Janssen Research & Development *

Clinical Protocol

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
AMENDMENT 7

DARZALEX®
JNJ-54767414 (daratumumab)

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Daratumumab and atezolizumab are being investigated in Phase 1, 2 and 3 clinical studies. Daratumumab and atezolizumab are approved for marketing in 2 indications each.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

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Original Protocol	25 July 2016
Amendment 1	1 September 2016
Amendment 2	22 March 2017
Amendment 3	24 August 2017
Amendment 4	26 February 2018
Amendment 5	19 April 2018
Amendment 6	14 August 2018
Amendment 7	4 October 2018

Amendments below are listed beginning with the most recent amendment.

Amendment 7 (4 October 2018)

The overall reason for the amendment:
This amendment provides guidance for the end-of-study data collection and permits subjects who are deriving clinical benefit from atezolizumab monotherapy to continue to receive treatment according to local regulatory approval and standard of care guidelines.[50,51]

Applicable Section(s)	Description of Change(s)

Rationale: Pursuant to the recommendations from the Data Monitoring Committee (DMC; [third planned review on 23 May 2018]), who determined that there was no increased benefit with combination daratumumab and atezolizumab therapy, treatment with daratumumab was discontinued and active subjects were allowed to continue on atezolizumab monotherapy (Amendment 6). For active subjects who are deriving clinical benefit, but do not have access to commercial atezolizumab, the Sponsor will continue to supply atezolizumab. The administration of atezolizumab will occur under the supervision of treating investigators in accordance with local regulatory approvals and standard of care guidelines.[50,51] With the clinical database now locked and subjects receiving only atezolizumab monotherapy, data from efficacy and safety evaluations performed according to local regulatory approvals and standard of care guidelines[50,51] will no longer be collected with the exception of serious adverse events that are to be reported and entered in the Sponsor safety repository.

Applicable Section(s)	Description of Change(s)
Synopsis (Overview of Study Design, Dosage and Administration, Efficacy Evaluations, and Safety Evaluations subsections); Table 1: Time and Events Schedule; 3.1 Overview of Study Design; 3.2 Study Conduct After DMC Recommendations; 6.2 Atezolizumab; 6.2.1 Management of Atezolizumab-specific Adverse Events 7 Treatment Compliance; 9.1.5 Follow-up Phase; 9.3 Guidance for Subjects Continuing on Study with Atezolizumab Monotherapy (per Amendment 7) (new section); 9.4 Efficacy Evaluations; 9.7 Safety Evaluations; 9.8 Sample Collection and Handling; 12.5 Safety Reporting for Atezolizumab Monotherapy Subjects (per Amendment 7) (new section); 14.5 Drug Accountability; 17.5 Case Report Form Completion; 17.9.1 Study Completion/End of Study; References.	Clarified that, as of the implementation of Amendment 7, subjects who are deriving clinical benefit from atezolizumab monotherapy, but do not have access to commercial atezolizumab, may continue treatment according to local regulatory approvals and standard of care guidelines.[50,51] Clarified that, as of the implementation of Amendment 7, data from efficacy and safety evaluations performed according to local regulatory approvals and standard of care guidelines[50,51] will no longer be collected with the exception of serious adverse events that are to be reported and entered in the Sponsor safety repository.
Rationale: Minor grammatical, formatting, or spelling changes were made for consistency with the other changes in this amendment, including updating the abbreviations list	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 6 (14 August 2018)

The overall reason for the amendment:
As of 25 May 2018, the Sponsor notified the sites to terminate further enrollment into this study, 54767414LUC2001 (CALLISTO), in which the combination of daratumumab and atezolizumab is being studied in subjects with non-small cell lung cancer. At the third planned DMC review on 23 May 2018, the DMC reviewed the subject data (n=88, 44 per arm) for this study. The DMC determined that there was no observed benefit within the combination treatment arm, daratumumab plus atezolizumab, over atezolizumab alone, and recommended stopping enrollment of the study. In addition, the DMC recommended discontinuation of daratumumab treatment to all active subjects receiving combination therapy (subjects randomized to the combination Arm B, as well as subjects randomized to Arm A who crossed over into Arm B). Although no unexpected imbalances in on-treatment toxicities were observed, the DMC noted a clear difference in the number of deaths between the atezolizumab monotherapy and combination arm. Therefore, enrollment is discontinued in this study, treatment with the combination of daratumumab and atezolizumab will be discontinued, and ongoing subjects will be given the option to continue on atezolizumab monotherapy until the subject meets one or more of the treatment discontinuation criteria in Section 10.2.

In addition, since the subcutaneous administration of daratumumab (Phase 1b Dara-SC cohort) was never implemented, this is removed from the protocol.

Guidelines on managing immune-related nephritis are added based on recent information on this risk with atezolizumab.

Applicable Section(s)	Description of Change(s)
Rationale: Enrollment is discontinued in this study, treatment with the combination of daratumumab and atezolizumab is discontinued, and ongoing subjects will be given the option to continue on atezolizumab monotherapy. Note that to preserve the history of the protocol design, certain sections have not been changed (eg, objectives).	
Synopsis; Time and Events Schedule Tables 2 through 7 (removed); 1.4 Overall Rationale for the Study; 3.1 Overview of Study Design; 3.2 Study Conduct After DMC Recommendations (new); 3.4 Study Design Rationale; 4 Subject Population; 4.3 Inclusion and Exclusion Criteria for Crossover; 5 Treatment Allocation and Blinding; 9.1.1 Overview; 9.2 Procedures for Subjects Continuing on Study with Atezolizumab Monotherapy (per Amendment 6) (new); 9.3 Efficacy Evaluations; 9.3.1 Disease Assessments, Table 19; 9.5 Biomarker Assessments; 9.6 Safety Evaluations; 10.2 Discontinuation from Study Treatment/Withdrawal from the Study; 12.4 Safety Reporting for Atezolizumab Monotherapy Subjects (per Amendment 6) (new); 14 Study Drug Information; 17.8 Monitoring; 17.9.1 Study Completion/End of Study	Time and Events Schedules for biomarkers, pharmacokinetics, immunogenicity, and crossover (Tables 2-7) were removed because of the discontinuation of daratumumab combination treatment. Described the rationale for terminating enrollment into the study and clarified the assessments that will be performed for subjects that remain in the study. New Sections 3.2 and 9.2 were added to define study conduct changes. Removed rationale for crossover and noted that crossover will no longer be performed. Specified that those subjects who crossed over to Arm B should be carefully evaluated for potential benefit for atezolizumab monotherapy. Clarified that any treatment beyond disease progression requires prior discussion with and approval by the Sponsor's Study Responsible Physician; subjects with documented disease progression should discontinue study therapy. Table 19 (Imaging and Treatment after First Radiologic Evidence of Progressive Disease) and Section 10.2 are revised accordingly. Clarified that subjects who had crossed over to Arm B should be carefully evaluated to determine whether they will benefit from treatment with atezolizumab monotherapy. The blood type, Rh, and Indirect Antiglobulin Test (IAT) no longer needs to be performed in those who have discontinued daratumumab. Safety reporting will be limited for the atezolizumab monotherapy subjects. Daratumumab study drug information is removed. Study monitoring will be limited. The study completion/end of study definition is revised.

Applicable Section(s)	Description of Change(s)
Rationale: The subcutaneous administration for daratumumab (Dara-SC) was added in Amendment 5; however, this was not implemented due to daratumumab administration being discontinued in this study.	
Synopsis (Objectives, Endpoints, Overview of Study Design, Dosage and Administration, Pharmacokinetic and Immunogenicity Evaluations); Table 1: Time and Events Schedule-Safety Run-in, Randomized Arms (~~and Phase 1b Dara-SC Cohort~~);	Removed all text, figures, and assessments in tables regarding the Phase 1b Dara-SC cohort, including objectives and endpoints, dosing, pharmacokinetics, and immunogenicity assessments (including assessment of anti-rHuPH20 antibodies), and the rationale for Dara-SC administration Removed Phase 1b Dara-SC Cohort assessments in Table 1.
1.3.2 Daratumumab for Subcutaneous Administration (removed); 2.1.1 Objectives; 2.1.2 Endpoints; 3.1 Overview of Study Design, Figure 1 Schematic Overview of the Study; 3.4 Study Design Rationale (rationale for Dara-SC removed; Figures 2-4 removed); 4.1 Inclusion Criterion 5; 4.2 Exclusion Criteria (1, 6); 5 Treatment Allocation and Blinding; 6 Dosage and Administration; 6.1.2 Dara-SC Preparation; 6.1.3 Daratumumab Treatment Schedule and Administration; 6.1.4 Guidelines for Prevention of Daratumumab Infusion Reactions; 6.1.4.1 Predose Medications; 6.1.4.2 Postadministration Medications; 6.2 Atezolizumab; 6.3 Management of ~~Injection-site and~~ Infusion-Related Reactions; 6.3.1 Local Injection-site Reactions (removed); 9.4 Pharmacokinetics and Immunogenicity; 11.2 Sample Size Determination; 11.3 Efficacy Analyses; 11.5 Immunogenicity Analyses; 11.9 Data Monitoring Committee; 14 Study Drug Information; 16.1 Study-Specific Design Considerations	Removed Inclusion and Exclusion criteria specific for this cohort. Removed Dara-SC drug administration information. Removed statistical analyses for this cohort. Removed description of Dara-SC study drug.

Applicable Section(s)	Description of Change(s)
Rationale: Added information of immune-related nephritis, which was recently added as an important identified risk with atezolizumab.	
6.2.1.11 Immune-Related Nephritis; Attachment 7 Table 30 Management Guidelines for Immune-Related Nephritis (new)	Information on immune-related nephritis and management guidelines have been added.
Rationale: Minor grammatical, formatting, or spelling changes were made for consistency with the other changes in this amendment, including updating the abbreviations list.	
Throughout the protocol	

Amendment 5 (19 April 2018)

The overall reason for the amendment: [redacted]

Applicable Section(s)	Description of Change(s)
Rationale: [redacted]	
Synopsis; Time and Events Schedules – Tables 1, 2, 4 (new pharmacokinetic table), 5, 7; 1.3.2 Daratumumab for Subcutaneous Administration (new);	[redacted]
2.1.1 Objectives; 2.1.2 Endpoints; 3.1 Overview of Study Design; 3.3 Study Design Rationale	A new primary objective and endpoint is added for the new cohort. Safety criteria are specified for evaluating the first 6 subjects and for expansion of enrollment based on Data Monitoring Committee (DMC) evaluation. [redacted]

Applicable Section(s)	Description of Change(s)
4.1 Inclusion Criteria; 4.2 Exclusion Criteria;	[redacted] **Tumor cell PD-L1 score as determined by an IHC assay performed by the central laboratory on tissue obtained after the last line of therapy:** [redacted] - **Subjects with a tumor cell PD-L1 score of TC0 who are anti-PD-1 or anti-PD-L1 treatment naïve will be eligible for screening** - **Subjects who have disease progression on or after anti-PD-1 or anti-PD-L1 therapy and with any tumor cell PD-L1 score (TC0-3), will be eligible for screening.** **Randomized phase** **Subjects with a tumor cell PD-L1 score of TC1-3 who are anti-PD-1 or anti-PD-L1 treatment naïve will be eligible for screening** Exclusion Criterion 1 is modified: [redacted] Exclusion Criterion 6 is modified: [redacted]
5 Treatment Allocation and Blinding; 6.1 Daratumumab; 6.1.1 Daratumumab **IV** Preparation; 6.1.2 Daratumumab Subcutaneous Preparation (new); 6.1.3 Daratumumab Treatment Schedule and Administration; 6.1.4 Guidelines for Prevention of Daratumumab Infusion Reactions; 6.2 Atezolizumab; 6.3 Management of **Injection-site and** Infusion-Related Reactions; 6.3.1 Local Injection-site Reactions (new); 11.2 Sample Size Determination; 11.3 Efficacy Analyses; 11.9 Data Monitoring Committee; 14 Study Drug Information 16.1 Study-Specific Design Considerations	Added: [redacted]

Applicable Section(s)	Description of Change(s)
Synopsis; Section 2.1 Objectives and Endpoints; 2.1.1 Objectives; 2.1.2 Endpoints; 3.3 Study Design Rationale; 9.3 Pharmacokinetics and Immunogenicity; 11.5 Immunogenicity Analyses	[redacted]
Rationale: An optional Prescreening informed consent will be offered for the purpose of testing archival tumor tissue to assess PD-L1 status using the SP142 assay to help determine the likelihood of eligibility for participation in this study. However, final eligibility for study participation will be based on PD-L1 staining on the fresh biopsy required during the Screening Phase.	
Time and Events Schedules - Tables 1 and 2; 4 Subject Population; 9.1.2 Optional Prescreening Phase; 17.3 Subject Identification, Enrollment, **Prescreening**, and Screening Logs	The optional Prescreening Phase for archival testing to assess PD-L1 status is specified. Add “Prescreening” to the heading for 17.3.
Rationale: To obtain longer-term kinetics of immunological biomarkers, biomarker sample collection at Cycle 4 is added.	
Time and Events Schedules - Table 2 and 6	Cycle 4 Day 1 predose whole blood biomarker samples are added.
Rationale: Updated the incidence of IRRs for atezolizumab.	
1.4 Overall Rationale for the Study	IRRs occur in only approximately **1**% of patients treated with atezolizumab
Rationale: Minor errors were noted	
Throughout the protocol	Revisions and modifications were made throughout the protocol to increase clarity and consistency, to update the protocol based on revisions made during this amendment, or to correct omissions and errors. Minor grammatical, formatting, or spelling changes were made.

Amendment 4 (26 Feb 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to expand the Screening period for the informed consent and for PD-L1 testing, and to specify the PD-L1 score inclusion criterion. During its review of the study data at the initial interim analysis (40 evaluable subjects), the DMC determined that the study had enrolled a sufficient number of subjects with a PD-L1 score of TC0 and recommended continued enrollment only in subjects in the TC1-3 subgroups.
In addition, the safety management guidelines for atezolizumab have been updated based on the current Investigator's Brochure.
Note: where actual changes are shown in this amendment table, new text is in bold font and text that is removed is struck out.

Applicable Section(s)	Description of Change(s)
Rationale: To expand the Screening period for PD-L1 testing to prevent unnecessary Screening testing for subjects who do not qualify for the study; and to clarify the PD-L1 score criterion.	
Table 1 Time and Events Schedule; 4 Subject Population; Table 2 Biomarker Assessments – Safety Run-in and Randomized Arms	Expanded the Screening period for the informed consent and for PD-L1 testing to -56 to -1 days. In Table 2, added reference to the expanded period of -56 to -1 d for Screening PD-L1 testing.
3.1 Overview of Study Design, Figure 1; 5 Treatment Allocation and Blinding	Revised Figure 1 Schematic Overview of the Study to add the expanded Screening period for PD-L1 testing. Clarified that pursuant with DMC recommendations, only subjects with a PD-L1 score of TC1-3 will be eligible to enroll in the study, therefore, all subjects will have PD-L1 expression status of "other", and will only be stratified by histology (squamous vs. non-squamous), and number of previous lines of therapy (1 or >1).
Table 2 Biomarker Assessments – Safety Run-in and Randomized Arms footnote b, footnote c; Table 6 Biomarker Assessments Crossover, footnote c, footnote d; 9.4 Biomarker Assessments; 9.4.1 Tumor Tissue Samples	Specified that the collection of a fresh tumor biopsy is mandatory at Cycle 3 and at progression. Cycle 3 biopsy may be collected within 7 days prior to or up to 21 days after the Cycle 3 Day 1 dose, but must be prior to the Cycle 4 Day 1 dose. In addition, this biopsy must be performed following the first radiologic tumor assessment. The corresponding footnote in Table 5 (crossover) was also revised and a note was added to Section 9.4.1.

4 Study Population; 9.1.2 Screening Phase	Explanation added for enrolling subjects with TC1-3 PD-L1 score: During its review of the study data at the initial interim analysis (40 evaluable subjects), the DMC determined that the study had enrolled a sufficient number of subjects with a PD-L1 score of TC0 and recommended continued enrollment only in subjects in the TC1-3 subgroups. New text added for PD-L1 screening: The signing of the informed consent and collection of tumor specimen for PD-L1 testing may occur up to 56 days before the first administration of study drug. All other screening procedures must be performed only after PD-L1 results are available, and within 28 days before the first administration of study drug. For subjects who do not meet Inclusion Criterion 5, no further Screening procedures should be performed.
4.1 Inclusion Criteria	Criterion 5 is revised: ~~Known~~ **Tumor cell** PD-L1 **score of TC1-3 and immune cell PD-L1 score of IC0-3** ~~tumor status~~ as determined by an IHC assay performed by the central laboratory on tissue obtained **after the last line of therapy** ~~at Screening~~.
4.4 Prohibitions and Restrictions	New requirement is added: 3. Express understanding of the requirement for on-treatment biopsies during the study (ie, Cycle 3, after progression, crossover)
11.9. Data Monitoring Committee	Revised: 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, **including but not limited to future subject enrollment** (see Section 11.3). The DMC may request additional ad-hoc reviews as data accumulate **to monitor safety or efficacy in certain PD-L1 subgroups.**

Rationale: Updates the safety management guidelines for atezolizumab based on the current Investigator's Brochure. Added anticipated events based on the current

6.2 Atezolizumab; 6.2.1 Management of Atezolizumab-Specific Adverse Events; 6.3.2 Atezolizumab; Attachment 7: Management Guidelines for Atezolizumab;	Discontinuation of atezolizumab may not have an immediate therapeutic effect and, in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, ~~mycophenolate, or TNF α inhibitors~~**. or other immunosuppressive agents.** Sections 6.2.1.1 – 6.2.1.7 have been revised, including a new section on immune-mediated myocarditis. Sections 6.2.1.8 Dermatologic Events and 6.2.1.9 Neurologic Events have not changed. A new section on immune-related meningoencephalitis (6.2.1.10) has been added. Management of atezolizumab infusion-related reactions text has been revised: No premedication is indicated for the administration of atezolizumab in Cycle 1. Subjects who experience an IRR with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (eg, acetaminophen) for subsequent infusions. **Metamizole (dipyrone) is prohibited in treating atezolizumab associated infusion-related reactions, due to its potential for causing agranulocytosis.** Table 11 provides management guidelines for atezolizumab IRRs **in Cycle 1. For subsequent cycles, infusion-related reactions should be managed according to institutional guidelines.** Footnote a has been added to Table 16. The tables in Attachment 7 have also been revised, including a new table for immune-mediated myocarditis.
8.2 Prohibited Medications	Dipyrone is added to the list of prohibited medications.
Attachment 4 Anticipated Events	Endocrinopathies (diabetes mellitus, pancreatitis, adrenal insufficiency, or hyperthyroidism, **hypophysitis**) Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome, systemic immune activation, infusion reactions syndrome, **immune-mediated myocarditis, vasculitis, severe cutaneous adverse reactions autoimmune hemolytic anemia**

Rationale: To modify planned statistical analysis as a result of DMC recommendation.	
Synopsis; 11.2 Sample Size Determination	The following text is revised: 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. ~~The statistical power of 80% is to reject the null hypothesis that there is no difference in ORR between the two treatment arms.~~ In the event that benefit from the combination is not observed across the ~~total~~ **overall** study population, target enrollment of subgroups, based on tumor PD-L1 expression level, may be adjusted, **based on DMC recommendations**. (see Section 11.3).~~ provides guidelines for the DMC to use when recommending sample size adjustments~~. **As such, approximately 50 additional subjects in the TC2/TC3 subgroups may be enrolled to 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 (ie, a positive signal in favor of the combination).**
Synopsis; 11.3 Efficacy Analyses	Number and percent of subjects in each response category will be tabulated, along with those for subjects who achieve overall response (CR or PR) and who achieve disease control (ie, CBR: CR, PR, or SD with duration of at least 16 weeks). ~~Treatment comparison will be made via a likelihood ratio test.~~ Odds ratio and its 95% confidence interval will be provided as a measure of treatment effect. Descriptive summaries (mean, standard deviation, median, and range) will be provided for time to response among those subjects who have CR or PR. For time-to-event endpoints (PFS, OS, and duration of response), Kaplan-Meier estimates of the survival functions will be presented. For PFS and OS, ~~treatment comparison will be made via a log-rank test.~~ Cox's regression will be performed to obtain the hazard ratio estimate and the corresponding 95% CI, which will be used as a measure for treatment effect.
Rationale: Revisions to the text in the RECIST and irRECIST criteria are made for consistency with current guidelines.	
Attachment 6 Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)	Text for new, non- measurable lesions, non-target lesions, and progressive disease (PD) are revised.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 3 (24 August 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to allow for the enrollment of subjects in certain PD-L1 subgroups to collect sufficient data to confirm clinical benefit.

