formalin-fixed, paraffin-embedded
GCP	good clinical practice
HIV	human immunodeficiency virus
ICF	informed consent form
INR	International Normalized Ratio
IRR	infusion-related reaction
ITT	intent-to-treat
IWRS	interactive web response system
LD	longest diamete
MedDRA	medical dictionary for regulatory activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI-CTCAE	national cancer institute common terminology criteria for adverse events
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
PrT	prothrombin time

PTT	partial thromboplastin time
RECIST	response evaluation criteria in solid tumors
SAD	short axis diameter
SAE	serious adverse event
SD	stable disease
SET	study evaluation team
SIPPM	site investigational product procedures manual
SOC	system organ class
SPD	sum of the products of the two largest perpendicular diameters
STD	Standard deviation
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VGPR	very good partial response

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of the analysis population(s), derived variables and statistical methods for Study 54767414 LUC2001.

1.1. Trial Objectives

Primary Objective

The primary objective of this study is to compare the overall response rate (ORR) in subjects treated with daratumumab in combination with atezolizumab versus atezolizumab alone.

Secondary Objectives

- To assess the safety of the combination of daratumumab and atezolizumab
- To compare the duration of response (DoR) in subjects treated with daratumumab in combination with atezolizumab versus atezolizumab alone
- To compare the clinical benefit rate (CBR) in subjects treated with daratumumab in combination with atezolizumab versus atezolizumab alone
- To compare progression-free survival (PFS) in subjects treated with daratumumab in combination with atezolizumab versus atezolizumab alone
- To compare overall survival (OS) in subjects treated with daratumumab in combination with atezolizumab versus atezolizumab alone
- To evaluate the pharmacokinetic and immunogenicity profile of daratumumab when given in combination with atezolizumab
- To evaluate the pharmacokinetic and immunogenicity profile of atezolizumab when given in combination with daratumumab

Exploratory Objectives

- To compare ORR evaluated by the Immune-Related Response Evaluation Criteria in Solid Tumors (irRECIST)
- To explore biomarkers predictive of response to therapy
- To evaluate potential pharmacodynamic biomarkers in response to therapy
- To explore the relationships between pharmacokinetics, pharmacodynamics, adverse event profiles, and clinical activity of daratumumab given in combination with atezolizumab in subjects with previously treated advanced or metastatic NSCLC
- To explore the benefit of daratumumab and atezolizumab treatment in subjects who had confirmed disease progression on atezolizumab monotherapy

1.2. Trial Design

The study begins with a 6-subject safety run-in cohort to be evaluated by the Study Evaluation Team (SET). After evaluation, if SET has determined that the combination therapy of daratumumab and atezolizumab are safe and tolerable, the study will proceed to the randomization phase in which 90 subjects are randomized into the two treatment arms

stratified by PD-L1 expression status (IC0 and TC0 vs. others), histology (squamous vs. non-squamous), and number of previous lines of therapy received (1 or >1):

Arm A: atezolizumab; Arm B: atezolizumab + daratumumab.

Subjects in Arm A (treated with atezolizumab monotherapy) who have confirmed disease progression based on RECIST 1.1 may cross over to Arm B and receive daratumumab and atezolizumab after crossover eligibility criteria are met.