Applicable Section(s)	Description of Change(s)
Rationale: To allow the Sponsor, based on the recommendation of the Data Monitoring Committee (DMC), to modify enrollment of subjects in certain PD-L1 subgroups in order to collect sufficient data to confirm clinical benefit.	
Synopsis, Overview Of Study Design; 3.1. Overview of Study Design	Added language related to enrollment of subjects in specific PDL-1 subgroups. **…including the expansion of enrollment of some PD-L1 subgroups, resulting in greater than 96 subjects.**
1.2. Clinical Experience with Atezolizumab	Added information for an immunohistochemistry (IHC) assay that has been used that measures specific PD-L1 expression signals in tumor infiltrating immune cells (ICs) and tumor cells (TCs). Deleted previous information about a prototype IHC assay. Added reference: Peters 2017. Added reference: Ventana 2016a. Added reference: Ventana 2016b. Added Table 7 for Tumor and Immune Cell PD-L1 Expression and Scoring. Cross references to tables are updated throughout the protocol.
3.3. Study Design Rationale, Rationale for Biomarker Evaluations	Added information that based on interim or final analyses, the DMC may recommend modification to enrollment of subjects to the study based on PD-L1 expression in accordance with the product label of the Ventana SP-142 assay. For additional details, refer to Section 11.3.
11.2. Sample Size Determination	Added information that in the event that benefit from the combination is not observed across the total study population, target enrollment of subgroups, based on tumor PD-L1 expression level, may be adjusted (see Section11.3). Table 17 provides guidelines for the DMC to use when recommending sample size adjustments. Added Table 17 for Target Enrollment based on PD-L1 Expression.
11.3. Efficacy Analyses	Added information that the primary endpoint will be evaluated after approximately 90 subjects have been enrolled. The DMC will perform additional interim analyses after approximately 40 subjects and 60 subjects have had at least 1 disease assessment, respectively. These analyses will include an evaluation of efficacy as a function of PD-L1 expression. Based on these results, the DMC may recommend restricting enrollment of subjects in PD-L1 subgroups in whom clinical benefit is not demonstrated or expanding enrollment by a maximum of 100 subjects in PD-L1 subgroups without adequate enrollment (see Section 11.2) in accordance with the product label of the Ventana SP-142 assay. Study sites will be notified in writing of any changes to enrollment based on DMC recommendations.

Rationale: Included an internal Janssen Data Monitoring Committee (DMC), independent of the study team, in this study to review efficacy and safety data.	
Synopsis, Overview Of Study Design; 3.1. Overview of Study Design	Added information about the DMC's role in this study.
11.9. Data Monitoring Committee	Added a new section for information about the structure of the DMC. The DMC will review the safety and efficacy data after approximately 40, 60, and 90 subjects have been enrolled, and will formulate recommendations on study conduct (see Section 11.3). The DMC may request additional ad-hoc reviews as data accumulate.
Rationale: Clarification that subjects must have progressed on or after prior platinum-based therapy to be eligible for this study. Clarified stage for NSCLC subjects.	
4.1. Inclusion Criteria, Criterion 3	Each potential subject must have histologically or cytologically confirmed advanced or metastatic NSCLC (Stage IIIb or **greater** ~~IV~~). Clarifications were added to indicate that subjects must have received at least 2 cycles of standard platinum-based therapy for Stage IIIb or **greater** ~~IV~~ NSCLC and had disease progression on or **after therapy**. Added a note to clarify that "**Subjects who have received fewer than 2 cycles of platinum-based therapy due to** intolerance ~~to~~ (history of hypersensitivity or allergic reactions and other adverse events which prevent continuation of platinum-based agent), ~~therapy~~ **are eligible for study participation, provided there is documentation of disease progression**.
Rationale: Clarification of ECG timepoints for subject monitoring.	
Table 1 Time and Events Schedule – 12-lead ECG	The C1D1 12-lead ECG may be omitted if the Screening ECG was performed ≤7 days earlier. ECGs should be performed and interpreted locally. During the treatment period, a single 12-lead ECG will be performed **pre-dose on D1 of Cycles 1-4 and then pre-dose, D1 of** every third cycle (Cycle ~~4,~~ 7, 10, **13**, etc.). Record new or worsened clinically significant abnormalities on the AE CRF.
Rationale: Clarification of imaging timepoint calculations using C1D1 as the first on study assessment and for subsequent assessment timing.	
Table 1 Time and Events Schedule – Tumor assessment	Added text that "**Imaging timepoints should be calculated from the date of C1D1**."
Rationale: Clarification. Instructions for laboratory assessments were updated.	
Table 1 Time and Events Schedule – Laboratory Assessments	- **Refer to Inclusion Criterion 6 for specific laboratory values that must be met prior to first dose of study drug administration.** - C1D1 laboratory assessments (hematology, chemistry) may be omitted if Screening test**s were** ~~was~~ performed ≤ 7 days prior to the first administration of study drug **and the results meet eligibility criteria**. After Cycle 1, predose laboratory tests can be conducted up to 72 hours prior to dosing. Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of study drug.

Rationale: Blood typing is not required for subjects in Arm A in the main study. Only subjects on combination therapy are required to have blood typing performed.

Table 1 Time and Events Schedule – Blood group and type assessment and indirect antiglobulin (IAT). ABO, Rh, IAT	Assessment for blood typing was moved from Screening to C1D1. "Up to" was deleted. Current text reads" C1D1 predose; run-in and Arm B only"

Rationale: Updates were made to text for Indirect Antiglobulin Test (IAT).standard text to align with current template language for daratumumab studies. Clarified the heading row for IAT assessments. References for daratumumab interference with blood compatibility testing were updated.

Table 1 Time and Events Schedule – Blood group and type assessment and indirect antiglobulin (IAT). ABO, Rh, IAT;	Assessment Heading Row Blood **group and type assessmen**t ~~typing~~ and indirect antiglobulin (IAT). ABO, Rh, IAT
9.5. Safety Evaluations, Indirect Antiglobulin Test (IAT) results	Blood Type**,** Rh**,** and Indirect Antiglobulin Test (IAT) should be done before the first dose of daratumumab. Subject red blood cell (RBC) phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either **method** must be completed prior to first daratumumab infusion. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015, **2016**). [10,**9**] Added reference: Chapuy 2016.

Rationale: Clarification that the Ventana label will be used for the PD-L1 assay.

Table 2 Biomarker Assessments footnote a	Footnote a The Screening assessment of PD-L1 status will be **assessed by a central laboratory using the** ~~done according to~~ the Ventana Medical Systems, Inc. PD-L1 (SP142) assay **in accordance with the assay instructions** ~~by the central laboratory.~~

Rationale: Inclusion of atezolizumab as an approved targeting antibody for PD-L1.

1.1. Background	**Three** ~~Two~~ PD-1 **or PD-L1** targeting antibodies, **(**nivolumab**,** ~~and~~ pembrolizumab, **and atezolizumab)** have been approved for use in previously treated NSCLC.

Rationale: Correction. Four studies are cited in the protocol.

1.2. Clinical Experience with Atezolizumab	The single-agent safety and efficacy data is summarized below from **4** ~~3~~ clinical studies:

Rationale: Clarification that laboratory-values must meet specified criteria for subjects to be eligible for the study. For added clarity, added a link from the Inclusion Criteria to Time and Events Schedule.

4.1. Inclusion Criteria, Criterion 6	~~The following l~~**L**aboratory **values** ~~results~~ **that meet the following criteria** ~~obtained~~ within 14 days prior to first administration of study drug **(see Table 1)**:

Rationale: For clarity and emphasis of information, moved the "Note" at the end of the exclusion criteria to the front of the inclusion criteria for each section.

4.1. Inclusion Criteria	Investigators should ensure that all study enrollment criteria have been met...describes the required documentation to support meeting the enrollment criteria. (Moved from Section 4.2).
4.3. Inclusion and Exclusion Criteria for Crossover	Investigators should ensure that all crossover eligibility criteria ~~enrollment criteria~~ have been met… must be discussed with and approved by the Sponsor on a case-by-case basis. (Moved from Section 4.3.2).

Rationale: All concomitant medications administered for adverse event/infusion-related reactions (AE/iRRs) should be recorded for subject monitoring.

8. Prestudy And Concomitant Therapy	The use of concomitant medications used to treat ~~Grade 2 or higher~~ adverse events or ~~any~~ infusion-related reactions will be collected in the CRF and recorded in the source documents beginning with the signing of the ICF until PD.

Rationale: The use of steroids should be permitted to premedicate a subject for whom CT scans with contrast are contraindicated as the subject will be receiving steroids for pre/post infusion medications.

8.2. Prohibited Therapies	Deleted text which does not apply to this study. • ~~Use of corticosteroids to premedicate subjects for whom CT scans with contrast are contraindicated (ie, subjects with contrast allergy or impaired renal clearance); in such subjects, non-contrast CT scans of the chest and non-contrast CT scans or MRIs of the abdomen and pelvis should be performed.~~

Rationale: Clarification of screening procedure timelines.

9.1.2. Screening Phase	**The Screening Phase begins with the signing of the ICF which** ~~The signed ICF~~ must be obtained before any study-specific procedures are performed **(except for tumor imaging assessments that were performed as part of the subject's routine standard of care). The Screening Phase may be extended by a maximum of 14 days in situations in which screening procedures require repetition or PD-L1 results are not available, after consultation with the Sponsor**. **However, all screening procedures, including standard of care tumor imaging assessments, must be performed within 28 days of first administration of study drug.** ~~The Screening Phase begins when the first protocol specified Screening assessment is performed (typically signing of the ICF).~~

Rationale: To comply with Janssen protocol template standards, the Company Sponsorship Statement was updated. Updated abbreviations list.

Title Page	Added text in bold: **Janssen Pharmaceutica NV;**
Abbreviations	**DMC Data Monitoring Committee** **ECPI European Commission Package Insert** **USPI United States Package Insert**

Rationale: Clarification that RECIST 1.1 is the response criteria, so it is not necessary to repeat wording "response criteria".

Synopsis, Primary Endpoint 2.1.2. Endpoints, Primary Endpoint	• The primary endpoint is ORR: the proportion of subjects with a partial response (PR) or complete response (CR) as defined by RECIST 1.1 ~~response criteria~~

Rationale: Reference to the Atezolizumab Investigator's Brochure was previously cited in this section.

1.2. Clinical Experience with Atezolizumab	Deleted redundant text in this section. ~~Refer to the Atezolizumab Investigator's Brochure for details on clinical activity in NSCLC patients treated to date.~~
Rationale: Numbering from previous amendment was corrected.	
4.2. Exclusion Criteria	**15.1** ~~14.1~~ Administration of a live, attenuated vaccine within 4 weeks before first administration of study drug.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2 (22 March 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to allow subjects in Arm A (atezolizumab monotherapy) to cross over to Arm B (atezolizumab + daratumumab combination therapy) after confirmed disease progression. Combination therapy of daratumumab and atezolizumab may provide clinical benefit in NSCLC subjects who had disease progression on atezolizumab monotherapy. The combination of daratumumab with atezolizumab may lead to an improvement in clinical responses in NSCLC by enhancing the anti-tumor T cell responses facilitated by checkpoint inhibition. Therefore, subjects in Arm A with confirmed disease progression based on RECIST 1.1 may cross over to Arm B, provided all crossover eligibility criteria are met.

Applicable Section(s)	Description of Change(s)
Rationale: Changes are made throughout the protocol for procedures related to Arm A subjects who crossover to also receive daratumumab (Arm B).	
Synopsis, Exploratory Objectives, Exploratory Endpoints, Overview of Study Design;	An exploratory objective and an exploratory endpoint are added to explore the benefit of daratumumab and atezolizumab treatment in subjects who had confirmed disease progression on previous atezolizumab monotherapy.
Time and Events Schedules; 2. Objectives, Exploratory Objectives, 2.1.2 Exploratory Endpoints; 3.1 Overview of Study Design, Figure 1; 3.3 Study Design Rationale, Rationale for Crossover; 4.3 Inclusion and Exclusion Criteria for Crossover; 9.1.1 Overview; 9.1.3 Open-Label Treatment Phase; 9.2 Efficacy Evaluations; 9.2.1 Disease Assessments; 9.2.2 Treatment After Initial Disease Progression; 9.3.1 Evaluations; 9.4.1 Tumor Tissue Samples; 9.5 Safety Evaluations; 10.2 Discontinuation of Study Treatment/Withdrawal from the Study; 11.3 Efficacy Analyses	Time and Events Schedule Tables 1 to 3 are revised to be specific for the Safety Run-in and Randomized cohorts. New Time and Events Schedules (Tables 4 to 6) are added for the crossover cohort. Cross references to the new tables are updated throughout the protocol. For subjects in Arm A who cross over to Arm B after confirmed disease progression, the last scan performed prior to the first crossover dose of study drug will be the crossover baseline scan. New eligibility criteria are added for crossover subjects. Certain clinical laboratory tests will not need to be performed in crossover, except as clinically indicated: Coagulation, calcium, urinalysis, thyroid panel, and serology. Exploratory analyses for overall survival may be performed to adjust for the effect of crossover.

Rationale: To better align with RECIST 1.1, the Immune-Related Response Evaluation Criteria in Solid Tumors (irRECIST) is being used instead of irRC

Abbreviations; Synopsis Exploratory Objectives; Exploratory Endpoints; 2.1.1 Exploratory Objectives; 2.1.2 Exploratory Endpoints; 9.2 Efficacy Evaluations; Attachment 5; Attachment 6	Reference to irRC is replaced with irRECIST. Changes to Attachment 5: *Minimum Size of Measurable Lesions* ≥10 mm in longest diameter (LD) **by CT scan of which slice is thickness no greater than 5 mm** ~~and 2X the slice thickness for extranodal lesions~~ ≥15 mm in short axis ~~diameter~~ (SA~~D~~) for nodal lesions **by CT scan of which slice is thickness no greater than 5 mm.** *Lymph Nodes* Lymph nodes are considered pathologically enlarged if >10 mm in SA~~D~~. To be measurable, nodal lesions must be ≥15 mm in SA~~D~~ **by CT scan of which slice is thickness no greater than 5 mm.** *Cystic Lesions* ~~Non-cystic lesions are preferable.~~ **If noncystic lesions are present in the same patient, they are preferred for selection as target lesions.** *Definition of Complete Response (CR)* CR requires: • The disappearance of all ~~extranodal~~ lesions. • **All lymph nodes must be non-pathological in size** (<10 mm SA~~D~~). • Normalization of tumor marker level. ~~the regression of all nodal lesions to <10 mm SAD and the normalization of tumor marker level.~~ *Definition of Progressive Disease (PD)* Added this sentence: **Furthermore, the appearance of 1 or more new lesions or unequivocal progression of a non-target lesion is also considered as PD.** *Overall Response* One overall response table integrates target, non-target and new lesions **for subjects with measurable disease;** and another table integrates non-target and new lesions for ~~the assessment of~~ subjects without measurable disease. *Confirmation of response* – removed this sentence: In these trials, subsequent confirmation of PR with one interim timepoint of SD is acceptable. Definitions of PR and SD are also added to this attachment. Changes to Attachment 6 (IRRC replaced with irRECIST): Removed (ie, ≥5 mm) in the first 2 rows for both New, measurable lesions and New, nonmeasurable lesions. For CR and PR: removed "in 2 consecutive observations not less than 4 weeks apart." *PD* – added text: At least 20% increase in the sum of the diameters for target lesions and/or unequivocal progression of non-target lesions, **compared with nadir (at any single time point including baseline). The sum must also demonstrate an absolute increase of at least 5 mm.** In both Attachment 5 and 6: replaced the word extranodal with non-nodal and index with target (lesion). Added references: Henze 2016 and Nishino 2013.

Rationale: Tumor imaging is clarified for Screening

Table 1 Time and Events Schedule – Safety Run-in and Randomized Arms; Table 4 Time and Events Schedule – Crossover	CT or MRI of head, chest, abdomen, and pelvis **are required. Include neck if clinically indicated and any other known site of active disease.** ~~(and known sites of active disease)~~

Rationale: Dosing for the Safety Run-in, Arm A, and Arm B is clarified.	
Synopsis, Dosage and Administration; 3.1 Overview of Study Design; 6 Dosage and Administration, 6.1 Daratumumab, 6.2 Atezolizumab	Dosing instructions are clarified for each cohort, including that daratumumab should always be administered before atezolizumab. For Arm A, atezolizumab will be administered at 1,200 mg IV on Day 1 of every 21-day cycle. For the Safety Run-in cohort and 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 will be administered at 1,200 mg IV on Day 2 of Cycle 1 and on Day 1 of every 21-day cycle thereafter. Clarifications are added for subjects who have crossed over: Subjects will continue on the assigned study treatment (atezolizumab alone or atezolizumab+daratumumab) until treatment discontinuation due to disease progression, unacceptable toxicity, or other protocol-defined treatment discontinuation criteria (see Section 10.2); **or until subjects in Arm A crossover**. Subjects in Arm B, who experience unacceptable toxicity directly attributable to one agent and who are experiencing clinical benefit (ie, stable disease or better) may stay on the other agent until treatment discontinuation criteria are met, after discussion with the Sponsor. **Subjects who have crossed over and experience unacceptable toxicity directly attributable to atezolizumab and who are experiencing clinical benefit (ie, stable disease or better) may stay on daratumumab until treatment discontinuation criteria are met, after discussion with the Sponsor.**
Rationale: Enrollment and dosing procedures for the Safety Run-in phase are clarified	
3.1 Overview of Study Design	After Cycle 1, subjects in the Safety Run-in cohort may continue to receive additional cycles of daratumumab + atezolizumab while enrollment into the Safety Run-in cohort is ongoing and after the study has proceeded to the randomization phase until they meet the protocol-specified treatment discontinuation criteria. Enrollment into the Safety Run-in cohort will continue until ≥2 subjects experience a DLT, at which time new subject enrollment will stop until after the SET convenes and makes recommendations regarding conduct of the study. While the SET is reviewing the DLT data, remaining subjects in the Safety Run-in cohort who have not experienced a DLT may continue to receive additional cycles of daratumumab + atezolizumab after consultation with the Sponsor.
Rationale: Clarifications to the Inclusion and Exclusion criteria	
Inclusion Criterion 3	Clarified stage for NSCLC subjects: Subjects must have received at least 2 cycles of standard platinum-based therapy for **Stage IIIb or IV** NSCLC
Inclusion Criterion 8	Revised contraception wording to align with current daratumumab standard wording regarding using 2 methods of reliable birth control simultaneously: 1 highly effective method and 1 additional effective method.

Exclusion Criterion 2	Revised: Other investigational agent or participation in another clinical study with therapeutic intent within 28 days or 5 half-lives of the investigational agent (whichever is longer) ~~to enrollment~~ **prior to first administration of study drug**. Added: Whole brain radiation within 28 days or other radiotherapy within 14 days prior to first administration of study drug. The text on corticosteroid use is revised with additional detail: Use of systemic corticosteroids **>10 mg/day prednisone equivalent within 14 days** ~~≤2 weeks before~~ **prior to first administration of study drug** ~~Cycle 1 Day 1~~. **Acute use of >10 mg/day prednisone equivalent may be allowed with Sponsor approval. Note: Steroids that are topical, inhaled, nasal (spray), or ophthalmic solution are permitted.**
Exclusion Criterion 3	The following text is added regarding CNS metastases and corticosteroid treatment: Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation. ~~during Screening and prior radiographic assessments~~. **Subjects with a history CNS metastases must have completed treatment for the CNS metastases (see Exclusion Criterion 2.1 for guidelines regarding timing of radiation therapy), be neurologically stable, and must have discontinued corticosteroids prior to first administration of study drug.** Leptomeningeal disease or spinal cord compression not definitively treated with surgery or radiation, **or requiring corticosteroid treatment at first administration of study drug**. For uncontrolled tumor-related pain, it is clarified for symptomatic lesions amenable to palliative radiotherapy and asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain should be treated prior to **Screening,** not randomization.
Exclusion Criterion 5	Revised: Malignancies other than NSCLC within 2 years prior to ~~randomization~~ **first administration of study drug**, with the exception of carcinoma in situ of the cervix or breast, basal or squamous-cell skin cancer, or other malignancy that in the opinion of the investigator and Sponsor~~'s Study Responsible Physician~~ is considered cured with a minimal risk of recurrence within 5 years.
Exclusion Criterion 7	To exclude subjects with a history of any type of pulmonary fibrosis to reduce the risk of immune mediated pulmonary events (ie, pneumonitis), the word idiopathic is removed: History of ~~idiopathic~~ pulmonary fibrosis.
Exclusion Criterion 8	Revised: Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal. Note that **spirometry** ~~FEV1 testing~~ is required **during the Screening period** for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal.
Exclusion Criterion 10; Section 9.5 Safety Evaluations	This exclusion is revised to align with current Janssen text, make other clarifications, and to specify when polymerase chain reaction testing should be done. The clinical laboratory test table is revised to add RNA PCR testing as needed.

Exclusion Criterion 11	Revised: Severe infections (including active tuberculosis) within 1 week prior to **first administration of study drug**, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.
Exclusion Criteria 12 and 13	To align with current text used in daratumumab protocols, revised text for cardiac-related exclusion is added (Exclusion Criterion 12). The revised text related to the former Exclusion Criterion 13 is included in Exclusion Criterion 12; therefore, the existing Exclusion Criterion 13 is removed.
Exclusion Criterion 15	Revised: Administration of a live, attenuated vaccine within 4 weeks before first **administration of study drug**.
Exclusion Criterion 20 (new)	Major surgery (eg, requiring general anesthesia) exclusion is added, per standard daratumumab wording.
Rationale: The end of study definition is revised to better align with current expectations for this study.	
17.9.1 Study Completion/End of Study Definition	The end of the study is anticipated to be approximately 6 to 12 months after the last patient has been enrolled (last patient in) and the study may be extended to allow for further treatment and follow-up of subjects.
Rationale: Additional changes have been made to improve the clarity of the protocol.	
Table 1 Time and Events Schedule – Safety Run-in and Randomized Arms	Vital signs assessments are clarified to describe difference between Arm A and the other arms: Measured at Screening and on study drug dosing days. Safety Run-in and Arm B only: C1D1: measure vital signs immediately before the start of the infusion; at 0.5, 1, 1.5, 2 and 3.5 hours after the start of the infusion; at the end of the infusion; and 0.5 and 1 hr after the end of the infusion. For all **subsequent** ~~other~~ **Safety Run-in and Arm B infusions** (daratumumab + atezolizumab) ~~infusions~~, measure immediately before the infusion start, at the end of the infusion, and as clinically indicated. **Arm A only: vital signs should be assessed at Screening, within 24 hours of the start of each infusion and at the end of each infusion.**
Table 4 Time and Events Schedule – Crossover	For all ~~other~~ **subsequent** ~~daratumumab and atezolizumab~~ infusions, measure immediately before the infusion start, at the end of the infusion, and as clinically indicated.
6.1.2 Daratumumab Treatment Schedule and Administration	As noted in Table 1 **and** Table 5 (Time and Events Schedules), vital signs **for subjects in the Safety Run-in and Arm B cohorts** should be monitored frequently on Cycle 1 Day 1 before, during, and after the first infusion of daratumumab. For all ~~other~~ **subsequent** infusions, vital signs should be measured before the start of infusion and at the end of the infusion.
6.1.3.2 Postinfusion Medication	This text is removed as it is clarified in Table 1 and Table 4: ~~Vital signs (temperature, blood pressure, and pulse rate) should be measured <24 hours prior to each planned dose of daratumumab, every 15 (±5) minutes during the first 2 hours of each infusion, every 60 (±10) minutes thereafter for the remainder of the infusion, and at the end of infusion.~~
Table 1 Time and Events Schedule – Safety Run-in and Randomized Arms	Clarified that the D8 and D15 hematology and chemistry assessments are for Cycle 1 and 2 only for Arm A and for Cycles 1-3 for the Safety Run-in and Arm B cohorts. Clarified that prior medications will be collected in addition to concomitant medications.

Table 1 Time and Events Schedule – Safety Run-in and Randomized Arms; Table 4 Time and Events Schedule – Crossover	Clarified the timing of study procedures relative to dosing: For every cycle, study procedures may occur ±3 days of the scheduled Day 1 dose, but prior to study drug administration, in order to accommodate the schedule of the site or subject. For Cycles 1 to 3, Day 8 and Day 15, study procedures may be done ±1 day of the scheduled dose, but prior to daratumumab administration. There should be at least 21 days between Day 1 of every dosing cycle (except for daratumumab in Cycle 1-3). For the Laboratory Assessments, added clarification on the timing of predose testing: After Cycle 1, predose laboratory tests can be conducted up to 72 hours prior to dosing. Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of study drug.
Time and Events schedules for biomarker assessments (Table 2 [new footnotes c, d, e] and Table 5 [new]); 6.2.1.9 Systemic Immune Activation; 9.4 Biomarker Assessments; 9.4.1 Tumor Tissue Samples	For the Diagnostic Archival Tissue or Fresh Biopsy, [redacted] For Cycle 3, biopsy may be collected at Cycle 3 Day 1 ±7 days but must be done following the first tumor assessment. If a biopsy sample(s) is collected at any time during the study for other reasons, a portion should be retained for biomarker analysis. In Section 9.4, this text is also revised: ~~All biomarker assessments will be performed centrally.~~ Tumor biopsies and blood samples will be taken from all **study** subjects ~~in both treatment groups~~ as outlined in the Time and Events Schedule for Biomarkers (**Table 2** and **Table 5**). In this study, mandatory archival or fresh tumor specimens from subjects at Screening will be evaluated for expression of PD-L1^{+}, CD38^{+}, **and other markers indicative of cell populations of interest** [redacted] Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-L1 therapy (Horn 2015; Spira 2015).[23,45] Evaluation of CD38^{+} expression will be performed to determine if elevated expression of CD38^{+} correlates with responses to daratumumab therapy. Fresh biopsies at Cycle 3 and at progressive disease are required, if clinically feasible, to evaluate biomarkers related to the clinical benefit of atezolizumab + daratumumab. **Additionally, if a biopsy is taken at any other time while a subject is on study, a sample is also requested for biomarker analysis.** Evaluation of biopsies ~~collected at Cycle 3~~ **by IHC and IF** may ~~be evaluated for~~ **include PD-L1 and CD38 expression in addition to other markers and cell populations** [redacted] to identify changes in ~~these~~ inflammatory populations in response to treatment. Collection of a tumor biopsy, at the time of radiographic progression will be evaluated for **immune infiltrate, PD-L1, and CD38 expression by IHC** ~~CD8^{+} T cells and regulatory T cell (CD3^{+}/Foxp3^{+}) infiltration will be evaluated by IHC~~ and is required in order to distinguish pseudoprogression/tumor-immune infiltration from true progression. In Section 9.4.1, the following text is added: For subjects enrolled in the crossover arm, if a biopsy was taken at the time of disease progression while enrolled in Arm A of this protocol, a new biopsy is not required at Cycle 1X Day 1 predose. New footnotes are added to Table 2: c. Cycle 3 biopsy may be collected at Cycle 3 Day 1 ±7 days but must be done following the first radiologic tumor assessment. d. If biopsy sample(s) is collected at any time during the study for other reasons, a portion should be retained for biomarker analysis. e. A serum sample for selected cytokines should be drawn within 6 hours of suspected cytokine-release syndrome, and submitted to the central laboratory. The Sponsor will closely monitor and evaluate the collection of cytokine samples and will notify the participating centers of any change to the collection requirements. The serum sample for cytokines is also specified in Section 6.2.1.9.

Time and Events schedules for pharmacokinetic and immunogenicity assessments (Table 3 and Table 6[new]); 9.3.2 Analytical Procedures	Cycle 1 Day 1 predose pharmacokinetic sample for atezolizumab will be for all arms (Safety Run-in, Arm A, Arm B, and crossover). The Cycle 1 Day 2 predose sample is removed. The every 8 Cycles after Cycle 8 (Day 1) samples are removed and replaced with Cycle 12 and Cycle 16 samples. Revised footnote a: Daratumumab should always be administered prior to atezolizumab. In subjects receiving both agents, predose PK and immunogenicity samples for daratumumab and atezolizumab should always be obtained up to 2 hours before the start of the daratumumab infusion, even in Cycle 1 when atezolizumab is administered one day later on Day 2. End of infusion samples are to be taken within 2 hours after the end of the infusion of the respective drug. ~~Predose sample to be taken up to 2 hours before the start of the infusion; end of infusion sample to be taken within 2 hours after the end of the infusion.~~ New footnote b (Table 3): If an Arm A subject crosses over to combination treatment, follow-up samples will not be obtained until after all dosing is complete (Table 6). In Section 9.3.2, this sentence is revised: Serum samples will be analyzed to determine concentrations of daratumumab, concentrations of atezolizumab, or the generation of antibodies to daratumumab or atezolizumab using validated immunoassay methods ~~by or under the supervision of the Sponsor's bio-analytical facility~~.
Time and Events schedules for biomarker assessments (Table 2 and new Table 5); Time and Events schedules for pharmacokinetic and immunogenicity assessments (Table 3, footnote a, and new Table 6)	It specified that if a dose delay occurs, then samples should be taken on the actual day of drug administration, not on the originally scheduled administration day.
Title page; 1 Introduction	Current approvals for atezolizumab and daratumumab are updated.
1.2 Clinical Experience with Atezolizumab	Recently published results are summarized for Study GO28915 (OAK): *A randomized, Phase 3, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in PD-L1 unselected patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen*
6.1.2 Daratumumab Treatment Schedule and Administration	This sentence is removed since the additional details specified are not included in the SIPPM: Additional details for administration times and rates, as well as preinfusion medications, will be provided in the Site Investigational Product Procedures Manual (SIPPM).
6.1.5 Toxicity Management; 6.2 Atezolizumab	Added that a delay in daratumumab dosing will result in a subsequent delay in atezolizumab dosing. Revised Table 12 to align with the dosing in this study. Added that if atezolizumab administration does not commence within the prespecified dosing window (±3 days), then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.
6.2.1.8 Neurologic Disorders	Revised this sentence: Myasthenia gravis, Guillain-Barré syndrome, **and meningoencephalitis** have been observed with single agent atezolizumab.

6.3.2 Atezolizumab, Table 14	In Table 14, Management Guidelines for Atezolizumab Infusion-related Reactions, for Grade 2 treatment examples are added: Administer aggressive symptomatic treatment **(eg, oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen)**.
Table 2 (biomarker assessments), footnote a; 9.1.2 Screening Procedures	This is added to Table 2 footnote a: using the **Ventana Medical Systems, Inc. PD-L1 (SP142)** kit. This sentence is revised: Subjects will be stratified based on PD-L1 status (IC0 and TC0 vs. others), **based on central laboratory assessment (using the Ventana Medical Systems, Inc. PD-L1 (SP142)**~~IHC~~ kit) and histology (squamous vs. non-squamous) ~~based on central laboratory assessment~~, as well as number of previous lines of therapy (1 or >1).
9.2 Efficacy Evaluations	This sentence is added at the end of the paragraph: **Subjects who have disease progression and continue to receive study treatment should continue to undergo disease evaluations including tumor assessments.**
9.2.2 Treatment After Initial Disease Progression	In Table 15 (Imaging and Treatment after First Radiologic Evidence of Progressive Disease), it is clarified to continue regularly scheduled imaging assessments for subjects who continue treatment and that repeat imaging is by RECIST 1.1. Also, it is clarified that for clinically unstable subjects whose repeat tumor imaging does not show PD, to continue regularly scheduled assessments per investigator's discretion and there should be consultation with the Sponsor to restart study treatment if the condition has improved or is clinically stable. The format of the table is revised to merge the additional imaging and treatment columns together.
10.2 Discontinuation of Study Treatment/Withdrawal from the Study	For discontinuation of treatment this bullet is revised: The subject experiences confirmed disease progression (per RECIST 1.1). **However,** subjects **in either Arm A or Arm B** may continue treatment in the setting of clinical benefit **with Sponsor approval. Subjects in Arm A with confirmed disease progression may cross over to Arm B, provided crossover eligibility criteria are met** (see Section 3.1 **and Section 4.3**).
10.3 Withdrawal From the Use of Research Samples	This is revised because there is no separate informed consent: The collected samples will be retained and used in accordance with the subject's original ~~separate~~ informed consent for optional research samples.
References	Henze, Nishino, and Rittmeyer are added.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made, including changing Medical Monitor and Study Responsible Physician to Sponsor.

Amendment 1 (1 September 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to update toxicity and adverse event management in response to Health Authority request, to remove the patient-reported outcomes assessments (PRO), and to add timepoints for biomarker sample collection.

Applicable Section(s)	Description of Change(s)
Rationale: The patient-reported outcome assessments were deemed by the Sponsor to be not needed for this Phase1b/2 study.	
Synopsis Objectives; Synopsis Endpoints; Table 1 Time and Events Schedule; Abbreviations; 2.1.1 Objectives; 2.1.2 Endpoints; 3.1 Overview of Study Design; 3.3 Study Design Rationale; 9.1.1 Overview; 9.5 Patient-reported Outcomes; 11.8 Patient-reported Outcomes Analyses; 15 Study-specific Materials; 18 References; Attachment 7; Attachment 8; Attachment 9	The PRO assessments measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Core 30 (EORTC-QLQ-C30), lung cancer symptom module (EORTC QLQ-LC13), and the European Quality of Life 5 Dimensions Questionnaire (EQ-5D-5L) have been removed.
Rationale: Clarification for pregnancy testing to be done only at Screening	
Table 1 Time and Events Schedule; 4.1 Inclusion Criteria	Clarified that pregnancy testing is not needed for Day 1, Cycles 1 to 3 (removed X in Table 1). Text specifying pregnancy testing for Day 1, Cycle 1 removed from Inclusion Criterion 7.
Rationale: Additional timepoints are added to further explore the effect of daratumumab and atezolizumab on the biomarkers in this study.	
Table 2 Biomarker Assessments	Biomarker sample collection for Flow/immunophenotyping, PBMC/CyTOF, and plasma-based biomarkers is added at the following timepoints: • Cycle 1, Day 8 and Day 15 • Cycle 2, Day 8 and Day 15
Rationale: Text added to clarify specific timepoints for predose and post-infusion PK/Immunogenicity collection for atezolizumab Cycle 1, Days 1 and 2.	
Table 3 Pharmacokinetics and Immunogenicity	Pharmacokinetic sample collection for atezolizumab is added/clarified at the following timepoints: • Cycle 1, Day 1 • Cycle 1, Day 2
Rationale: Chemistry and hematology sample collection during Cycles 1 and 2 is aligned for both Arms.	
Table 1 Time and Events Schedule	The chemistry and hematology sample collection and study visits for Arm A are aligned with Arm B to be weekly during Cycles 1 and 2.

Applicable Section(s)	Description of Change(s)
Rationale: Clarifying text and definition added to Inclusion Criteria 3 and 6 per Health Authority request	
4.1 Inclusion Criteria	Text added to Inclusion Criterion 3 to define intolerance to prior platinum-based therapy. Text added to Inclusion Criterion 6 to specify that, in the case of documented bone metastases, the parameter of ≤ 5x ULN applies only to alkaline phosphatase and does not include AST or ALT
Rationale: Clarification that subjects who had received prior treatment with vaccines are eligible for study participation.	
Section 4.2 Exclusion Criteria	Text in Exclusion Criterion 1 prohibiting the inclusion of subjects receiving prior vaccines was deleted.
Rationale: Correction of text regarding post-infusion corticosteroids to align with the product information for daratumumab	
6.1.3.2 Postinfusion Medication	Text outlining that post-infusion corticosteroids may be omitted in subsequent infusions if no IRR is observed has been deleted.
Rationale: Guidelines for daratumumab dose modification clarified per Health Authority request.	
6.1.5 Toxicity Management	Text modified to note that for all other adverse events, with cited exceptions outlined in the protocol, daratumumab should be withheld for Grade 3 or higher toxicities.
Rationale: Text specifying toxicity grade at which administration of daratumumab may be restarted modified per Health Authority request	
6.1.5 Toxicity Management	Text modified to note that administration of daratumumab may be restarted upon recovery from toxicity to Grade 1 or baseline.
Rationale: Text added outlining the risk of herpes zoster reactivation and recommendations for antiviral prophylaxis per Health Authority request	
6.1.5 Toxicity Management	Text outlining the risk of herpes zoster reactivation observed with daratumumab administration and recommendations for antiviral prophylaxis have been added.
Rationale: Clarification of text to indicate that in cases involving non-adverse event-related atezolizumab treatment discontinuation of > 105 consecutive days, drug can be restarted in subjects deriving clinical benefit with the approval of the Sponsor	
6.2 Atezolizumab	Text added to specify that restarting of atezolizumab after treatment discontinuation of > 105 consecutive days is limited to subjects whose holds are not caused by adverse events, with the approval of the Sponsor.

Applicable Section(s)	Description of Change(s)
Rationale: Guidelines for treatment interruption or discontinuation and management of specific adverse events for atezolizumab expanded and clarified per Health Authority request.	
6.2.1 Management of Atezolizumab-Specific Adverse Events; References; New Attachment 7	• Text added specifying that non-immune-mediated adverse events associated with atezolizumab administration should be managed according to standard medical practice. • Text previously allowing for continuation of atezolizumab treatment in patients meeting criteria for permanent discontinuation has been deleted. • Specific guidelines for immune-mediated events are provided in new Attachment 7. • Text added to specify that atezolizumab should be held in the event of Grade ≥ 3 infections. In addition, for all other non-immune mediated adverse events, with cited exceptions outlined in the protocol, atezolizumab is to be withheld for Grade ≥ 3 toxicity. Administration of atezolizumab to be restarted upon recovery from toxicity to Grade 1 or baseline. • Text referring adverse event management back to the atezolizumab Investigator's Brochure deleted and directed to new Attachment 7 in all subsections of Section 6.2.1. • Text added to specify that atezolizumab should be withheld and appropriate supportive care, including corticosteroid therapy, initiated in the event of systemic immune activation. • New references in Table 20 added to Reference List.
Rationale: Clarification of discontinuation timepoints for daratumumab and atezolizumab	
10.2 Discontinuation of Study Treatment/Withdrawal from the Study	• Bullet updated to indicate that subject's study treatment must be discontinued if the subject missed more than 2 consecutive planned doses due to daratumumab-related adverse events. • New bullet added to indicate that subject's study treatment must be discontinued if the subject missed more than 105 consecutive treatment days due to atezolizumab-related adverse events.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

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

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Primary Objective

- 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.