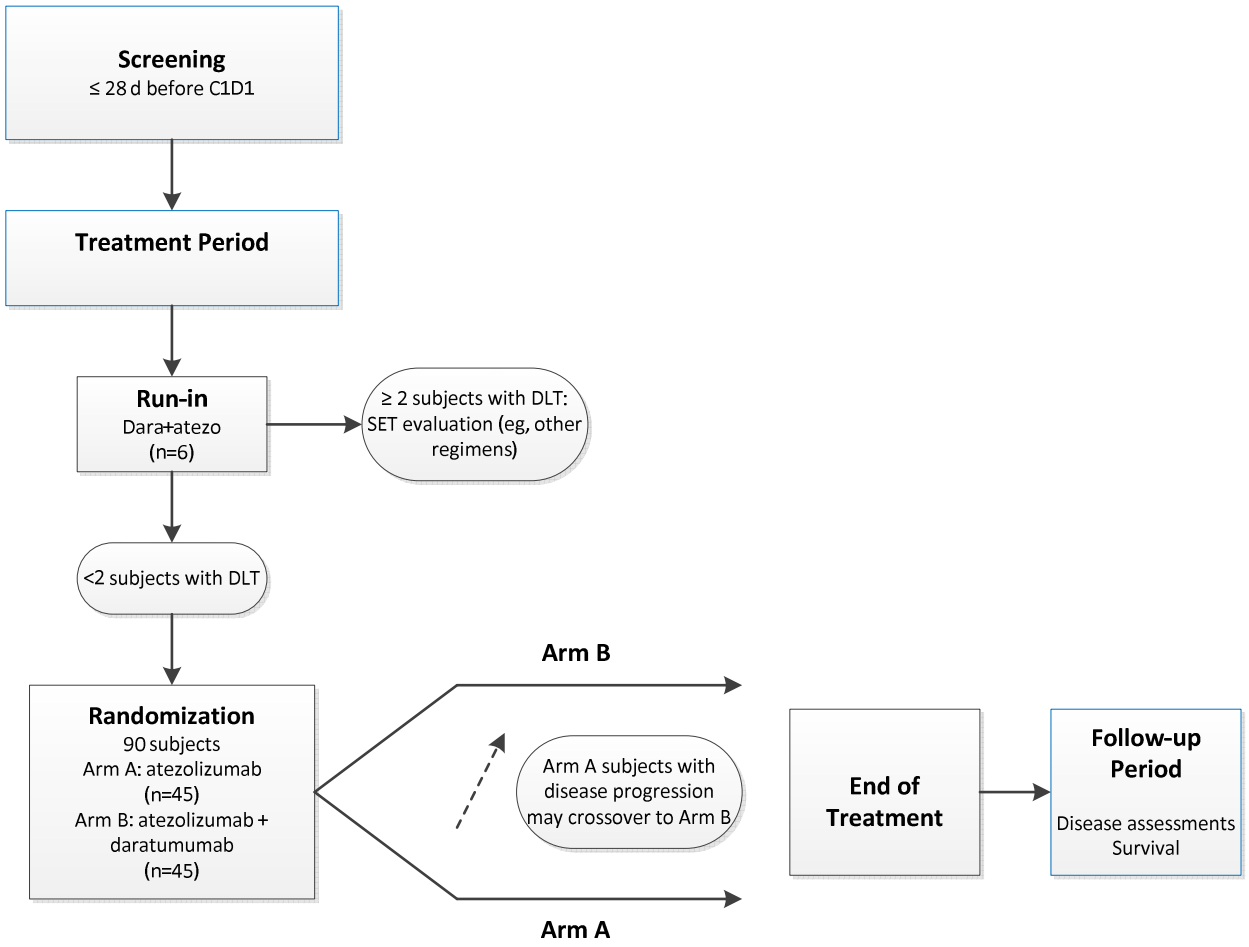
An internal Janssen Data Monitoring Committee (DMC), independent of the study team, will be established to review the efficacy and safety data in the randomization phase. The DMC will review the totality of data after approximately 40, 60, and 90 subjects have been enrolled, including activity within distinct PD-L1 expression subgroups. Based on these findings, the DMC may formulate recommendations on study conduct, including the expansion of enrollment of some PD-L1 subgroups, resulting in greater than 96 subjects. The DMC may request additional ad-hoc reviews as data accumulate.

For subjects in Arm A, Atezolizumab will be administered at 1200 mg IV on Day 1 of every 21-day cycle. For subjects in the safety run-in cohort and in Arm B, Daratumumab will be administered intravenously (IV) at 16 mg/kg weekly on Days 1, 8, and 15, for the first 3 cycles, then on Day 1 of each 21-day cycle thereafter. Atezolizumab for these subjects will be administered at 1200 mg IV on Day 2 of Cycle 1 and on Day 1 of every 21-day cycle thereafter. Pre-infusion medication is administered before first infusion of study medication to prevent infusion-related reactions. Post-infusion medication is administered to reduce the risk of delayed infusion reactions in all subjects.

The combination therapy and the monotherapy will continue until treatment discontinuation due to disease progression, unacceptable toxicity, or other protocol-defined treatment discontinuation criteria. Subjects enter the Follow-up phase after the End-of-Treatment visit, or 30 (+7) days after the discontinuation of the study drugs. Subjects will be followed for survival every 12 weeks after confirmed disease progression or start of new anticancer therapy.

The end of the study is anticipated to be 6 to 12 months after the last subject has been enrolled (last subject in) or when the last subject has the last assessment in this study (eg, last survival follow- up for the last subject), whichever occurs first, and the study may be extended to allow for further treatment and follow-up of subjects.

Figure 1: Schematic Overview of the Study Design



1.3. Statistical Hypothesis for the Primary Objective

The primary hypothesis is that the combination therapy of atezolizumab with daratumumab will significantly improve ORR compared to atezolizumab monotherapy in subjects with NSCLC.

1.4. Sample Size Determination

A 6-subject safety run-in cohort will be evaluated by the Safety Evaluation Team to determine the safety and tolerability of atezolizumab administered in combination with daratumumab before proceeding with the randomized phase of the study.

For the randomization part, assuming that the ORR for atezolizumab monotherapy is approximately 20%, and the addition of daratumumab would improve ORR by 20% to 40%, 90 subjects need to be randomized with a 1:1 ratio in order to achieve 80% power to detect this difference with a one-sided alpha of 0.10. If benefit from the combination is not observed across the overall study population, targeted enrollment of subgroups, based on tumor PD-L1 expression level, may be implemented, based on DMC recommendations. As such, approximately 50 additional subjects in the TC2/TC3 subgroups may be enrolled to preliminarily evaluate the treatment effect. If the ORR is 25% for atezolizumab monotherapy and 50% for the

atezolizumab + daratumumab combination in the TC2/TC3 subgroup, the lower bound of the 90% CI for the difference in ORR would exclude 0 (i.e., a positive signal in favor of the combination).

1.5. Randomization and Blinding

Central randomization will be implemented following the safety run-in evaluation. Subjects will be randomly assigned to 1 of 2 treatment arms based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by centrally determined PD-L1 expression status (TC0 and IC0 vs. others), histology (squamous vs. non- squamous), and number of prior therapies (1 vs >1).

2. GENERAL ANALYSIS DEFINITIONS

All tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects falling within each category. Continuous variables will be summarized by descriptive statistics including N, mean, standard deviation, median, minimum, and maximum.

2.1. Baseline, Relative Day

Baseline value is defined as the last non-missing value obtained prior to the first dosing date/time of study medication.

Day 1 is the first dosing date of study medication. Study Day is defined as assessment date – first dose date + 1 for any assessment done on or after first dose date; otherwise, study day is defined as assessment date – first dose date.

Unless specified otherwise, data to be analyzed or presented over time will be presented by visit and time point (as appropriate) that are recorded in the eCRF.

2.2. Pooling Algorithm for Analysis Centers

Data from all study centers will be pooled for analyses.

2.3. Analysis Sets

2.3.1. Intent-To-Treat Analysis Set

Intent-to-Treat (ITT) analysis set includes all subjects who have entered the randomization phase of the study. Subject information, demographics, baseline disease characteristics, and efficacy summaries will be based on this analysis set.

2.3.2. Safety Analysis Set

Safety analysis set includes all subjects who have received at least 1 administration of any study medication. This analysis set will be used for all exposure and safety analyses.

2.3.3. Response-evaluable Analysis Set

Response-evaluable analysis set includes all randomized subjects who have received at least 1 administration of study medication and have at least 1 adequate post baseline disease assessment. Response related endpoints will also be analyzed based on this analysis set as appropriate.