Primary Endpoint

- The primary endpoint is ORR: the proportion of subjects with a partial response (PR) or complete response (CR) as defined by RECIST 1.1

Secondary Endpoints

- Incidence of adverse events
- DoR: the duration from the date of the initial documentation of a response to the date of the first objectively documented evidence of recurrence or progressive disease or death, whichever status is recorded first.
- CBR: the proportion of subjects who achieve disease control (CR, PR, or SD with duration of at least 16 weeks).
- PFS: the duration from the date of randomization to the date of objectively documented progression or death due to any cause, whichever status is recorded first.
- OS: the duration from the date of randomization to the date of death due to any cause.
- Serum daratumumab concentration (C_{min}, C_{max}) and incidence of anti-daratumumab antibodies
- Serum atezolizumab concentration (C_{min}, C_{max}) and incidence of anti-atezolizumab antibodies

Exploratory Endpoints

- ORRi: the proportion of subjects with a partial response (PR) or complete response (CR) evaluated by irRECIST
- ORR, DoR, CBR, incidence of adverse events, daratumumab and atezolizumab serum concentration and incidence of anti-daratumumab antibodies and anti-atezolizumab antibodies

Refer to Section 9, Study Evaluations for related evaluations.

Hypothesis

The primary hypothesis is that daratumumab in combination with atezolizumab will significantly improve ORR compared to atezolizumab alone in subjects with NSCLC.

OVERVIEW OF STUDY DESIGN

This is a randomized, open-label, parallel-group, multicenter Phase 1b/2 study assessing the anti-tumor activity and safety of daratumumab in combination with atezolizumab compared with atezolizumab alone in subjects with previously treated advanced or metastatic NSCLC. Approximately 96 subjects will be enrolled in this study, including 6 subjects in a safety run-in cohort followed by 90 subjects randomly assigned in a 1:1 ratio to 2 treatment arms. The subjects in the safety run-in cohort will be administered the combination of daratumumab and atezolizumab and will be evaluated by the Safety Evaluation Team (SET) for dose-limiting toxicity.

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.

Beginning with the implementation of Amendment 7, the Sponsor will continue to supply atezolizumab to active subjects who are deriving clinical benefit from atezolizumab monotherapy, but do not have access to commercial atezolizumab. The administration of atezolizumab will occur under the supervision of treating investigators in accordance with local regulatory approvals and standard of care guidelines.[50,51] Data from efficacy and safety evaluations performed according to local regulatory approvals and standard of care guidelines[50,51] will no longer be collected with the exception of serious adverse events that are to be reported and entered in the Sponsor safety repository.

SUBJECT POPULATION

Subjects 18 years and older with advanced or metastatic NSCLC who had at least 2 cycles of standard platinum-based therapy with disease progression or intolerance to therapy are eligible.

DOSAGE AND ADMINISTRATION

For Arm A, atezolizumab will be administered at 1,200 mg IV on Day 1 of every 21-day cycle. For the Safety Run-in cohort and 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 will be administered at 1200 mg IV on Day 2 of Cycle 1 and on Day 1 of every 21-day cycle thereafter. Subjects will continue to receive study treatment until confirmed disease progression, unacceptable toxicity, or any other treatment discontinuation criteria are met.

Beginning with the implementation of Amendment 7, subjects who are deriving clinical benefit from atezolizumab monotherapy, but do not have access to commercial atezolizumab, may continue treatment under the supervision of the treating investigator in accordance with local regulatory approvals and standard of care guidelines.[50,51]

EFFICACY EVALUATIONS

Subjects will undergo tumor assessments until radiographic disease progression per RECIST 1.1, or withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. For subjects who discontinue treatment for reasons other than progression (eg, adverse event), disease assessments will continue to be performed until disease progression or a new cancer therapy is initiated, or another study withdrawal criterion is met.

Beginning with the implementation of Amendment 7, efficacy evaluations will be performed by the investigator according to local regulatory approvals and standard of care guidelines.[50,51] These data will no longer be collected by the Sponsor.

SAFETY EVALUATIONS

Safety assessments include the incidence and severity of adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, and ECOG performance status score.

Beginning with the implementation of Amendment 7, safety evaluations will be performed by the investigator according to local regulatory approvals and standard of care guidelines.[50,51] These data will no longer be collected by the Sponsor with the exception of serious adverse events that are to be reported and entered in the Sponsor safety repository.

STATISTICAL METHODS

The primary analysis population for the efficacy endpoint will be the intent-to-treat population in the randomized phase of the study. 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.

Number and percent of subjects in each response category will be tabulated, along with those for subjects who achieve overall response (CR or PR) and who achieve disease control (ie, CBR: CR, PR, or SD that lasts at least 16 weeks). Odds ratio and its 95% confidence interval will be provided as a measure of treatment effect. Descriptive summaries (mean, standard deviation, median, and range) will be provided for time to response among those subjects who have CR or PR. The primary hypothesis is that daratumumab in combination with atezolizumab will significantly improve ORR compared to atezolizumab alone in subjects with NSCLC.

Table 1: Time and Events Schedule – Safety Run-in, Randomized Arms

Beginning with the implementation of Amendment 7, subjects who continue to derive benefit from atezolizumab treatment, may continue to receive atezolizumab under the supervision of treating investigators in accordance with local regulatory approvals and standard of care guidelines.[50,51] Data from efficacy and safety evaluations performed according to local regulatory approvals and standard of care guidelines[50,51] will no longer be collected with the exception of serious adverse events that are to be reported and entered in the Sponsor safety repository.

Assessments	Prescreening (optional)	Screening		Treatment Period (21-day cycles)						EOT (30 +7d after last dose)	Follow-up Period	
				Arm	Cycles 1-3				Cycle 4 and beyond		Pre-PD	Post-PD Survival
Day	Any time prior to start of Screening	-56 to -1	-28 to -1		D1 (±3)	D2	D8 (±1)	D15 (±1)	D1 (±3)			q12 weeks (±1 wk)
Procedures For every cycle, study procedures may occur ±3 days of the scheduled Day 1 dose, but prior to study drug administration (except for those routinely needed after administration), in order to accommodate the schedule of the site or subject. For Cycles 1 to 3, Day 8 and Day 15, study procedures may be done ±1 day of the scheduled dose, but prior to daratumumab administration. Day 2 visit is only required for Safety Run-in and Arm B subjects during Cycle 1 only.												
Prescreening Informed Consent	X											
Archival tumor tissue (Section 9.1.2)	X											
Informed Consent		X										
Eligibility Criteria			X									
Demographics			X									
Medical and cancer history			X		4							
Tumor tissue specimen for PD-L1 testing (central lab)		X			X – Cycle 3 and at time of radiographic progression							
Vital signs (pulse, blood pressure, and temperature) and Weight Measured at Screening and on study drug dosing days.[a]			X	Arm A	X				X			
				Safety Run-in, Arm B	X	C1 only	X	X	X	X		
Physical exam, height Complete physical exam at Screening; height only measured at Screening. During the treatment period, perform a limited, symptom-directed examination as clinically indicated. Record new or worsened clinically significant abnormalities on the AE CRF.			X		---------- X ----------							

Table 1: Time and Events Schedule – Safety Run-in, Randomized Arms

Beginning with the implementation of Amendment 7, subjects who continue to derive benefit from atezolizumab treatment, may continue to receive atezolizumab under the supervision of treating investigators in accordance with local regulatory approvals and standard of care guidelines.[50,51] Data from efficacy and safety evaluations performed according to local regulatory approvals and standard of care guidelines[50,51] will no longer be collected with the exception of serious adverse events that are to be reported and entered in the Sponsor safety repository.

Assessments	Prescreening (optional)	Screening		Treatment Period (21-day cycles)						EOT (30 +7d after last dose)	Follow-up Period	
				Arm	Cycles 1-3				Cycle 4 and beyond		Pre-PD	Post-PD Survival
Day	Any time prior to start of Screening	-56 to -1	-28 to -1		D1 (±3)	D2	D8 (±1)	D15 (±1)	D1 (±3)			q12 weeks (±1 wk)
ECOG performance status			X		X				X	X		
12-lead ECG The C1D1 12-lead ECG may be omitted if the Screening ECG was performed ≤7 days earlier. ECGs should be performed and interpreted locally. During the treatment period, a single 12-lead ECG will be performed predose on D1 of Cycles 1-4 and then predose, D1 of every third cycle (Cycle 7, 10, 13, etc.). Record new or worsened clinically significant abnormalities on the AE CRF.			X		X				X	X		
FEV-1 Only for subjects with known or suspected COPD; FEV1 <50% of predicted normal is excluded.			X									
Tumor assessment CT or MRI imaging of all disease sites documented at Screening should be performed using the same methodology throughout the study. Tumor assessments will be performed per RECIST 1.1. For subjects who discontinue treatment for reasons other than progression (eg, adverse event), tumor assessments will continue to be performed until documented disease progression or a new cancer therapy is initiated.			CT or MRI of head, chest, abdomen, and pelvis are required. Include neck if clinically indicated and any other known site of active disease.		X CT or MRI of chest and abdomen (and known sites of active disease) Every 6 weeks (±1 week) for the first 12 months of treatment and every 9 weeks (±1 week) thereafter regardless of treatment delays. Same frequency for all subjects. Imaging timepoints should be calculated from the date of C1D1.						

Table 1: Time and Events Schedule – Safety Run-in, Randomized Arms

Beginning with the implementation of Amendment 7, subjects who continue to derive benefit from atezolizumab treatment, may continue to receive atezolizumab under the supervision of treating investigators in accordance with local regulatory approvals and standard of care guidelines.[50,51] Data from efficacy and safety evaluations performed according to local regulatory approvals and standard of care guidelines[50,51] will no longer be collected with the exception of serious adverse events that are to be reported and entered in the Sponsor safety repository.

Assessments	Prescreening (optional)	Screening		Treatment Period (21-day cycles)						EOT (30 +7d after last dose)	Follow-up Period	
				Arm	Cycles 1-3				Cycle 4 and beyond		Pre-PD	Post-PD Survival
Day	Any time prior to start of Screening	-56 to -1	-28 to -1		D1 (±3)	D2	D8 (±1)	D15 (±1)	D1 (±3)			q12 weeks (±1 wk)
Laboratory Assessments: - Refer to Inclusion Criterion 6 for specific laboratory values that must be met prior to first dose of study drug administration. - C1D1 laboratory assessments (hematology, chemistry) may be omitted if Screening tests were performed ≤ 7 days prior to the first administration of study drug and the results meet eligibility criteria. After Cycle 1, predose laboratory tests can be conducted up to 72 hours prior to dosing. Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of study drug.												
Hematology (see Section 9.7; performed by local lab)			X		X		X Arm A: Cycle 1 & 2 only; Safety Run-in, Arm B	X	X	X		
Chemistry (see Section 9.7; performed by local lab); see below for amylase, lipase			X		X		X Arm A: Cycle 1 & 2 only; Safety Run-in, Arm B	X	X	X		
HBV/HCV Serology (see Section 9.7; performed by local lab)			X									
Coagulation (see Section 9.7; performed by local lab)			X									
Thyroid function (see Section 9.7; performed by local lab) Amylase, lipase (see Section 9.7; performed by local lab) Screening, C4D1, every third cycle thereafter (ie, C7, C10, C13, etc.) and EOT			X						X	X		
Urinalysis – dipstick			X									
Pregnancy test – serum at Screening within 14 days prior to first study drug administration; serum or urine thereafter if clinically indicated			X									

Table 1: Time and Events Schedule – Safety Run-in, Randomized Arms

Beginning with the implementation of Amendment 7, subjects who continue to derive benefit from atezolizumab treatment, may continue to receive atezolizumab under the supervision of treating investigators in accordance with local regulatory approvals and standard of care guidelines.[50,51] Data from efficacy and safety evaluations performed according to local regulatory approvals and standard of care guidelines[50,51] will no longer be collected with the exception of serious adverse events that are to be reported and entered in the Sponsor safety repository.

Assessments	Prescreening (optional)	Screening		Treatment Period (21-day cycles)						EOT (30 +7d after last dose)	Follow-up Period	
				Arm	Cycles 1-3				Cycle 4 and beyond		Pre-PD	Post-PD Survival
Day	Any time prior to start of Screening	-56 to -1	-28 to -1		D1 (±3)	D2	D8 (±1)	D15 (±1)	D1 (±3)			q12 weeks (±1 wk)
Blood group and type assessment and indirect antiglobulin (IAT). ABO, Rh, IAT A wallet card with subject blood type and IAT will be provided					C1D1 predose; Run-in, Arm B							
Study Drug Administration For subjects in the Safety Run-in and Arm B, the daratumumab infusion should precede the atezolizumab infusion on Day 1 of each cycle, starting with Cycle 2. Only one agent will be infused at a time. See the SIPPM for additional details. There should be at least 21 days between Day 1 of every dosing cycle (except for daratumumab in Cycles 1-3).												
Atezolizumab				Arm A	X				X			
				Run-in, Arm B	C2/ C3	C1 only			X			
Daratumumab IV (*daratumumab will no longer be administered per Amendment 6*)				Run-in, Arm B	X		X	X	X			
Ongoing Subject Review												
Adverse events [b]		Continuous from ICF through 30 days (or 90 days for SAEs) after the last dose of study drug or start of subsequent anticancer therapy, if earlier (see Section 12.3.1)										
Prior and Concomitant Medications		Continuous 30 days prior to 1st administration of study drug through 30 days after last dose of study drug										
Survival and subsequent anti-cancer therapy												X

AE=adverse event, C=cycle, CRF=case report form, COPD=chronic obstructive pulmonary disease, CT=computed tomography, D or d=day, ECOG= Eastern Cooperative Oncology Group Performance Status, EOT=end of treatment, FEV-1=forced expiratory volume; maximal amount of air forcefully exhaled in 1 sec., HBV=hepatitis B virus, HCV=hepatitis C virus, IAT=indirect antiglobulin test, ICF=informed consent form, MRI=magnetic resonance imaging, PD=progressive disease, PD-L1=programmed death-ligand 1, Ph=phase, q=every, SIPPM=Site Investigational Product Procedures Manual

a. Safety Run-in and Arm B only: C1D1: measure vital signs immediately before the start of the infusion; at 0.5, 1, 1.5, 2 and 3.5 hrs after the start of the infusion; at the end of the infusion; and 0.5 and 1 hr after the end of the infusion. For all subsequent Safety Run-in and Arm B administrations (daratumumab + atezolizumab), measure immediately before the administration start, at the end of the atezolizumab infusion, and as clinically indicated. Arm A only: vital signs should be assessed at Screening, within 24 hrs of the start of each infusion and at the end of each infusion.

b. Beginning with the implementation of Amendment 7, only serious adverse events will be reported and entered in the Sponsor safety repository for subjects who continue to be treated according to local regulatory approval and standard of care guidelines.[50,51]

ABBREVIATIONS

ADCC	antibody dependent cell-mediated cytotoxicity
AE	adverse event
ALK	anaplastic lymphoma kinase
Breg	regulatory B cell
CBC	complete blood count
CBR	clinical benefit rate
CDC	complement-dependent cytotoxicity
COPD	chronic obstructive pulmonary disease
CR, sCR	complete response; stringent complete response
CRF	case report form(s) (paper or electronic as appropriate for this study)
CT	computed tomography
CyTOF	cytometry time of flight
DCF	data clarification form
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group Performance Status
UCPI	European Commission Package Insert
EGFR	epidermal-growth factor receptor
EOT	end of treatment
EOTX	end of treatment for crossover
FEV-1	forced expiratory volume; maximal amount of air forcefully exhaled in 1 sec.
FFPE	formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
HBc	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IAT	indirect antiglobulin test
IC	tumor-infiltrating immune cells
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IF	immunofluorescence
Ig	immunoglobulin
IHC	immunohistochemistry
IMiD	immunomodulatory agent
INR	International Normalized Ratio
IRB	institutional review board
IRR	infusion-related reaction
irRECIST	Immune-Related Response Evaluation Criteria in Solid Tumors
IV	intravenous
IWRS	interactive web response system
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MDSC	myeloid-derived suppressor cell
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
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PQC	product quality complaint
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
SD	stable disease
SET	safety evaluation team
SIPPM	Site Investigational Product Procedures Manual
SUSAR	suspected unexpected serious adverse reaction
SVR	sustained virologic response
TC	tumor cell
Treg	regulatory T cell
ULN	upper limit of normal
USPI	United States Package Insert
VGPR	very good partial response
β-hCG	β-human chorionic gonadotropin

1. INTRODUCTION

This is an open-label, randomized, Phase 1b/2 study of the combination of 2 monoclonal antibodies, TECENTRIQ® (atezolizumab) and DARZALEX® (daratumumab) in subjects with previously treated advanced or metastatic non-small cell lung cancer (NSCLC). Both atezolizumab and daratumumab are investigational medicinal products (IMPs) in this study.

Atezolizumab is a humanized immunoglobulin G (IgG) 1 monoclonal antibody (mAb) that was engineered to target cells expressing programmed death ligand-1 (PD-L1) and inhibits its interaction with its receptor, programmed death-1 (PD-1). Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells (Butte 2007).[7] Atezolizumab is approved by the US FDA for treatment of patients with urothelial carcinoma that has relapsed from or has become resistant to treatment with platinum-based agents (see the Product Information for atezolizumab for the specific indication). Atezolizumab is also currently approved for patients with metastatic NSCLC who have disease progression during or following platinum-containing therapy. It is currently being studied as a therapy for other solid tumors and hematologic malignancies in humans.

Daratumumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds CD38-expressing cells with high affinity. Daratumumab is approved by the US FDA for the treatment of patients with multiple myeloma who have received at least 3 lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double-refractory to a PI and an IMiD; and in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. It is also approved in the European Union for the treatment of adults with relapsed and refractory multiple myeloma (see the Product Information for daratumumab for the specific indication). It is also being studied as a therapy for other hematologic malignancies including non-Hodgkin lymphoma and amyloidosis.

For the most comprehensive nonclinical and clinical information regarding atezolizumab and daratumumab, refer to the latest versions of the respective Investigator's Brochures.

The term "Sponsor" used throughout this document refers to the entities listed in the Contact Information page, which will be provided as a separate document.

1.1. Background

Non-small Cell Lung Cancer Background

Lung cancer is the leading cause of cancer deaths globally (WHO 2015).[56] In the United States (US), lung cancer is the second most commonly diagnosed cancer with over 200,000 people diagnosed annually. It is the leading cause of cancer-related deaths, with almost 160,000 people estimated to succumb to the disease each year (Am Cancer Society 2014).[1] Similar data from Europe estimate that there were 313,000 new cases of lung cancer and 268,000 deaths in 2012 (GLOBOCAN 2012).[16] Approximately 80% to 85% of the newly diagnosed cases of lung cancer

are NSCLC (adenocarcinoma, squamous carcinoma, and large-cell carcinoma) and 15% to 20% are small-cell lung carcinoma (Molina 2008; Howlader 2011).[30, 24]

Treatment of Advanced or Metastatic Non-Small Cell Lung Cancer

Patients with Stage I, II, or III NSCLC are generally treated with curative intent using surgery or radiation therapy, sometimes combined with concurrent or adjuvant chemotherapy (Goldstraw 2007).[17] In contrast, systemic therapy is generally appropriate for patients with Stage IIIB or Stage IV disease at presentation. Systemic therapy is also used for patients who have relapsed with advanced disease after definitive treatment.

The choice of treatment for a patient with advanced NSCLC depends on the histologic subtype and the presence or absence of characteristic molecular abnormalities, as well as the patient's age, functional status, comorbidities, and prior therapy. Initial systemic therapy (chemotherapy or targeted agents) may delay disease progression and prolong survival in patients with advanced NSCLC; however, almost all patients eventually develop progressive disease (PD).