2.3.4. DLT Analysis Set

Dose-limiting Toxicity (DLT) analysis set includes any subject in the safety run-in phase who has a DLT regardless of dose received or who did not have a DLT but received at least 75% of the planned dose during the DLT evaluation period, which is 21 days starting from the day of the first dose of study drug.

Criteria for DLT are listed in Attachment 1. This analysis set will be used to summarize the dose-limiting toxicity.

2.3.5. Safety Run-in Analysis Set

Safety run-in analysis set includes all subjects in the safety run-in phase who have received at least 1 administration of study medication.

2.3.6. Immunogenicity-evaluable Analysis Set

The immunogenicity-evaluable analysis set includes all subjects who receive at least 1 dose of atezolizumab or daratumumab and have appropriate samples for detection of antibodies to atezolizumab or daratumumab. This analysis set will be used for immunogenicity related analyses.

2.3.7. Pharmacokinetics-evaluable Analysis Set

Pharmacokinetics-evaluable analysis set includes all subjects who have received at least 1 dose of daratumumab or atezolizumab and have at least 1 post-infusion sample collected. This analysis set will be used for PK analyses.

2.4. Definition of Subgroups

The following subgroups are to be performed for exploratory efficacy and/or safety analyses. Additional subgroup analyses may be planned if deemed necessary.

Subgroup	Definition	Analysis Type
Sex	Male, Female	Efficacy, Safety
Age	< 65, ≥ 65	Efficacy, Safety
Race	White, Other	Efficacy, Safety
PD-L1 expression status	Negative (IC0 and TC0), High (TC3 and IC any), Low (others), based on SP-142 assay	Efficacy

2.5. Imputation of Missing Data

Data imputation will be limited and detailed rules will be specified in DPS.

2.6. Other General Definitions

2.6.1. Treatment Groups

The treatment groups are atezolizumab (Arm A) and atezolizumab + daratumumab (Arm B).

2.6.2. Month and Year

One year equals to 365.25 days. One month equals to 365.25/12 days.

2.6.3. Years since Initial NSCLC Diagnosis

This is calculated as date of first dose – date of initial NSCLC diagnosis + 1, divided by 365.25.

2.6.4. Total Dose Received

For Daratumumab, total dose (mg/kg) is the sum of the administered doses per kilogram at each visit, which is calculated as the total dose (mg) recorded on the eCRF divided by body weight (kg) at that visit. For Atezolizumab, total dose (mg) is the sum of the administered doses at each visit, which is calculated as the total dose (mg) recorded on the eCRF.

2.6.5. Duration of Treatment

Duration of treatment in months is derived as last non-zero Daratumumab/Atezolizumab dosing date – first non-zero Daratumumab/Atezolizumab dosing date + 1, divided by 365.25/12.

2.6.6. Maximum number of Treatment Cycles

A subject is considered as treated in a cycle if he/she receives any nonzero dose of Daratumumab/Atezolizumab in that cycle. The maximum number of treatment cycle for each subject is the largest cycle number in which a subject receives any nonzero dose of Daratumumab/Atezolizumab.

2.6.7. Relative Dose Intensity

For Daratumumab, the relative dose intensity (%) is the ratio of total dose received (mg/kg) and total planned dose (mg/kg), calculated as the planned dose times the number of administered infusions. For Atezolizumab, the relative dose intensity (%) is the ratio of total dose received (mg) and total planned dose (mg), calculated as the planned dose times the number of administered infusions.

2.6.8. End of Follow-up and Duration of Follow-up

The end of follow-up is the date of death for subjects who died. For those who still alive, the end of follow-up is defined as the maximum date of the following study evaluations: labs (hematology, chemistry, serology, coagulation, thyroid function), adverse events, vital signs, ECOG performance status, study drug administration, 12-lead ECG, disposition, pre-infusion medications, post-infusion medications, concomitant medications, Subsequent anti-cancer treatment, tumor assessment, clinical events/disease response per investigator and date of last known to be alive.

Duration of follow-up (in months) equals the end of follow-up minus the first dose date plus 1, divided by 365.25/12.

2.6.9. Relationship of Adverse Events to Study Medication

For each adverse event, its relationship to study medication is determined by investigator and recorded on the eCRF. An adverse event is considered as related to study medication if the relationship is possible, probable or very likely.

2.6.10. Treatment Emergent Adverse Events

Treatment emergent adverse events (TEAEs) are defined as any AE with onset date and time on or after that of the first dose through 30 days after the last study drug administration, or the day prior to start of subsequent therapy, whichever is earlier; or any AE that is considered related to (very likely, probably, or possibly related) study medication regardless of the start date of the event. AEs with missing or partial onset date and time will be considered as treatment-emergent unless the onset date and time of an AE can be determined as earlier than that of the first dose, or later than 30 days after last study drug administration.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

An internal Janssen DMC, independent of the study team, will be established to review the efficacy and safety data in the randomization phase. The DMC will consist of a minimum of 3 members with at least 1 clinician and a statistician, 1 of whom will chair the committee. The DMC will review the totality of data after approximately 40, 60, and 90 subjects have been enrolled, and will formulate recommendations on study conduct (see protocol Section 11.3). The DMC may request additional ad-hoc reviews as data accumulate.

Additional details will be specified in a separate DMC charter.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Disease Characteristics

Subject eligibility will be summarized for all subjects with a non-missing informed consent date. Number of subjects who did not meet all inclusion/exclusion criteria will be summarized, together with the specific non-met criterion. A listing of subjects who didn't meet all inclusion/exclusion criteria will be provided.

Subject enrollment will be summarized by country and site.

The following baseline demographic and disease characteristics will be summarized:

- Demographics: age (continuous), age category (< 65 years and ≥ 65 years), sex (male, female), race (white, non-white, unknown, and not reported), ethnicity (Hispanic, Non-Hispanic, unknown, and not reported), height (cm), weight (kg), and ECOG performance status score (0, 1).

- Baseline disease characteristics: Tumor stage at initial diagnosis and study entry (0, I, II, III, IV, not applicable, unknown), time since initial diagnosis (years), and diagnosis subtype (squamous, non-squamous).

In addition, baseline laboratory tests will be summarized, as appropriate. The frequencies of CTC toxicity grade for these laboratory parameters at baseline will be provided, if applicable.

General medical history will be summarized by body system and condition status as reported on eCRF. A listing will be generated for abnormal medical history.

A listing for procedures performed after date of informed consent will be provided.

Vital signs, including body temperature, pulse, systolic blood pressure and diastolic blood pressure at baseline will be summarized.

ECG results at baseline will be summarized by overall interpretation: normal, abnormal and clinically significant, abnormal and not clinically significant, and other.

Spirometry measurement of percent predicted FEV1 will be summarized, if applicable.

Categorical summary of the stratification factors will be also be presented.

4.2. Disposition Information

Number of subjects who discontinued from treatment will be summarized, together with reason reported on eCRF. Number of subjects who discontinued from study and the reported reason on eCRF will be presented similarly. A listing for subject disposition will also be provided.

4.3. Treatment Compliance

Refer to section 4.4.

4.4. Extent of Exposure

Duration of treatment in months will be summarized, together with the number of treatment cycles. Descriptive statistics for the total dose received, total number of infusions, and relative dose intensity (%) will be provided for Daratumumab and Atezolizumab, respectively.

The frequencies of actions planned prior to infusion start and taken during infusion will be summarized, together with reasons reported on eCRF.

For cross-over subjects, exposure data after initiation of cross-over treatment may be summarized separately, as applicable.

4.5. Protocol Deviations

The incidence of major protocol deviation, together with the corresponding deviation terms will be summarized. A listing of all major protocol deviations will be provided.

4.6. Prior and Concomitant Medications

The number of lines of prior systemic therapy will be summarized descriptively as well as by the following categories: 1 and > 1. Frequency will also be presented for subjects selected types of prior therapies. A listing will be provided for prior cancer-related surgery or radiotherapy.

Use of concomitant therapies will be provided by therapeutic class, pharmacologic class, and preferred term.