Therapy should be individualized based on molecular and histologic features of the tumor. Whenever possible, patients should have tumor tissue assessed for the presence of a driver mutation that stimulates tumor growth. These mutations define subsets of patients likely to respond to specific inhibitors that target the protein produced by the relevant mutation (NCCN Guidelines).[32] Patients with a known driver mutation in the epidermal growth factor receptor (EGFR) are managed initially with an EGFR tyrosine kinase inhibitor (Moran and Sequist 2012, and Gridelli 2012).[31,18] Those with an anaplastic lymphoma kinase (ALK) fusion oncogene in their tumor are treated initially with an ALK inhibitor, such as crizotinib (Kwak 2010, Camidge 2012, Shaw 2012).[26,8,44]

Chemotherapy is the primary treatment for patients with advanced NSCLC whose tumor does not have an activating mutation of EGFR or the *ALK* fusion oncogene. Current American Society of Clinical Oncology (ASCO) guidelines suggest that 2-drug cytotoxic combinations should be administered for no more than 6 cycles (Azzoli 2009)[3] for treatment of NSCLC. There is no single optimal chemotherapy combination (Schiller 2002, Scagliotti 2002, Ohe 2007).[43,42,34] However, randomized studies suggest that cisplatin-based regimens are slightly more effective than carboplatin-based combinations or nonplatinum regimens (Ardizzoni 2007).[2]

Most patients with advanced NSCLC eventually develop PD. Based on results of Phase 3 studies, docetaxel and pemetrexed are approved for second-line chemotherapy after progression on an earlier chemotherapy regimen. In this setting, treatment with these agents results in few objective responses, which, generally, are of short duration, and results in limited improvement in PFS and OS. The choice of agent is influenced by the chemotherapy regimen used in the initial treatment setting. For patients whose tumor contains a driver mutation, those who were initially treated with cytotoxic chemotherapy should be treated with the appropriate targeted therapy.

Among the innovative treatment approaches currently undergoing evaluation in clinical studies, immunotherapies with immune checkpoint-inhibitors, including those targeting PD-L1 or PD-1, appear to be the most promising (Ruiz 2014).[40] Several anti-PD-1 antibodies have demonstrated promising clinical activity with prolonged responses in various tumor types, including NSCLC. Three PD-1 or PD-L1 targeting antibodies (nivolumab, pembrolizumab, and atezolizumab) have been approved for use in previously treated NSCLC. Nivolumab was approved on the basis of an overall survival benefit versus docetaxel (hazard ratio [HR] 0.59 and 0.73 in squamous and non-squamous, respectively) independent of PD-L1 expression status; pembrolizumab was approved for use on the basis of an overall response rate of 41% in NSCLC patient expressing PD-L1 on >50% of their tumor cells.

Pharmacologic Profile

Atezolizumab

Blockade of PD-L1 or PD-1 with mAbs results in potent and often rapid anti-tumor effects in multiple murine tumor models (Iwai 2002; Strome 2003).[25,48] These data suggest that tumor-specific T cells may be present in the tumor microenvironment in an inactive or repressed state, and that inhibition of the PD-L1/PD-1 pathway reinvigorates tumor-specific T-cell responses. Reports from Phase 1 oncology studies of molecules targeting either PD-L1 or PD-1 have demonstrated activity in patients with advanced stage and metastatic disease that is refractory to standard therapy (Brahmer 2015; Topalian 2012).[6,50]

Daratumumab

Daratumumab is a targeted immunotherapy directed toward cells that express high levels of CD38, such as plasma cells from patients with multiple myeloma. Once binding to CD38 occurs, daratumumab induces cell death through diverse immune-mediated mechanisms (complement-dependent cytotoxicity [CDC], antibody-dependent cell-mediated cytotoxicity [ADCC], antibody dependent cellular phagocytosis [ADCP]), and induction of apoptosis (de Weers 2011; Overdijk 2015).[12,36]

Translational biomarker studies of Phase 1 and Phase 2 multiple myeloma daratumumab patient samples (GEN501 and MMY2002, respectively) reveal immunomodulatory effects of daratumumab (Krejcik 2016).[27] Daratumumab leads to the elimination of highly immunosuppressive subsets of $CD38^+$ T-regulatory cells (Tregs), $CD38^+$ myeloid derived suppressor cells (MDSCs), and $CD38^+$ B regulatory cells (Bregs). It has also been shown that daratumumab may modulate the enzymatic activity of CD38 and may lead to a reduction in immunosuppressive adenosine levels (Horenstein 2013).[22] This shift away from an immunosuppressive environment may lead to the generation of protective immune responses. Elimination of these highly immunosuppressive cell subsets in parallel with increases in the absolute number of activated T cells may potentiate the activity of an anti-PD-L1 antibody in NSCLC and other PD-L1 expressing malignancies.

1.2. Clinical Experience with Atezolizumab

Atezolizumab is currently being tested in multiple Phase 1, 2, and 3 studies, both as monotherapy and in combination with several anti-cancer therapies (see the Atezolizumab Investigator's Brochure). The single-agent safety and efficacy data is summarized below from 4 clinical studies:

- Study PCD4989g: A Phase 1 study of atezolizumab monotherapy assessing the PK and safety in locally advanced or metastatic solid tumors or hematologic malignancies
- Study GO28753 (POPLAR): A randomized, Phase 2, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in PD-L1 unselected patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen
- Study GO28754 (BIRCH): A Phase 2, single-arm trial of atezolizumab as first-line or subsequent therapy for locally advanced or metastatic PD-L1-selected NSCLC
- Study GO28915 (OAK): A randomized, Phase 3, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in PD-L1 unselected patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen.

The PCD4989g, POPLAR, BIRCH, and OAK trials used an immunohistochemistry (IHC) assay to measure PD-L1 protein expression in tumor infiltrating immune cells (ICs) and tumor cells (TCs) (Ferenbacher 2016, Peters 2017, Rittmeyer 2017, Herbst 2016).[15,37,39,20] This IHC assay has been approved as a complementary diagnostic PD-L1 IHC assay for use with atezolizumab in NSCLC by the US FDA (Ventana 2016a [USPI])[53] and the European Commission (Ventana 2016b [ECPI])[54].

PD-L1 staining categories in ICs are defined as IC0, IC1, IC2, and IC3 and are defined in TCs as TC0, TC1, TC2, and TC3 according to Table 2.

Table 2: Tumor and Immune Cell PD-L1 Expression and Scoring

Percentage PD-L1 Expression at any Intensity	Score
Immune Cells	
<1% Immune Cells in the tumor area	IC0
≥1% and <5% Immune cells in the tumor area	IC1
≥5% and <10% Immune cells in the tumor area	IC2
≥10% Immune cells in the tumor area	IC3
Tumor Cells	
<1% Tumor cells	TC0
≥1% and <5% Tumor cells	TC1
≥5% and <50% Tumor cells	TC2
≥50% Tumor cells	TC3

Single-Agent Clinical Activity in Patients with NSCLC in Study PCD4989g

Preliminary results suggest that PD-L1 expression in tumor tissue is likely to be associated with response to atezolizumab. Table 3 summarizes the overall response rate (ORR) by PD-L1 tumor expression in NSCLC patients in the Phase 1 study (PCD4989g), in which atezolizumab monotherapy is administered to patients with locally advanced or metastatic solid tumors or hematologic malignancies. As of the clinical cutoff date, 8 of 20 patients have continued to respond after 7+ to 27+ weeks. The median duration of response (DoR) is 17 months. The most frequently reported adverse events (occurring in ≥10% of patients) included fatigue, decreased appetite, nausea, pyrexia, constipation, and cough.

Table 3: Patients with NSCLC in Study PCD4989g: Confirmed Objective Response Rate by Tumor PD-L1 Expression and Best Overall Response Rate (per RECIST, Version 1.1)

PD-L1 IHC Expression Category	ORR (n = 88)	PR	SD
TC3 or IC3	50% (11 of 22) 95% CI: 28.2%–71.8%	50% (11 of 22)	18.2% (4 of 22)
TC3 or IC2/3	31.6% (12 of 38) 95% CI: 17.5%–48.6%	31.6% (12 of 38)	28.9% (11 of 38)
TC0/1/2 and IC0/1/2	12.1% (7 of 58) 95% CI: 5.7%–22.5%	12.1% (7 of 58)	36.2% (21 of 58)
TC0/1/2 and IC0/1	14.3% (6 of 42) 95% CI: 6.4%–27.7%	14.3% (6 of 42)	33.3% (14 of 42)

IC=tumor-infiltrating immune cell; IHC=immunohistochemistry; NSCLC=non–small cell lung cancer; ORR = objective response rate; PD-L1=programmed death–ligand 1; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; TC=tumor cell.
Notes: This table is based on a data cutoff date of 21 April 2014 of patients with NSCLC dosed by 21 October 2013. Objective response is per RECIST 1.1.

Single-Agent Clinical Activity in Patients with Advanced or Metastatic NSCLC in Study GO28753 (POPLAR)

GO28753 (POPLAR) is a randomized Phase 2 study in advanced or metastatic NSCLC patients who failed prior platinum therapy (Ferenbacher 2016).[15] Two hundred eighty-seven (287) patients were enrolled and randomly allocated to atezolizumab or docetaxel in a 1:1 ratio. At a minimum follow-up of 13 months (60% of patients had died), atezolizumab significantly improved overall survival compared with docetaxel (12.6 vs 9.7 months; HR 0.73 [95% CI 0.53, 0.99], p=0. 04). The overall survival benefit from atezolizumab increased with increasing PD-L1 expression on tumor cells, tumor infiltrating immune cells, or both.

The most frequently observed adverse events in the POPLAR study (occurring in ≥20% of atezolizumab-treated patients) included fatigue, nausea, diarrhea, constipation, cough, dyspnea, and decreased appetite.

Single-Agent Clinical Activity in Patients with Locally Advanced or Metastatic NSCLC in Study GO28754 (BIRCH)

GO28754 (BIRCH) is a single-arm Phase 2 study in locally advanced or metastatic PD-L1 expressing NSCLC (Besse 2015).[5] Six-hundred and sixty seven (667) patients with PD-L1 positive tumors (TC2/3 or IC2/3) were enrolled and treated with atezolizumab monotherapy. Table 4 summarizes the efficacy findings including ORR, progression-free survival (PFS) and overall survival (OS) by number of prior lines of therapy and PD-L1 expression status.

Table 4: Patients with NSCLC in Study GO28754: ORR, PFS, and OS by Tumor PD-L1 Expression and Number of Prior Lines of Therapy

	First-line		Second-line		Third-line+	
	TC3 or IC3	TC2/3 or IC2/3	TC3 or IC3	TC2/3 or IC2/3	TC3 or IC3	TC2/3 or IC2/3
N	65	139	122	267	115	253
ORR %	26	19	24	17	27	17
6-mo PFS %	48	46	34	29	39	31
6-mo OS %	79	82	80	76	75	71

The safety profile of atezolizumab monotherapy in the BIRCH study was consistent with the other studies in this population. Thirty-eight percent (38%) of patients had a Grade 3 or 4 adverse event (AE); 11% had a treatment-related Grade 3 or 4 AE. The most common related AEs were fatigue (18%) and nausea (10%). Six percent (6%) of patients discontinued study treatment due to an AE (eg, pneumonitis, 0.6%; pneumonia, 0.5%).

Single-Agent Clinical Activity in Patients with Locally Advanced or Metastatic NSCLC in Study GO28915 (OAK)

GO28915 is an ongoing, randomized, open-label Phase 3 study in advanced or metastatic NSCLC patients who failed prior platinum therapy, in which 1,225 patients were enrolled and were randomly allocated to atezolizumab or docetaxel in a 1:1 ratio (Rittmeyer 2016)[39]. The primary analysis population consists of the first 850 randomized patients. Atezolizumab significantly improved OS compared with docetaxel; the results of GO28915 with a median follow-up of 21 months are presented in Table 5. Of the 850 patients, 16% were classified as having high PD-L1 expression, defined as having PD-L1 expression on ≥50% of TC or ≥10% of IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27,0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in patients who did not have high PD-L1 expression.

Table 5: Overall Survival in Study GO28915 (OAK)

	Atezolizumab n=425	Docetaxel n=425
Overall Survival		
Deaths %	271 (64%)	298 (70%)
Median, months (95% CI)	13.8 (11.8, 15.7)	9.6 (8.6, 11.2)
Hazard ratio[a]	0.73 (0.62, 0.87)	
p-value[b]	0.0003	

CI=confidence interval

a. Stratified by PD-L1 expression in tumor infiltrating immune cells, the number of prior chemotherapy regimens, and histology.

b. Based on the stratified log-rank test.

Safety data in Study GO28915 are consistent with previously reported safety data from the atezolizumab Phase 2 study in patients with previously treated NSCLC (POPLAR). The percentage of Grade 3 or 4 adverse events in the atezolizumab and docetaxel were 37% and 54%, respectively, with fewer treatment-related adverse events with atezolizumab compared with docetaxel. Among the 609 patients treated with atezolizumab in this study, the following were the most common atezolizumab-related adverse events of any grade (event, percentage of patients with the event): fatigue (14%), nausea (9%), decreased appetite (9%), and asthenia (8%). Immune-mediated adverse events reported with atezolizumab included pneumonitis (any grade: 6 patients, 1%; Grade 3: 4 patients, <1%); hepatitis (Grade 3, 2 patients <1%); and colitis (Grade 2, 2 patients <1%). Adverse events leading to treatment discontinuation occurred in 46 (8%) of 609 patients with atezolizumab and in 108 (19%) of 578 patients with docetaxel. There were no deaths related to atezolizumab and 1 related to docetaxel (respiratory tract infection).

Given the mechanism of action of atezolizumab, events associated with inflammation or immune-mediated adverse events have been closely monitored during the atezolizumab clinical program. These include immune-mediated dermatologic, hepatic, endocrine, gastrointestinal, and respiratory events. Refer to the atezolizumab Investigator's Brochure for details on immune-mediated adverse events and other adverse events that were observed in patients treated with atezolizumab.

1.3. Clinical Experience with Daratumumab

This is the first clinical study of daratumumab in NSCLC. Current clinical information is based on studies of patients with multiple myeloma.

1.3.1. Daratumumab IV

Human Pharmacokinetics and Immunogenicity

Daratumumab clearance decreases with increasing dose and repeated dosing, indicating target-mediated pharmacokinetics. Following the approved multiple myeloma schedule and dose of 16 mg/kg, the mean serum maximum observed concentration (C_{max}) at the end of 8 weeks of weekly dosing was 915 µg/mL, approximately 2.9-fold higher than following the first infusion. The mean predose (trough) serum concentration at the end of weekly dosing was 573 µg/mL. Based on the population pharmacokinetic (PK) analysis, daratumumab steady state is achieved approximately 5 months into the every-4-week dosing period (by the 21st infusion), and the mean ratio of C_{max} at steady-state to C_{max} after the first dose was 1.6. The mean estimated terminal half-life associated with linear clearance was approximately 18 days.

Of the 199 total subjects in Studies GEN501 and MMY2002 that were evaluable for immunogenicity, none were positive for anti-daratumumab antibodies.

Efficacy/Safety Studies

The US FDA and European Commission (EC) have approved daratumumab for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an IMiD or who are double-refractory to a PI and an IMiD. These approvals were based on data from the pivotal study MMY2002 and key supportive study GEN501.

Integration of data from Study MMY2002 and Part 2 of Study GEN501 resulted in an ORR of 31% with duration of response of 7.6 months. Median time to first response is slightly less than 1 month, corresponding to the first disease assessment. The response at the dose of 16 mg/kg was consistent across all subgroups, regardless of the number of prior lines of therapy, refractory status, or geographic region. The rate of very good partial response (VGPR) or better induced by single-agent daratumumab was 11% across Study MMY2002 and Study GEN501. Following treatment with daratumumab, 3 stringent complete responses (sCRs), 2 complete responses (CRs), and 12 VGPRs were observed across both studies. The CR/sCR rate was 3%.

The integrated safety analysis of these studies (MMY2002 and GEN501) included 156 subjects who received at least one dose of daratumumab 16 mg/kg monotherapy. The most frequently reported treatment-emergent AEs were fatigue, nausea, anemia, neutropenia, back pain, cough, and thrombocytopenia. Infusion-related reactions were reported for 51% of subjects. Grade 3 infusion-related reactions were reported for 4% of subjects; no Grade 4 infusion-related reaction (IRR) was reported. Most of the IRRs (91%) occurred with the first infusion; they were managed well with preinfusion and postinfusion medications, and no IRR resulted in discontinuation of treatment.

Refer to the Daratumumab Investigator's Brochure for details on the clinical experience in patients treated with daratumumab.

1.4. Overall Rationale for the Study

This Phase 1b/2 Study will inform future clinical development of daratumumab and atezolizumab in NSCLC patients. Despite recent improvements in treatment, the prognosis for patients with advanced NSCLC remains dismal, with a median OS of approximately 12.3 months (Sandler 2006).[41] Patients who receive second-line treatment for their disease have an even more limited prognosis, with a median survival duration of approximately 8 to 9 months (Stinchcombe 2008).[47]

Inhibition of PD-L1 signaling has been shown to produce durable responses in some patients, and expression of PD-L1 by TCs in several tumor types (including NSCLC) correlates with response to therapy (Topalian 2012)[50] and improved OS (Ferenbacher 2016; Herbst 2016).[15,20] Data from the Phase 1a Study PCD4989g evaluating single-agent atezolizumab in several tumor types, including NSCLC, suggest that PD-L1 expression in TCs and ICs as determined by IHC correlates with response to atezolizumab. An ORR of 31.6% was observed in patients with high levels of PD-L1 staining in TCs or ICs (TC3 or IC2/3 group) compared with an ORR of 14.3% in patients with low or no PD-L1 staining in TCs and ICs (TC0/1/2 and IC0/1 group). Additionally, data from the GO28754 (BIRCH) study provide evidence that response rates are generally consistent in both treatment naive and previously treated patients with varying degrees of PD-L1 expression status. Despite these encouraging data, it is clear that the majority of patients in these studies do not respond to PD-L1 inhibition. Therefore, new therapeutic approaches are needed.

Expansion of Tregs and MDSCs in the lung tumor microenvironment is part of the mechanism by which cancer cells escape from host immune surveillance and may limit response to checkpoint inhibitors (Peterson 2006; Dasanu 2012; Srivastava 2012).[38,11,46] Daratumumab is a first-in-class human monoclonal CD38 targeting antibody that induces deep clinical responses in multiple myeloma. Flow cytometry analysis revealed a previously unknown immunomodulatory role of daratumumab, by way of induction of T cell expansion through the reduction of immune suppressive cell populations $CD38^+$ MDSC, $CD38^+$ Treg, and $CD38^+$ Breg cells. Therefore, the combination of daratumumab with atezolizumab may lead to an improvement in clinical responses in NSCLC by enhancing the anti-tumor T cell responses facilitated by checkpoint inhibition.

[redacted]

Overlapping toxicities of daratumumab and atezolizumab are not expected. While infusion-related reactions (IRRs) are observed in approximately half of patients treated with daratumumab, IRRs occur in only approximately 1% of patients treated with atezolizumab.

As of 25 May 2018, the Sponsor terminated further enrollment into this study after the third planned Data Monitoring Committee (DMC) review on 23 May 2018. At that time

(n=88, 44 subjects per arm), the DMC determined that there was no observed benefit within the combination treatment arm, daratumumab plus atezolizumab, over atezolizumab alone, and recommended stopping enrollment of the study. In addition, the DMC recommended discontinuation of daratumumab treatment to all active subjects receiving combination therapy (subjects randomized to the combination Arm B, as well as subjects randomized to Arm A who crossed over into Arm B). Although no unexpected imbalances in on-treatment toxicities were observed, the DMC noted a numerical increase in the number of deaths in the combination arm. Therefore, enrollment is discontinued in this study, treatment with daratumumab will be discontinued, and ongoing subjects will be given the option to continue on atezolizumab monotherapy until the subject meets one or more of the treatment discontinuation criteria in Section 10.2. Additionally, Phase 1b expansion to explore the subcutaneous formulation as outlined in Amendment 5 will not be implemented.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

- 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.