Pre-infusion medications will be grouped by analgesics, antihistamines, and corticosteroids (intermediate and long-acting). The incidence of pre-infusion medications will be presented by the aforementioned groups and preferred terms. The same summary will be provided for post-infusion medications.

4.7. Subsequent Anti-cancer Treatments

Subsequent anti-cancer treatments, including radiotherapy, surgery, and systemic therapy, will be summarized.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

All 95% confidence intervals presented will be 2-sided.

5.1.2. Data Handling Rules

There is no imputation planned for missing efficacy endpoint values.

For cross-over subjects, efficacy data after initiation of cross-over treatment may be summarized separately, as applicable.

5.2. Primary Efficacy Endpoint

The primary efficacy endpoint is overall response rate (ORR).

Definition

The primary endpoint is overall response rate (ORR), defined as the proportion of subjects who achieve a response of partial response (PR) or better.

Analysis Methods

Analysis will be based on the ITT population, and response evaluable population. The number and percentage of subjects along with two-sided 95% exact confidence interval (CI) will be provided by treatment group in the following response categories: CR, PR, ORR, stable disease (SD), clinical benefit rate (CBR), progressive disease (PD), and not evaluable (NE).

Odds ratio of achieving response for Arm B over Arm A and its 95% confidence interval will be provided.

ORR will also be presented by the subgroups specified in Section 2.4, as appropriate.

5.3. Major Secondary Efficacy Endpoints

5.3.1. Duration of Response

Definition

Duration of response (DoR) is measured from date of first documented disease response to date of first objectively documented evidence of recurrence or progressive disease or death, whichever occurred first. DoR will be evaluated in subjects who have achieved response of PR or better. Duration of response is calculated in months as follows:

$$\text{DoR} = (\text{date of PD or censoring} - \text{date of first disease response} + 1) / (365.25/12),$$

Deaths due to disease progression will be treated as an event on the date of death, unless disease progression is documented before death. Subjects who start Subsequent anti-cancer treatment for NSCLC will be censored at the last disease assessment no later than the start of Subsequent anti-cancer treatments Subjects, who are lost to follow-up, withdraw consent, withdraw from study without disease progression, or die due to causes other than disease progression will be censored at the last disease assessment date.

Analysis Methods

The Kaplan-Meier method will be used to summarize DoR for responders in each treatment group. The 25% Quantile, Median, and the 75% Quantile and their corresponding 95% CI will be provided.

5.3.2. Clinical Benefit Rate

Definition

Clinical benefit rate is defined as proportion of subjects who achieve disease control (CR, PR, or SD).

Analysis Methods

Analysis will be based on the ITT population, and response evaluable population. The number and percentages of subjects achieving clinical benefit will be provided by treatment group. In addition, two-sided 95% exact CI will also be provided. Odds ratio of achieving response for Arm B over Arm A, and its 95% confidence interval will be calculated, similar to ORR.

Stratified analysis may also be performed as sensitivity analysis.

5.3.3. Progression Free Survival

Definition

Progression-free survival (PFS) is measured from randomization until the first documented disease progression or death, whichever occurs first. PFS will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who have no documented progression and are still alive prior to data cutoff, dropout, lost to follow-up or the initiation of Subsequent anti-cancer treatment. Subjects with no tumor assessments after randomization their PFS will be censored on the date of randomization. PFS is calculated in months as follows:

PFS = (date of PD/death or censoring – date of randomization + 1) / (365.25/12).

Analysis Methods

The number and percentage of subjects who had a PFS event or were censored will be reported. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment group, and the median PFS with 95% CI will be provided. In addition, the Kaplan-Meier PFS curve will also be presented by treatment group.

Hazard ratio (Arm B vs. Arm A) and its 95% confidence interval will be presented. In addition, 3, 6, 12-months of PFS rate with 95% CI will be estimated by Kaplan-Meier method and reported for each treatment group.

PFS will also be presented by the subgroups specified in Section 2.4, as appropriate.