2.1.2. Endpoints

Primary Endpoint

- The primary endpoint is ORR: the proportion of subjects with a partial response (PR) or complete response (CR) as defined by RECIST 1.1

Secondary Endpoints

- Incidence of adverse events
- DoR: the duration from the date of the initial documentation of a response to the date of the first objectively documented evidence of recurrence or progressive disease or death, whichever status is recorded first.
- CBR: the proportion of subjects who achieve disease control (CR, PR, or SD with duration of at least 16 weeks).
- PFS: the duration from the date of randomization to the date of objectively documented progression or death due to any cause, whichever status is recorded first.
- OS: the duration from the date of randomization to the date of death due to any cause.
- Serum daratumumab concentration (C_{min}, C_{max}) and incidence of anti-daratumumab antibodies
- Serum atezolizumab concentration (C_{min}, C_{max}) and incidence of anti-atezolizumab antibodies

Exploratory Endpoints

- ORRi: the proportion of subjects with a partial response (PR) or complete response (CR) evaluated by irRECIST
- ORR, DoR, CBR, incidence of adverse events, daratumumab and atezolizumab serum concentration and incidence of anti-daratumumab antibodies and anti-atezolizumab antibodies

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

The primary hypothesis is that daratumumab in combination with atezolizumab will significantly improve ORR compared to atezolizumab alone in subjects with NSCLC.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, open-label, parallel-group, multicenter Phase 1b/2 study assessing the anti-tumor activity and safety of daratumumab in combination with atezolizumab compared with atezolizumab alone in subjects with previously treated advanced or metastatic NSCLC. Approximately 96 subjects will be enrolled in this study, including 6 subjects in a safety run-in cohort followed by 90 subjects randomly assigned in a 1:1 ratio to 2 treatment arms. In addition to safety and efficacy, pharmacokinetics, and biomarkers will also be assessed.

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.

Beginning with the implementation of Amendment 7, the Sponsor will continue to supply atezolizumab to active subjects who are deriving clinical benefit from atezolizumab monotherapy, but do not have access to commercial atezolizumab. The administration of atezolizumab will occur under the supervision of treating investigators in accordance with local regulatory approvals and standard of care guidelines.[50,51] Data from efficacy and safety evaluations performed according to local regulatory approvals and standard of care guidelines[50,51] will no longer be collected with the exception of serious adverse events that are to be reported and entered in the Sponsor safety repository.

Safety Run-in Phase

A 6-subject Safety Run-in cohort will be evaluated by the Safety Evaluation Team (SET; see Section 3.2) to determine the safety and tolerability of atezolizumab administered in combination with daratumumab before proceeding with the randomized phase of the study.

- Enrollment into the safety run-in will be staggered, with at least 48 hours between initiation of daratumumab + atezolizumab combination therapy (Cycle 1 Day 1) of individual subjects.
- 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 will be administered at 1,200 mg IV on Day 2 of Cycle 1 and on Day 1 of every 21-day cycle thereafter.
- After Cycle 1, subjects in the Safety Run-in cohort may continue to receive additional cycles of daratumumab + atezolizumab while enrollment into the Safety Run-in cohort is ongoing and after the study has proceeded to the randomization phase until they meet protocol-specified discontinuation criteria.
- If <2 of the first 6 subjects experience a dose-limiting toxicity (DLT; see Section 3.2) during the first treatment cycle (ie, 21 days), the selected doses and dose regimens for

daratumumab + atezolizumab combination therapy will be considered tolerable in subjects with advanced or metastatic NSCLC, and the study will proceed to the randomized phase after the SET provides approval.

- If ≥2 subjects experience a DLT, new subject enrollment into the Safety Run-in cohort will stop until after the SET convenes to review DLT data from those subjects and makes recommendations regarding the conduct of the study. The SET may consider the exploration of alternate doses and dose regimens. While the SET is reviewing the DLT data, remaining subjects in the Safety Run-in cohort who have not experienced a DLT may continue to receive additional cycles of daratumumab + atezolizumab after consultation with the Sponsor.

Randomized Phase

Approximately 90 subjects were to have been stratified based on PD-L1 expression status (IC0 and TC0 vs. others), histology (squamous vs. non-squamous), and number of previous lines of therapy (1 or >1), and then assigned randomly in a 1:1 ratio into 2 treatment arms as follows:

Arm A: atezolizumab

Arm B: atezolizumab + daratumumab IV

Treatment

Note: subjects will only be eligible to receive atezolizumab monotherapy (per Amendment 6), see Section 3.2.

For Arm A, atezolizumab will be administered at 1,200 mg IV on Day 1 of every 21-day cycle. Subjects in Arm A who experience confirmed disease progression based on RECIST 1.1 will be eligible to crossover to Arm B provided crossover eligibility criteria are met.

For 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 will be administered at 1,200 mg IV on Day 2 of Cycle 1 only and then on Day 1 of every 21-day cycle thereafter. Measures to prevent infusion-related reactions will include preinfusion medication (see Section 6.3). Subjects will be monitored closely for immune-mediated adverse events including pneumonitis, enterocolitis, hepatitis, dermatitis, neuropathies, and endocrinopathies.

Study visits for subjects receiving daratumumab (Safety Run-in and Arm B) will occur weekly during the first 3 cycles and every 3 weeks for all cycles thereafter. Study visits for subjects randomized to Arm A (atezolizumab alone) will occur weekly during the first 2 cycles and every 3 weeks thereafter. Subjects will continue on the assigned study treatment (atezolizumab alone or atezolizumab + daratumumab) until treatment discontinuation due to disease progression, unacceptable toxicity, or other protocol-defined treatment discontinuation criteria (see Section 10.2); or until subjects in Arm A crossover. Subjects in Arm B, who experience unacceptable toxicity directly attributable to one agent and who are experiencing clinical benefit (ie, stable disease or better) may stay on the other agent until treatment discontinuation criteria

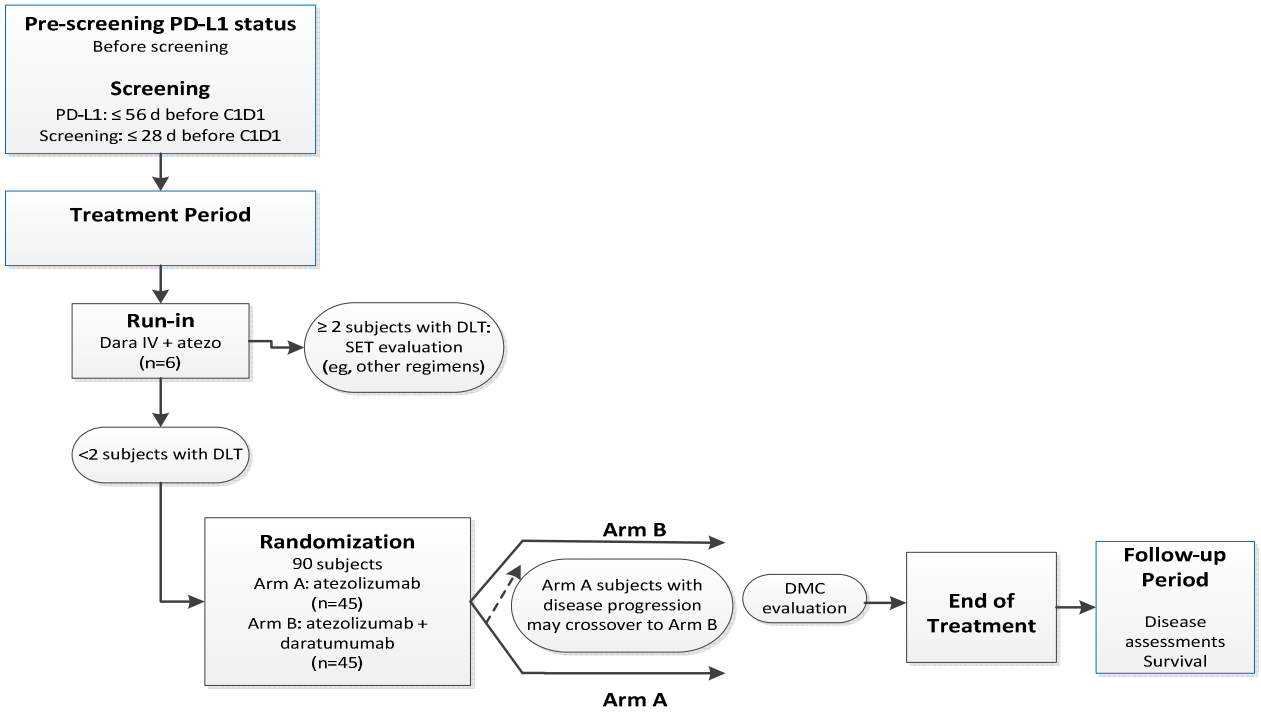
are met, after discussion with the Sponsor. Subjects who have crossed over and experience unacceptable toxicity directly attributable to atezolizumab and who are experiencing clinical benefit (ie, stable disease or better) may stay on daratumumab until treatment discontinuation criteria are met, after discussion with the Sponsor.

Follow-up

The Follow-up phase will begin after the End-of-Treatment visit, 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. For subjects who discontinue treatment for reasons other than progression (eg, adverse event), disease assessments will continue to be performed until disease progression or a new cancer therapy is initiated (or another study withdrawal criterion is met, see Section 10.2).

The timing of assessments is provided in the Time and Events Schedule (Table 1). A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



3.2. Study Conduct After DMC Recommendations

As of 25 May 2018, the Sponsor terminated further enrollment into this study. Ongoing treatment with daratumumab will be discontinued in all active subjects receiving combination therapy (subjects randomized to the combination Arm B, as well as subjects randomized to Arm A who have crossed over into Arm B). Crossover to Arm B is also no longer permitted. Ongoing subjects will be given the option to continue on atezolizumab monotherapy until the subject meets one or more of the treatment discontinuation criteria in Section 10.2. For subjects remaining on the study, protocol procedures and the atezolizumab dosing schedule will continue according to Section 9.2 and the Time and Events Schedule (Table 1) until locking of the clinical database. All procedures outlined in previous versions of this protocol pertaining to patients randomized to treatment other than atezolizumab monotherapy (in Table 2 through Table 7, which were removed beginning with the implementation of Amendment 6) will no longer be performed. For safety reporting changes, see Section 12.4. Upon clinical database closure, only serious adverse events will be reported and entered in the Sponsor safety repository for subjects who continue to be treated according to local regulatory approval and standard of care guidelines.[50,51]

The changes to study conduct and status implemented in Amendment 7 were also pursuant to these recommendation from the DMC.

A clinical study report (CSR) will be prepared based on the interim analysis data reviewed by the DMC at the third DMC review (prior to discontinuation of enrollment and daratumumab dosing).

3.3. Safety Evaluation

Dose-Limiting Toxicity (DLT)

Toxicities will be graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. During the 6-subject Safety Run-in phase, the DLT evaluation period is 21 days starting from the day of the first dose of study drug. Only toxicities that occur during the DLT evaluation period will be considered for DLT assessment. Subjects who are not evaluable for DLT can be replaced. A DLT evaluable subject (DLT evaluable analysis set) is:

- Any subject who has a DLT regardless of dose received or
- A subject who did not have a DLT but received at least 75% of the planned dose during the DLT evaluation period.

Dose-limiting toxicity is defined as any of the events listed in Table 6. Toxicities with a clear alternative explanation (eg, due to disease progression) or transient toxicities (≤72 hours) and abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination can be deemed a non-DLT.

Table 6: Criteria for Dose-limiting Toxicity

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.

Safety Evaluation Team (SET)

Ongoing safety evaluation during the safety run-in phase of this open-label study will be overseen by the SET. The SET established by the Sponsor will monitor all available treatment-emergent data on an ongoing basis throughout study conduct for the purpose of ensuring the continued safety of subjects enrolled in this study. The SET will also be responsible for reviewing the safety data during the safety run-in phase and making a formal determination of whether the study will proceed to the 90-subject randomized phase based on the DLT rules set forth above.

The SET will be chaired by the Sponsor's Study Responsible Physician. Membership will include a Sponsor clinical scientist, statistician, clinical pharmacologist, along with additional Sponsor staff, as appropriate. Additionally, the investigators who have enrolled the 6 safety run-in subjects will participate. The team will meet approximately monthly during the safety run-in phase and as necessary during the conduct of the remainder of the study. Documentation of meeting outcomes will be maintained by the Sponsor in the Study Master File. Decisions with the potential to affect subject safety (eg, unfavorable change in benefit/risk assessment) will be promptly communicated to investigators and regulatory authorities as appropriate.

3.4. Study Design Rationale

Rationale for Study Design

Clinical study experience with the use of atezolizumab monotherapy in NSCLC has established its safety and tolerability in the population under study. Targeting $CD38^+$ immunosuppressive cells with daratumumab may synergistically combine with PD-L1 blockade to increase the activity of effector T cells and lead to improved clinical responses in NSCLC.

Adequate steps have been taken to ensure the validity of data in an open-label study design. This includes performing tumor assessments at the same frequency in both arms, adhering to protocol-defined schedules, and determining the strategy for the final analysis of the primary endpoint prior to study start, including predefined methods for handling missing data and censoring rules.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups. To further minimize imbalance across treatment arms and to allow for balanced enrollment in important subgroup analyses, subjects will initially be stratified based on centrally determined PD-L1 expression status (TC0 and IC0 vs. others; see Section 1.2), histology (squamous vs. non-squamous), and number of prior therapies (1 vs >1).

Rationale for Daratumumab IV Dose Selection

The dose used in this study (16 mg/kg) is the approved dose of daratumumab for the treatment of subjects with relapsed and refractory multiple myeloma. This dose selection was based on an acceptable safety profile, maximal clinical activity, and pharmacokinetics consistent with saturation of the target. This dose and similar schedules have been shown to be tolerable in several combination studies.

Based on these data, the initial dose and schedule for NSCLC subjects in combination with atezolizumab is 16 mg/kg weekly for 3 cycles (Day 1, 8 and 15), and Day 1 of every 21-day cycle thereafter. This is a slight modification of the approved multiple myeloma schedule (weekly for 8 weeks, every 2 weeks for 16 weeks, and every 4 weeks thereafter) to match dosing frequency of atezolizumab for patient convenience. A similar daratumumab schedule was previously used and shown to be safe and efficacious in the Phase 3 MMY3004 study (weekly during Cycles 1, 2 and 3), every 3 weeks until the end of Cycle 8 (ie, the end of bortezomib/dexamethasone treatment per the bortezomib label), and then alone every 4 weeks (ie, daratumumab only from Cycles 9 onward).

Rationale for Atezolizumab Dose Selection

The fixed dose of 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) was selected on the basis of nonclinical studies and available clinical data from Study PCD4989g as described below and has been used in subsequent studies evaluating atezolizumab as a monotherapy in NSCLC, including GO28753 and GO287504 (as described in Section 1.2).

The target exposure for atezolizumab was projected on the basis of nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, the observed atezolizumab interim pharmacokinetics in humans, and other factors. The target trough concentration (C_{trough}) was projected to be 6 μg/mL on the basis of several assumptions, including the following: 1) 95% tumor-receptor saturation is needed for efficacy and 2) the tumor-interstitial concentration to plasma ratio is 0.30 based on tissue distribution data in tumor-bearing mice.

The atezolizumab dose is also informed by available clinical activity, safety, pharmacokinetics, and immunogenicity data. Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg. The maximum tolerated dose (MTD) of atezolizumab was not reached, and no DLTs have been observed at any dose in Study PCD4989g. Currently available pharmacokinetic and anti-drug antibody data suggest that the 15-mg/kg atezolizumab every 3-week regimen (or fixed-dose equivalent) for Phase 2 and Phase 3 studies would be sufficient to both maintain C_{trough} ≥6 μg/mL and further safeguard against both interpatient variability and the potential effect of anti-drug antibodies that could lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab every 3 week regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, moving further to the 20-mg/kg atezolizumab every 3-week regimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15-mg/kg atezolizumab every 3 week level.

Simulations (Bai 2012)[4] do not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight. Therefore, a fixed dose of 1200 mg has been selected (equivalent to an average body weight–based dose of 15 mg/kg). Selection of an every-21-day dosing interval is supported by this preliminary pharmacokinetics evaluation.

Rationale for ORR as the Primary Endpoint

Objective response is generally accepted as a convincing measure of anti-tumor activity for the reason that spontaneous regression fulfilling criteria for at least partial response is uncommon. Furthermore, durable and objective response rates have been accepted by regulatory authorities as reasonably likely to predict clinical benefit.

Rationale for Pharmacokinetics and Immunogenicity Assessments

The demographic characteristics of the NSCLC population differ significantly from previously studied daratumumab subject populations and may affect the pharmacokinetic profile. Therefore, samples will be obtained from all subjects for assessment of minimum and maximum observed concentrations (C_{min} and C_{max}). Data may also be used for a population pharmacokinetic analysis to estimate additional pharmacokinetic parameters and provide information about the determinants of inter-subject variability in this population.

Immunogenicity to atezolizumab and daratumumab is possible, and the incidence of anti-drug antibody generation in subjects with NSCLC may be different from previously studied populations because these subjects are expected to be less immune compromised. Therefore, samples to determine the presence of antibodies to atezolizumab and daratumumab (immunogenicity) will be collected during treatment and after the last dose in the study.

Rationale for Biomarker Evaluations

Biomarker samples will be collected to evaluate biomarkers of biologic activity of atezolizumab+daratumumab in subjects with NSCLC. Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-L1 therapy (Horn 2015; Spira 2015).[23,45] Mandatory tumor specimens from subjects at Screening will be evaluated and used to initially stratify patients by PD-L1 status to minimize imbalance between the treatment groups. In addition, based on interim or final analyses, the DMC may recommend modification to enrollment of subjects to the study based on PD-L1 expression in accordance with the product label of the Ventana SP-142 assay. For additional details, refer to Section 11.3.

Tumor specimens from subjects at Screening, on-treatment, and at progression will be retrospectively evaluated for $CD38^+$ expression, [redacted] Evaluation of $CD38^+$ expression will be performed to determine if elevated $CD38^+$ expression at Screening and decreases with daratumumab treatment correlate with responses to combined therapy. Circulating immune cells and $CD38^+$ immunosuppressive cells will be evaluated by flow cytometry as potential pharmacodynamic and response biomarkers.

4. SUBJECT POPULATION

Subjects 18 years and older with advanced or metastatic NSCLC who had at least 2 cycles of standard platinum-based therapy with disease progression or intolerance to therapy will be eligible for this study.

An optional Prescreening informed consent will be offered for the purpose of testing archival tumor tissue to assess PD-L1 status using the SP142 assay (Section 9.1.2) to help determine the likelihood of eligibility for participation in this study. However, final eligibility for study participation will be based on PD-L1 staining on the fresh biopsy required during the Screening Phase, unless the archival tumor sample used in the Prescreening Phase was obtained after completion of the most recent line of therapy with no intervening therapies, and is less than 1 year old. The signing of the main study informed consent and collection of tumor specimen for PD-L1 testing may occur up to 56 days before the first administration of study drug. All other screening procedures must be performed only after PD-L1 results are available, and within 28 days before the first administration of study drug. For subjects who do not meet Inclusion Criterion 5, no further Screening procedures should be performed. For subjects in the randomized phase, treatment should start within 72 hours after randomization.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate Sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

During its review of the study data at the initial interim analysis (40 evaluable subjects), the DMC determined that the study had enrolled a sufficient number of subjects with a PD-L1 score of TC0 and recommended continued enrollment only in subjects in the TC1-3 subgroups. After this DMC recommendation, the sites were notified that only subjects with a PD-L1 score of

TC1-3 will be eligible to enroll in the study, and the protocol was amended to reflect this DMC recommendation (Section 4.1).

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

After the third data review by the DMC, this study is closed to further enrollment.

4.1. Inclusion Criteria

Investigators should ensure that all study enrollment criteria have been met at Screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 9.1.3, Screening Phase, describes options for retesting. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. ≥18 years of age
2. ECOG performance status of 0 or 1.
3. Criterion modified per Amendment 2.

   3.1 Criterion modified per Amendment 3.

   3.2 Have histologically or cytologically confirmed advanced or metastatic NSCLC (Stage IIIb or greater).

   - Subjects must have received at least 2 cycles of standard platinum-based therapy for Stage IIIb or greater NSCLC and had disease progression on or after therapy.

   Note: Subjects who have received fewer than 2 cycles of platinum-based therapy due to intolerance (history of hypersensitivity or allergic reactions and other adverse events which prevent continuation of platinum-based agent), are eligible for study participation, provided there is documentation of disease progression.

   - Subjects who received prior treatment with vaccines or investigational agents, are eligible for study participation.
   - Subjects with known genetic alterations of *ALK, EGFR,* and *ROS1* are not eligible for study participation.
4. Criterion modified per Amendment 2.

   4.1 Measurable disease, as defined by RECIST 1.1.
5. 5.1 Criterion modified per Amendment 4.

   5.2 Criterion modified per Amendment 5

   5.3 Criterion modified per Amendment 6

   Tumor cell PD-L1 score as determined by an IHC assay performed by the central laboratory on tissue obtained after the last line of therapy:

   Randomized phase of the study

   - Subjects with a tumor cell PD-L1 score of TC1-3 who are anti-PD-1 or anti-PD-L1 treatment naïve will be eligible for screening.
6. Criterion modified per Amendment 2.

   6.1 Criterion modified per Amendment 3.

6.2 Laboratory values that meet the following criteria within 14 days prior to first administration of study drug (see Table 1):

- ANC >1.5 × 10^9/L (without growth factor support 1 week before 1st administration)
- Platelets >100 × 10^9/L
- Hemoglobin >9 g/dL
  - Transfusion is acceptable to meet the hemoglobin and platelet criteria if stable for 1 week prior to first administration of study drug
- Calculated creatinine clearance >50 mL/min per Cockroft-Gault formula
- INR or aPTT ≤1.5 x ULN
  - Applies only to subjects who are not receiving therapeutic anticoagulation; subjects receiving therapeutic anticoagulation should be on a stable dose for at least 4 weeks.
- AST, ALT, and alkaline phosphatase:
  - ≤2.5 × ULN, if no liver metastases
  - ≤5 × ULN with documented liver metastases
  - ≤5 × ULN alkaline phosphatase (not AST or ALT) with documented bone metastases
- Total bilirubin ≤2.0 x ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≤2.0 x ULN)
- Serum ionized calcium ≤1.5 mmol/L or serum calcium ≤12 mg/dL or corrected serum calcium <ULN)

7. A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) at Screening within 14 days prior to study drug administration.

8. Criterion modified per Amendment 2.

   8.1 Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies.

   Before enrollment, a woman must be either:

   a. Not of childbearing potential defined as:

   - postmenopausal
     A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - permanently sterile
     Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

   b. Of childbearing potential and

   - practicing 2 methods of reliable birth control simultaneously: 1 highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and 1 additional effective method.

     Examples of highly effective contraceptives include:

     - user-independent methods:

       implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (s*exual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*)

- user-dependent methods:

combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.

Examples of additional effective contraceptive methods include:

- male latex or synthetic condom, diaphragm, or cervical cap

- agrees to remain on the 2 contraception methods (1 highly effective and 1 additional reliable method) throughout the study and for at least 3 months after last dose of daratumumab or 5 months after the last dose of atezolizumab. In addition, during the study and for 3 months after receiving the last dose of daratumumab or 5 months after the last dose of atezolizumab, a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.

Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active) a woman must begin a highly effective method of contraception and 1 additional reliable method, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

9. During the study and for a minimum of approximately 3 months after the last dose of daratumumab or 5 months after the last dose of atezolizumab, in addition to the highly effective method of contraception, a man
   - who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository)
   - who is sexually active with a woman who is pregnant must use a condom
   - must agree not to donate sperm.
10. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.
11. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Criterion modified per Amendment 5.

   1.1 Criterion modified per Amendment 6.

   1.2 Received any of the following prescribed medications or therapies in the past:

   - Randomized Phase: Anti-CD38 therapy (including daratumumab), CD137 agonists, and immune checkpoint inhibitors including but not limited to anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapies

2. Criterion modified per Amendment 2.

   2.1 Received any of the following prescribed medications or therapies within the specified period:

   - Approved anti-cancer therapy, including chemotherapy, within 3 weeks prior to first administration of study drug.

- Other investigational agent or participation in another clinical study with therapeutic intent within 28 days or 5 half-lives of the investigational agent (whichever is longer) prior to first administration of study drug.
- Whole brain radiation within 28 days or other radiotherapy within 14 days prior to first administration of study drug.
- Use of systemic corticosteroids >10 mg/day prednisone equivalent within 14 days prior to first administration of study drug. Acute use of >10 mg/day prednisone equivalent may be allowed with Sponsor approval. Note: Steroids that are topical, inhaled, nasal (spray), or ophthalmic solution are permitted.

3. Criterion modified per Amendment 2.

   3.1 Has any of the following conditions:

   - Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation. Subjects with a history of CNS metastases must have completed treatment for the CNS metastases (see Exclusion Criterion 2.1 for guidelines regarding timing of radiation therapy), be neurologically stable, and must have discontinued corticosteroids for the treatment of the CNS metastases prior to first administration of study drug.
   - Leptomeningeal disease or spinal cord compression not definitively treated with surgery or radiation, or requiring corticosteroid treatment at first administration of study drug.
   - Uncontrolled tumor-related pain:
     - Symptomatic lesions amenable to palliative radiotherapy (eg, bone metastases, or metastases causing nerve impingement) should be treated prior to Screening.
     - Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (eg, epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to Screening.

4. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently); indwelling catheters are allowed.

5. Criterion modified per Amendment 2.

   5.1 Malignancies other than NSCLC within 2 years prior to first administration of study drug, with the exception of carcinoma in situ of the cervix or breast, basal or squamous-cell skin cancer, or other malignancy that in the opinion of the investigator and Sponsor is considered cured with a minimal risk of recurrence within 5 years.

6. Criterion modified per Amendment 2.

   6.1 Criterion modified per Amendment 5.

   6.2 Criterion modified per Amendment 6.

   6.3 History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.

   - Subjects with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible (with Sponsor approval).
   - Subjects with controlled Type I diabetes mellitus on a stable dose of insulin regimen are

eligible.

- Subjects with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (eg, subjects with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
  - Rash must cover less than 10% of body surface area (BSA)
  - Disease is well controlled at baseline and only requiring low potency topical steroids
  - No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)

7. Criterion modified per Amendment 2.

   7.1 History of pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan; history of radiation pneumonitis in the radiation field (fibrosis) is permitted.

8. Criterion modified per Amendment 2.

   8.1 Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal. Note that spirometry is required during the screening period for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal.

9. Known to be seropositive for human immunodeficiency virus (HIV).

10. Criterion modified per Amendment 2.

    10.1 Active hepatitis B, defined by a positive test for hepatitis B surface antigen (HBsAg) or prior history of hepatitis B, defined by presence of antibodies to hepatitis B core antigen [anti-HBc], regardless of hepatitis B surface antibody [anti-HBs] status; active hepatitis C or prior history of hepatitis C (anti-HCV positive), except in the setting of a sustained virologic response (SVR), defined as aviremia 12 weeks after completion of antiviral therapy.

    - If hepatitis C virus (HCV) antibodies are detected, an HCV RNA test for viral load by polymerase chain reaction (PCR) should be performed at least 12 weeks after completion of antiviral therapy to rule out active infection.

11. Severe infections (including active tuberculosis) within 1 week prior to first administration of study drug, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.

12. Criterion modified per Amendment 2.

    12.1 Clinically significant cardiac disease, including:

    - Myocardial infarction within 6 months before first administration of study drug, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV)
    - Uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities.
    - Screening 12-lead ECG showing a baseline corrected QT interval (QTc) >470 msec.

13. Criterion deleted per Amendment 2.

14. Prior allogeneic bone marrow transplantation or solid organ transplant.

15. Criterion modified per Amendment 2.

15.1 Administration of a live, attenuated vaccine within 4 weeks before first administration of study drug.

16. Women who are pregnant, lactating, or intending to become pregnant during the study or within at least 3 months after last dose of daratumumab or 5 months after the last dose of atezolizumab; men who intend to father a child during the study or within at least 3 months after the last dose of daratumumab or 5 months after the last dose of atezolizumab.
17. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
18. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the daratumumab or atezolizumab formulation.
19. Any other concurrent medical or psychiatric condition, diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the subject at high risk from treatment complications.
20. Major surgery (eg, requiring general anesthesia) within 2 weeks before Screening, not fully recovered from surgery, or surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study treatment. Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate after consultation with the Sponsor. Kyphoplasty or vertebroplasty are not considered major surgery.

4.3. Inclusion and Exclusion Criteria for Crossover

Crossover will no longer be performed in this study; therefore, this section is no longer applicable.

Subject Population

The inclusion and exclusion criteria listed in this section apply only to those subjects crossing over from Arm A to Arm B. Subjects who satisfy all of the criteria below are eligible to crossover from Arm A to Arm B at the investigator's discretion. If there is a question about the inclusion or exclusion criteria below, then the investigator must consult with the appropriate Sponsor representative and resolve any issues before enrolling a subject in the crossover arm. Note that subjects must complete the End of Treatment Visit prior to screening for crossover.

Investigators should ensure that all crossover eligibility criteria have been met at the time of screening for crossover. If a subject's status changes, then the subject should be excluded from crossing over. Subjects who fail to meet the inclusion and exclusion criteria for crossover may be rescreened if their condition changes. Rescreening must be discussed with and approved by the Sponsor on a case-by-case basis.

4.3.1. Inclusion Criteria for Crossover

In order to be eligible to cross over from Arm A to Arm B, subjects must meet the following criteria:

1X. Subjects must have been randomized to Arm A of the study and had radiographic disease progression according to RECIST 1.1 (disease progression confirmed by principal investigator and reported to the Sponsor).

2X. Subjects must have ECOG performance status of 0 or 1.

3X. Subjects must have a mandatory biopsy at the time of disease progression according to RECIST 1.1 prior to crossing over. If not clinically feasible, discussion with Sponsor is required.

4X. The first dose of atezolizumab in the crossover arm should be within 42 days of last dose but no less than 21 days from the last dose prior to crossing over.

5X. The following laboratory results obtained within 28 days prior to first administration of study drug after crossing over:

- ANC >1.5 × 10^9/L (without growth factor support 1 week before first administration of study drug after crossing over)
- Platelets >100 × 10^9/L
- Hemoglobin >9 g/dL
  - Transfusion is acceptable to meet the hemoglobin and platelet criteria if stable for 1 week prior to administration of study drug
- AST, ALT, and alkaline phosphatase:
  - ≤2.5 × ULN, if no liver metastases
  - ≤5 × ULN with documented liver metastases
  - ≤5 × ULN alkaline phosphatase (not AST or ALT) with documented bone metastases
- Total bilirubin ≤2.0 x ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≤2.0 x ULN)

6X. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies.

Before crossing over, a woman must be either:

c. Not of childbearing potential defined as:

- postmenopausal

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- permanently sterile

  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

d. Of childbearing potential and

- practicing 2 methods of reliable birth control simultaneously: 1 highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and 1 additional effective method.

  Examples of highly effective contraceptives include:
  - user-independent methods:

    implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (s*exual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence*

needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)

- user-dependent methods:

combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.

Examples of additional effective contraceptive methods include:

- male latex or synthetic condom, diaphragm, or cervical cap

- agrees to remain on the 2 contraception methods (1 highly effective and 1 additional reliable method) throughout the study and for at least 3 months after last dose of daratumumab or 5 months after the last dose of atezolizumab. In addition, during the study and for 3 months after receiving the last dose of daratumumab or 5 months after the last dose of atezolizumab, a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.

Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active) a woman must begin a highly effective method of contraception and 1 additional reliable method, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

7X. During the study and for a minimum of approximately 3 months after the last dose of daratumumab or 5 months after the last dose of atezolizumab, in addition to the highly effective method of contraception, a man

- who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository)
- who is sexually active with a woman who is pregnant must use a condom
- must agree not to donate sperm.

8X. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.3.2. Exclusion Criteria for Crossover

Subjects who meet any of the following criteria prior to crossing over to Arm B will be excluded from participating in the study:

1X. Received any subsequent anti-cancer therapies from the time between the last dose of atezolizumab prior to the first administration of study drug after crossing over

2X. Whole brain radiation within 28 days or other radiotherapy within 14 days prior to first administration of study drug after crossing over.

3X. Has any of the following conditions:

- Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI).
- Leptomeningeal disease or spinal cord compression not definitively treated with surgery or radiation, or requiring corticosteroid treatment at first administration of study drug after crossing over.
- Uncontrolled tumor-related pain

Prior to crossing over, symptomatic lesions amenable to palliative radiotherapy (eg, bone metastases or metastases causing nerve impingement) should be treated, and treatment must be completed at least 14 days prior to the first administration of crossover study drug. Imaging assessments obtained after completion of radiotherapy will be used to determine crossover eligibility and must show evidence of measureable disease according to RECIST 1.1.

4X. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently); indwelling catheters are allowed.

5X. Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal.

6X. Severe infections (including active tuberculosis) within 1 week prior to first administration of study drug after crossing over, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia

7X. Clinically significant cardiac disease, including:

- Unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV)
- Uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities.
- QTc >470 msec.

8X. Women who are pregnant, lactating, or intending to become pregnant during the study or within at least 3 months after last dose of daratumumab or 5 months after the last dose of atezolizumab; men who intend to father a child during the study or within at least 3 months after the last dose of daratumumab or 5 months after the last dose of atezolizumab.

9X. Any other concurrent medical or psychiatric condition, diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the subject at high risk from treatment complications.

4.4. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 8 Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow the contraceptive requirements as noted in the inclusion criteria.

3. Express understanding of the requirement for on-treatment biopsies during the study (ie, Cycle 3, after progression, crossover)

5. TREATMENT ALLOCATION AND BLINDING

Procedures for Randomization and Stratification

Following the safety run-in, central randomization will be implemented in this study. Subjects were stratified by PD-L1 status (TC0 and IC0 vs other), histology (squamous vs. non-squamous), and number of prior therapies received (1 vs. >1) and assigned randomly 1:1 using permuted blocks to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the Sponsor. Pursuant to DMC recommendations after the first interim analysis of study data, enrollment was closed to subjects with PD-L1 score of TC0 (Section 4) as of 16 Jan 2018. Therefore, subjects will be stratified by histology (squamous vs. non-squamous), and number of prior therapies received (1 vs. >1).

The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant subject details to uniquely identify the subject.

As of 25 May 2018, this study was closed to further enrollment.

6. DOSAGE AND ADMINISTRATION

Daratumumab will no longer be administered.

6.1. Daratumumab

Daratumumab will be administered to subjects as described in the Time and Events Schedule (Table 1). Daratumumab should always be administered prior to atezolizumab (Safety Run-in and Arm B). Subjects will continue to receive daratumumab until disease progression, unacceptable toxicity, or other reasons as listed in Section 10.2.

6.1.1. Daratumumab IV Preparation

Infusion solution will be prepared as a 1,000-mL (first dose) or 500-mL (second and subsequent doses) dilution of daratumumab in sterile, pyrogen-free 0.9% NaCl. Preparation of infusion bags should be done on the day of the planned infusion. Daratumumab must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump. The study drug must be filtered by using an inline filter (0.2 µM) during the infusion. Manuals with detailed descriptions for preparation and administration of daratumumab will be supplied to each pharmacy and site.

6.1.2. Daratumumab Treatment Schedule and Administration

Daratumumab will be administered on Days 1, 8, and 15, for the first 3 cycles, then on Day 1 of each 21-day cycle thereafter until one or more treatment discontinuation criteria are met (eg, disease progression or unacceptable toxicity).

Daratumumab will be administered IV at 16 mg/kg. Each subject's dose will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. The dose of daratumumab will remain constant throughout the study, unless the subject's weight changes more than 10% from Cycle 1 Day 1. All infusions will be planned as outpatient visits. Subjects will receive preinfusion medications and postinfusion medications as outlined in Section 6.1.3.

The dilution volumes, initial infusion rates, and increment of infusion rates for the first, second, and subsequent doses in the absence of an infusion-related reaction >Grade 1 are provided in Table 7. The first infusion, with a volume of 1,000 mL, takes approximately 8 hours; the second and subsequent infusions, with volumes of 500 mL, take approximately 4 hours. The maximum infusion rate for all infusions is 200 mL/hour. The Sponsor may modify the infusion rates or the preinfusion medications prospectively based upon the information collected to date from this and other studies.

Table 7: Daratumumab Infusion Rates

	Dilution Volume	Initial Infusion Rate (first hour)	Incremental Increases in Infusion Rate[a]	Maximum Infusion Rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200. mL/hour

a. Consider titration of the infusion rate only in the absence of infusion reactions.
b. Dilution volume of 500 mL should be used only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL.
c. Use a modified initial rate for subsequent infusions (ie, third infusion onwards) only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hr in the first two infusions. Otherwise, continue to use instructions for the second infusion.

As noted in Table 1 (Time and Events Schedule), vital signs for subjects in the Safety Run-in and Arm B cohorts should be monitored frequently on Cycle 1 Day 1 before, during, and after the first infusion of daratumumab. For all subsequent infusions, vital signs should be measured before the start of infusion and at the end of the infusion. If the subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event.

6.1.3. Guidelines for Prevention of Daratumumab Infusion Reactions

6.1.3.1. Predose Medications

Predose medications for subjects receiving daratumumab will be administered on dosing days (see the Time and Events Schedule Table 1). Subjects will receive the medications approximately 1 hour prior to daratumumab administration; premedication up to 3 hours before the dose of daratumumab is permitted.

If necessary, all oral (PO) preinfusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken within 3 hours before the infusion.

In addition to the medications specified below, a leukotriene inhibitor (optional; montelukast 10 mg PO or equivalent) can be administered up to 24 hours before infusion as per investigator discretion. Substitutions for methylprednisolone are allowed, please refer to Attachment 2.

Predose Medications

- Paracetamol (acetaminophen) 650-1000 mg IV or orally (PO).
- An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent). Avoid the use of IV promethazine (see Attachment 1 for a list of antihistamines that may be used).
- Methylprednisolone 100 mg IV or PO or equivalent. Following the second infusion of daratumumab, the dose of corticosteroid may be reduced (IV methylprednisolone 60 mg or equivalent) (Table 8).

Table 8: Pre- and Postinfusion Methylprednisolone Doses (or equivalent) for Dara-IV

Cycle/Day	Methylprednisolone	
	Predose	Postdose 1st and 2nd day following Dara-IV infusion day
C1D1	100 mg	20 mg
C1D8	100 mg	20 mg
C1D15 +	60 mg	20 mg

6.1.3.2. Postadministration Medications

Postadministration medication should be given to reduce the risk of delayed infusion reactions in all subjects. For subjects with a history of COPD, consider administering medications such as short- and long-acting bronchodilators and inhaled corticosteroids. Following the first 4 infusions, if the subject experiences no major infusion reactions, these additional inhaled medications may be discontinued. Refer to Section 6.3 for additional details on the management of infusion reactions.

Postinfusion Medications

- Oral corticosteroid (20 mg methylprednisolone or equivalent) on the first and second day following the day of all infusions (Table 8).

6.1.4. Dose Delay and Modification

Dose modification of daratumumab is not permitted. Dose delay is the primary method for managing daratumumab-related toxicities.

6.1.5. Toxicity Management

Cycle Delays

On the first day of each new treatment cycle and before each daratumumab dose, the subject will be evaluated by the treating physician for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to NCI-CTCAE, Version 4.03. Dose delays will be made based on the toxicity experienced during the previous infusion or newly encountered on Day 1 of a new cycle.

The study treatment must be held if any of the following criteria below are met, to allow for recovery from toxicity, regardless of relationship to daratumumab.