5.3.4. Overall Survival

Definition

Overall survival (OS) is defined as time from date of randomization to date of subject's death from any cause. For subjects who are still alive at the end of study or lost to follow-up, OS will be censored on the date the subjects were last known to be alive. Overall survival is calculated in months as follows:

OS = (date of death or censoring – date of randomization + 1) / (365.25/12).

Analysis Methods

The number and percentage of subjects who were died or still alive will be reported. The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group, and the median OS with 95% CI will be provided. In addition, the Kaplan-Meier PFS curve will also be presented by treatment group.

Hazard ratio (Arm B vs. Arm A) and its 95% confidence interval will be presented. In addition, 3, 6, 12-months of OS rate with 95% CI will be estimated by Kaplan-Meier method and reported for each treatment group.

OS will also be presented by the subgroups specified in Section 2.4, as appropriate.

6. SAFETY

The safety profiles of Daratumumab will be evaluated by the incidence of adverse events (AEs), death, laboratory results, vital signs, physical examination findings, ECG results, and ECOG score overtime.

Safety summaries will be provided by treatment received. The severity of AEs and the toxicity of laboratory parameters will be assessed using NCI CTC version 4.03. Adverse events are coded using latest version of MedDRA coding dictionary.

For cross-over subjects, safety data after initiation of cross-over treatment may be summarized separately, as appropriate.

6.1. Adverse Events

Unless otherwise specified, only TEAEs will be summarized.

6.1.1. Treatment Emergent Adverse Events

The following summaries will be provided for all TEAEs:

- An overview of TEAE will be provided, including the incidence of TEAE, serious TEAE, maximal grade of TEAE, treatment discontinuation due to TEAE, , and death due to TEAE.
- A listing of all TEAEs.

In addition, the following summaries will be generated:

- TEAEs by system organ class (SOC) and preferred term (PT)
- TEAEs by SOC, PT, and relationship to study medication
- TEAEs by SOC, PT, and grade 3/4
- Most common (at least 10%) TEAEs by SOC, PT, and grade 3/4
- TEAEs by SOC, PT, and worst grade

- Serious TEAEs by SOC and PT
- Serious TEAEs by SOC, PT, and grade 3/4
- Most common (at least 1%) serious TEAEs by SOC, PT, and grade 3/4

- Grade 3 or 4 TEAEs by SOC and PT
- Grade 3 or 4 TEAEs by SOC, PT, and relationship to study medication

The following summaries of treatment modifications due to TEAEs will be provided:

- Infusion delay due to TEAE by SOC, PT and relationship to study medication

- Infusion skipped due to TEAE by SOC, PT and relationship to study medication
- Infusion interruption due to TEAE by SOC, PT and relationship to study medication
- Infusion rate decreased due to TEAE by SOC, PT and relationship to study medication
- Infusion aborted due to TEAE by SOC, PT and relationship to study medication

In addition, the following summaries will be generated:

- Study drug discontinuation due to TEAEs by SOC, PT, and grade 3/4
- Treatment discontinuation due to TEAEs by PT and grade 3/4
- Death due to TEAEs by PT and grade 3/4

6.1.2. Adverse Events of Clinical Interest

6.1.2.1. Infusion Related Reactions

The incidence of infusion related reactions (IRRs), as flagged on the eCRF, will be presented by SOC, PT, and toxicity grade 3/4. Treatment modifications due to IRRs will also be summarized.

A listing of all IRRs will be provided.

6.1.2.2. Dose Limiting Toxicity

The dose limiting toxicity observed during the safety run-in phase will be listed.

6.1.2.3. Immune-mediated Adverse Event

The incidence of immune-mediated adverse event, as flagged on the eCRF, will be presented by SOC, PT, and toxicity grade 3/4. Treatment modifications due to these events will also be summarized.

A listing of all immune-mediated AEs will be provided.

6.2. Deaths

Number of subjects who died during the study and the primary cause of death will be summarized. In addition, all deaths within 30 days of last infusion will be summarized.

A listing will be generated for all subjects who died during the study.

6.3. Clinical Laboratory Tests

Descriptive statistics for values and changes from baseline over time for these laboratory parameters will be provided. In addition, shifts from baseline toxicity grade to worst toxicity grade during treatment will be generated.

6.4. Vital Signs and Physical Examination Findings

Descriptive statistics will be provided for values and changes from baseline over time for vital signs.

6.5. Electrocardiogram

Frequencies of overall interpretation of ECG results (normal, abnormal and clinically significant, abnormal and not clinically significant) over time will be provided.

6.6. Other Safety Parameters

6.6.1. ECOG Performance Status

Frequencies of ECOG performance status (0, 1, 2, >2) over time will be summarized.

7. PHARMACOKINETICS/IMMUNOGENICITY/PHARMACODYNAMICS

For cross-over subjects, pharmacokinetics/immunogenicity/pharmacodynamics data after initiation of cross-over treatment may be summarized separately, as appropriate.

7.1. Pharmacokinetics

Pharmacokinetic analyses will be performed on the pharmacokinetic-evaluable population. All serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Descriptive statistics (e.g., number of observations, mean, standard deviation, median, and range) will be used to summarize daratumumab and atezolizumab serum concentrations at each sampling time point. Line plot of mean (±SD) daratumumab and atezolizumab serum peak and trough concentrations over time will be provided. In addition, coefficient variation and geometric mean will be provided in the pharmacokinetic concentration summary.

7.2. Immunogenicity

Immunogenicity analyses will be performed on the immunogenicity-evaluable population. The incidence of anti-daratumumab and anti-atezolizumab antibodies will be summarized for all subjects who receive a dose of daratumumab or atezolizumab and have appropriate samples for detection of antibodies to daratumumab or atezolizumab. In addition, subjects who are positive for antibodies to daratumumab or atezolizumab will also be listed.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

8. BIOMARKER

For each biomarker of interest, baseline values will be summarized by treatment group. . In addition, for each biomarker of interest, the values over time and change from baseline will be presented by treatment group. Appropriate figures may also be generated to aid data visualization.

9. HEALTH ECONOMICS

Not applicable.

REFERENCES

1. (FDA) 2007. Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. US Food and Drug Administration, Rockville, MD.
2. Wolchok JD, Hoos A, O'Day S, et al 2009. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009; 15(23):7412-7420.

Attachment 1: Criteria For Dose Limiting Toxicity (Protocol Table 6)

DLT criteria for Non-hematologic Toxicity[a]	
AST or ALT	Grade 3 persisting ≥14 days after treatment with corticosteroids, Grade 4, or any case meeting Hy's Law criteria[b]
Laboratory abnormality	Grade 3 persisting ≥7 days despite BSC[c] or Grade 4
Any other[d]	Grade 3 persisting ≥7 days despite BSC[c] or Grade 4; except Grade ≥3 asymptomatic or mildly symptomatic rash that can be adequately managed with supportive care or resolves to become asymptomatic or Grade ≤2 within 7 days of supportive therapy.
Infusion-related Reaction	Grade 4 infusion-related reaction that occurs during or within 24 hours after the infusion of atezolizumab or daratumumab.
Ocular toxicity	Grade 2 or higher episcleritis, uveitis, or iritis
DLT criteria for Hematologic Toxicity[a]	
Neutropenia	Grade 3 persisting >7 days despite BSC[c], febrile neutropenia, or any Grade 4
Thrombocytopenia	Grade 3 with bleeding or Grade 3 persisting >7 days despite BSC[c], or any Grade 4
Any other	Grade 3 persisting ≥7 days despite BSC[c] or Grade 4

ALT=alanine aminotransferase, AST=aspartate aminotransferase, ALP=alkaline phosphatase

a. Toxicity graded according to the NCI-CTCAE, Version 4.03.
b. Hy's Law criteria, defined as ALT or AST value ≥3 x upper limit of normal (ULN), total bilirubin ≥2 x ULN, and ALP ≤2 x ULN; with no alternative etiology.
c. Best supportive care (BSC) if available, according to institutional standards.
d. With the exception of alopecia and Grade 3 fatigue in a subject with Grade 1 or Grade 2 fatigue at baseline.