The criteria for a dose delay are:

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia
- Grade 3 or higher thrombocytopenia with bleeding
- Febrile neutropenia
- Neutropenia with infection, of any grade
- For all other adverse events, daratumumab should be withheld for Grade 3 or higher toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 1 or baseline, with the exception of Grade 2 laryngeal edema, Grade 2 bronchospasm or febrile neutropenia, which must be fully recovered. If daratumumab administration does not commence within the prespecified window (Table 9) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up. A delay in daratumumab dosing will result in a subsequent delay in atezolizumab dosing.

Table 9: Daratumumab-related Toxicity Management

Cycles	Frequency	Dose Held	Dosing Re-start
Cycle 1, 2, 3	Weekly (q1wk)	>3 days	Next planned weekly dosing date

Cycle 4 and beyond	Every 3 weeks (q3wks)	>7 days	Next planned every 3-week dosing date

If 2 consecutive planned doses of daratumumab are missed due to any adverse event, then consultation with the Sponsor is required before dosing may be continued.

For subjects whose dose is held for more than 28 days for any drug related adverse event or who miss ≥3 consecutive planned doses of daratumumab due to any adverse event, then the treatment should be permanently discontinued.

If a dose is delayed beyond 5 days in Cycles 2 to 20, then the dates of all subsequent doses must be adjusted accordingly. If a dose delay occurs, then pharmacokinetic and biomarker assessments should be performed on the actual daratumumab administration day, not on the originally scheduled administration day.

Herpes Zoster Virus Reactivation

In monotherapy studies, herpes zoster was reported in 3% of patients. Accordingly, prophylaxis for herpes zoster virus reactivation is recommended (Section 8.1).

6.2. Atezolizumab

Beginning with the implementation of Amendment 7, subjects who are deriving clinical benefit from atezolizumab monotherapy, but do not have access to commercial atezolizumab, may continue treatment under the supervision of the treating investigator in accordance with local regulatory approvals and standard of care guidelines.[50,51] Prior to the administration of atezolizumab, investigators will be required to submit documentation of subject response and clinical status to the Sponsor, either electronically or via facsimile.

For subjects in Arm A, atezolizumab will be administered at 1,200 mg IV on Day 1 of every 21-day cycle. For subjects in the Safety Run-in and Arm B, atezolizumab will be administered on Day 2 of Cycle 1 and on Day 1 of every 21-day cycle thereafter. Atezolizumab should always be administered after daratumumab. A delay in daratumumab dosing will result in a subsequent delay in atezolizumab dosing. All study subjects should continue to be treated until one or more treatment discontinuation criteria are met (Section 10.2).

Refer to the SIPPM for detailed instructions on drug preparation, storage, and administration. Dose modifications to atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided below.

Subjects may temporarily suspend study treatment for up to 105 days beyond the last dose if they experience an adverse event that requires a dose to be withheld. If atezolizumab is withheld because of adverse events for >105 days, then the subject will be discontinued from atezolizumab treatment and will be followed for safety and efficacy as specified in Section 9.1.5.

If, in the judgment of the investigator, the subject is likely to derive clinical benefit from atezolizumab after a hold of >105 consecutive days that is not adverse event-related, study drug may be restarted with the approval of the Sponsor.

If a subject must be tapered off steroids used to treat adverse events, atezolizumab may be withheld for additional time beyond 105 days from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤10 mg/day. The acceptable length of interruption will depend on agreement between the investigator and the Sponsor.

Dose interruptions for reason(s) other than adverse events, such as surgical procedures, may be allowed with Sponsor approval. The acceptable length of interruption will depend on agreement between the investigator and the Sponsor.

If atezolizumab administration does not commence within the prespecified dosing window, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

6.2.1. Management of Atezolizumab-Specific Adverse Events

Beginning with the implementation of Amendment 7, toxicities associated or possibly associated with atezolizumab treatment, including non-immune mediated adverse events, should be managed according to local regulatory approvals and standard of care guidelines.[50,51] Additional tests, such as autoimmune serology or biopsies, should be used to determine a possible immunogenic etiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect and, in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit-risk balance a given subject may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in subjects with life-threatening, immune-mediated adverse events. Specific guidelines for immune-mediated events are provided in Attachment 7.

For all other non-immune mediated adverse events, including infections, atezolizumab should be withheld for Grade 3 or higher toxicity with the following exceptions:

- Grade 3 nausea that responds to antiemetic treatment within 7 days
- Grade 3 vomiting that responds to antiemetic treatment within 7 days
- Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
- Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of atezolizumab
- Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of atezolizumab

Administration of atezolizumab may be restarted upon recovery from toxicity to Grade 1 or baseline.

6.2.1.1. Pulmonary Events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Subjects will be assessed for pulmonary signs and symptoms throughout the study and will also have CT scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated, as follows, for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. For specific management guidelines, please see Attachment 7.

6.2.1.2. Hepatic Events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible subjects must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment.

While in this study, subjects who present with right upper-quadrant abdominal pain or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

If LFTs increase, concurrent medications, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

For specific management guidelines, please see Attachment 7.

6.2.1.3. Gastrointestinal Events

Immune-mediated colitis has been associated with the administration of atezolizumab.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. If the event is of significant duration or magnitude or is associated with signs of systemic inflammation or acute phase reactants (eg, increased C-reactive protein [CRP], platelet count, or bandemia), the following are recommended:

- Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with 3 to 5 specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates for confirmation of the diagnosis of colitis.

For specific management guidelines, please see Attachment 7.

6.2.1.4. Endocrine Events

Thyroid disorders, type 1 diabetes mellitus, adrenal insufficiency, and pituitary disorders have been associated with the administration of atezolizumab.

Subjects with unexplained symptoms such as fatigue, myalgias, impotence, constipation, or mental status changes, should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. An endocrinologist should be consulted if an endocrinopathy is suspected. Thyroid stimulating hormne (TSH), triiodthyronine 3 (T3), and free thyroxine (T4) levels should be obtained to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (eg, TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels and ACTH stimulation test) and MRI of the brain (with detailed pituitary sections) may help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

For specific management guidelines, please see Attachment 7.

6.2.1.5. Ocular Events

An ophthalmologist should evaluate visual complaints (eg, uveitis, retinal events).

For specific management guidelines, please see Attachment 7.

6.2.1.6. Immune-Related Myocarditis

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any subject presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, eg, in a subject who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of pre-existing cardiac conditions, or progression of malignancy.

All subjects with possible myocarditis should be evaluated urgently by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated. Subjects with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Attachment 7.

6.2.1.7. Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests.

For specific management guidelines, please see Attachment 7.

6.2.1.8. Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent or severe rash or pruritus. A biopsy should be considered unless contraindicated.

For specific management guidelines, please see Attachment 7.

6.2.1.9. Neurologic Disorders

Myasthenia gravis, Guillain-Barré syndrome, and meningoencephalitis have been observed with single agent atezolizumab. Subjects may present with signs and symptoms of sensory or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternate etiologies.

For specific management guidelines, please see Attachment 7.

6.2.1.10. Immune-Related Meningoencephalitis

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any subject presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process. All subjects being considered for meningoencephalitis should be evaluated urgently with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted. For specific management guidelines, please see Attachment 7.

6.2.1.11. Immune-related Nephritis

Immune-related nephritis is an identified risk associated with the administration of atezolizumab. Immune-related nephritis is a relatively rare complication of checkpoint inhibitor therapy with the most common reported underlying pathology being acute tubulo-interstitial nephritis (ATIN). The most common presentation is asymptomatic increase in creatinine levels. In the absence of alternative etiologies (eg, prerenal and postrenal causes, and concomitant medications), immune-related nephritis is defined as renal dysfunction requiring steroids treatment and/or confirmed by biopsy. For specific management guidelines, please see Attachment 7.

6.2.1.12. Systemic Immune Activation

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for subjects who, in the absence of an alternate etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- Complete blood count (CBC) with peripheral smear
- Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, total bilirubin
- Lactate dehydrogenase (LDH)
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)
- Serum sample for cytokine analysis

If systemic immune activation is still suspected after the initial evaluation, atezolizumab should be withheld with the provision of appropriate supportive medical care, including corticosteroid therapy. The Sponsor should be contacted for additional recommendations.

For specific management guidelines, please see Attachment 7.

6.3. Management of Infusion-related Reactions

6.3.1. Infusion-related Reactions

Subjects should be observed carefully during infusions. Trained study staff at the clinic should be prepared to intervene in case of an IRR, and resources necessary for resuscitation must be available. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

For infusion reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of infusion reactions may require reduction in the rate of infusion, or discontinuation of daratumumab (see Table 10).

Table 10: Management Guidelines for Daratumumab Infusion-related Reactions

Severity	Management
Grade 1-2 (mild to moderate)	Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience any further reaction symptoms, then infusion rate escalation may resume at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hr (see Table 7).
Grade 3 (severe)	Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience additional symptoms, then resume infusion rate escalation at increments and intervals as outlined in Table 7. Repeat the procedure above in the event of recurrence of Grade 3

	symptoms. Permanently discontinue daratumumab if the subject experiences a ≥Grade 3 infusion-related symptom at the subsequent infusion.
Grade 4 (life threatening)	Permanently discontinue daratumumab treatment.

IRR = infusion-related reaction; IV = intravenous.

6.3.2. Atezolizumab

No premedication is indicated for the administration of atezolizumab in Cycle 1. Subjects who experience an IRR with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (eg, acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab associated IRRs, due to its potential for causing agranulocytosis. Table 11 provides management guidelines for atezolizumab IRRs in Cycle 1. For subsequent cycles, infusion-related reactions should be managed according to institutional guidelines.

Table 11: Management Guidelines for Atezolizumab Infusion-related Reactions

Severity	Management
Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If tolerated, the infusion rate may then be increased to the original rate.
Grade 2	• Interrupt atezolizumab infusion. • Administer aggressive symptomatic treatment (eg, oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Restart only after the symptoms have adequately resolved to baseline grade. • The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the IRR. • At next cycle, administer oral premedication with antihistamine and anti-pyretic and monitor closely for IRR.
Grades 3–4	• Stop infusion. • Proper medical management which may include oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen • Discontinue atezolizumab.[a] • Contact the Sponsor if atezolizumab is discontinued.

IRR = infusion-related reaction; IV = intravenous.

a. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Study Responsible Physician.

7. TREATMENT COMPLIANCE

Study drugs (daratumumab and atezolizumab) will be administered by qualified site staff, and the details of each administration will be recorded in the case report form (CRF). Additional details are provided in the SIPPM.

Beginning with the implementation of Amendment 7, subjects who are deriving clinical benefit from atezolizumab monotherapy, but do not have access to commercial atezolizumab, may continue treatment under the supervision of treating investigators in accordance with local regulatory approvals and standard of care guidelines.[50,51] Study drug accountability must continue to be monitored and documented by the study site.

8. PRESTUDY AND CONCOMITANT THERAPY

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.2. The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

All prior treatments for malignancies, including those since diagnosis, must be recorded at Screening.

Routine systemic use of the following concomitant medications will be collected in the CRF and recorded in the source documents beginning with signing of the ICF to PD or until the start of subsequent anticancer treatment, if earlier: growth factors, transfusions, anti-infectives (antibacterials, antivirals, and antimycotics), corticosteroids, anti-arrhythmics and other cardiac supportive therapy, anti-epileptics, centrally acting psychiatric medication, anti-histamines and other medications targeting postinfusion systemic reactions, bisphosphonates, and any anticancer therapy (including radiation).

The use of concomitant medications used to treat adverse events or infusion-related reactions will be collected in the CRF and recorded in the source documents beginning with the signing of the ICF until PD.

Prestudy therapies administered up to 30 days before first dose of study drug must be recorded at Screening. Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study drug until the end of treatment assessment. Concomitant therapies should also be recorded beyond 30 days after the last dose of study drug only in conjunction with serious adverse events that meet the criteria outlined in Section 12.3.2, Serious Adverse Events.

8.1. Permitted Therapies

Subjects are to receive full supportive care during the study. The following medications and supportive therapies are examples of support therapies that may be used during the study:

- Antivirals (antiviral prophylaxis should be considered for the prevention of herpes zoster virus reactivation)
- Granulocyte colony stimulating factors and transfusion of platelets
- Oral contraceptives
- Hormone-replacement therapy
- Palliative radiotherapy (eg, treatment of known bony metastases) provided it does not interfere with the assessment of tumor target lesions (eg, the lesion being irradiated is not the only site of disease, as that would render the subject not evaluable for response by tumor assessments according to RECIST 1.1). It is not a requirement to withhold atezolizumab during palliative radiotherapy; discuss with the Sponsor
- Mineralocorticoids (eg, fludrocortisone)
- Corticosteroids are allowed for the treatment of immune-related adverse events, infusion-related reactions, and as pre-infusion or pre-injection medication for daratumumab. Acute use of systemic corticosteroids >10 mg/day prednisone equivalent, or acute use of higher equivalent doses may be allowed with Sponsor approval.

Other symptoms may be managed according to institutional guidelines provided prohibited therapies are not administered (see Section 8.2).

Premedication with antihistamines may be administered for any atezolizumab infusions after Cycle 1.

In general, investigators should manage subject care with supportive therapies as clinically indicated per local standards. Subjects who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, or famotidine or another H2 receptor antagonist per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (eg, supplemental oxygen and β_2-adrenergic agonists).

8.2. Prohibited Therapies

Use of the treatments listed below is prohibited during the study:

- Other agents that target CD38, PD-1 or its ligand, PD-L1.
- Any concomitant therapy intended for the treatment of cancer, including NSCLC, whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the anti-cancer agent (see Section 4.2), and during study treatment until disease progression is documented and subject has discontinued study treatment. This includes but is not limited to chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (unless otherwise noted).
- Denosumab; subjects who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while in the study.
- Dipyrone (metamizole)
- Any live, attenuated vaccine (eg, FluMist®) within 4 weeks prior to administration of study drug or during treatment or within 5 months following the last atezolizumab dose.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule (Table 1) summarize the frequency and timing of assessments applicable to this study.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

As of Amendment 6, subject screening and enrollment has been terminated, combination treatment will be discontinued, and subjects will be given the option to receive atezolizumab monotherapy, following the treatment procedures for Arm A (Section 6.2). Limited data collection will subsequently be performed, see Section 9.2.

9.1.2. Optional Prescreening Phase

The optional Prescreening Phase, which will include a separate informed consent, will allow for the collection of archival formalin-fixed paraffin-embedded (FFPE) tumor tissue to be submitted for PD-L1 determination using the SP142 assay, before the formal screening process for the full study. Given the inter-assay differences in PD-L1 determination, these results can help determine the likelihood of eligibility for study participation, prior to signing of informed consent for study participation (Hirsch 2016)[21]. Unless the archival tumor sample used in the Prescreening Phase was obtained after completion of the most recent line of therapy with no intervening therapies and is less than 1 year old, the subject will be required to have a fresh biopsy performed during the Screening Phase (Section 9.6.1 Tumor Tissue Samples), which will be used to formally determine study eligibility based on tumor cell PD-L1 status. Archival PD-L1 staining may not correlate with PD-L1 staining using a fresh tumor specimen.

9.1.3. Screening Phase

The Screening Phase begins with the signing of the ICF, which must be obtained before any study-specific procedures are performed (except for tumor imaging assessments that were performed as part of the subject's routine standard of care). The screening for PD-L1 status may occur within 56 days prior to first administration of study drug. Tumor samples must meet the same requirements as outlined in Section 9.6.1. All other screening procedures must be performed only after PD-L1 results are available, and within 28 days before the first administration of study drug. For subjects who do not meet Inclusion Criterion 5, no further Screening procedures should be performed. The Screening Phase may be extended by a maximum of 14 days in situations in which screening procedures require repetition or PD-L1 results are not available, after consultation with the Sponsor. However, screening procedures, including standard of care tumor imaging assessments, must be performed within 28 days of first administration of study drug. During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Events Schedule (Table 1). Subjects were initially stratified based on PD-L1 status (IC0 and TC0 vs. others), based on central laboratory assessment (using the Ventana Medical Systems, Inc. PD-L1 [SP142] assay), and histology (squamous vs. non-squamous), as well as number of previous lines of therapy (1 or >1), see Section 5 for the current stratification procedures. Screening procedures will be performed within 28 days before enrollment. Subjects may be retested for laboratory values that do not meet eligibility criteria within the 28-day Screening Phase.

If a subject does not meet all inclusion and exclusion criteria (is a screen failure) but at some point in the future is expected to meet the subject eligibility criteria, the subject may be rescreened on 1 occasion. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new Screening Phase.

9.1.4. Open-Label Treatment Phase

Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedule (Table 1). Subjects in the randomized phase should start study treatment within 72 hours after randomization. A window of ±1 day for Cycles 1 to 3 for subjects receiving daratumumab and ±3 days for all other drug administration visits is allowed for drug

administration visits to the clinic. Clinical evaluations and laboratory studies may be repeated more frequently than outlined in the Time and Events Schedule, if clinically indicated. If treatment is discontinued, the subject will complete the End-of-Treatment assessment, and enter the Follow-up Phase.

End of Treatment

Unless a subject withdraws consent for study participation or is lost to follow up, an End-of-Treatment Visit is to occur at 30 days after the last dose of study treatment. A delay of this visit to up to 7 days is permitted. Every effort should be made to conduct the End-of-Treatment Visit before the subject starts subsequent treatment. If a subject is unable to return to the site for the End-of-Treatment Visit, then the subject should be contacted to collect information on Grade 2 or higher adverse events and concomitant medications used to treat Grade 2 or higher adverse events, any immune-related AE, or any infusion-related reactions until disease progression. Additional information on reporting of AEs is presented in Section 12.

9.1.5. Follow-Up Phase

The posttreatment Follow-up Phase will begin once the subject completes the End-of-Treatment evaluation. Reasons for discontinuation of study treatment are listed in Section 10.2. Subjects who discontinue treatment before disease progression must continue to have disease evaluations as described in Table 1 and Section 9.4 (every 6 weeks [±1 week] for the first 12 months of after the start of treatment and every 9 weeks [±1 week] thereafter regardless of treatment delays). After disease progression is confirmed, follow-up for survival status and subsequent anti-cancer therapy will be obtained at least every 12 weeks after the last dose of study drug, until the subject has died, is lost to follow-up, or has withdrawn consent. If the information on survival status is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented on the CRF.

The end of the study is anticipated to be 24 months after the last subject has been enrolled (last patient 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.

Investigators may recontact the subject to obtain long-term follow-up information regarding the subject's safety or survival status as noted in the informed consent form (refer to Section 16.2.3, Informed Consent).

Subjects will be instructed that study drug will not be made available to them after they have completed/discontinued study drug and that they should return to their primary physician to determine standard of care.

Beginning with the implementation of Amendment 7, data from safety evaluations performed according to local regulatory approvals and standard of care guidelines[50,51] will no longer be collected with the exception of serious adverse events that are to be reported and entered in the Sponsor safety repository.

9.2. Procedures for Subjects Continuing on Study with Atezolizumab Monotherapy (per Amendment 6)

Subjects who had received combination therapy will have the opportunity to receive atezolizumab monotherapy, per the schedule in Table 1 and Section 6.2, and will complete adverse event follow up as defined in Section 12.4.

Subjects remaining in the study on atezolizumab monotherapy will no longer require pharmacokinetic, immunogenicity, or biomarker assessments. Therefore, only the Table 1 assessments will be performed for these subjects (assessments in Table 2 through Table 7 included in previous versions of this protocol will no longer be followed and were removed). Treatment-related information, such as exposure data, adverse events, and disease assessments, will continue to be collected and treatment with atezolizumab will continue until the criteria in Section 10.2 is met. As no new subjects will be initiating therapy, treatment beyond initial radiographic progression will no longer be allowed without prior consultation with the Sponsor's Study Responsible Physician.

Safety Assessments

Safety reporting for those continuing on atezolizumab monotherapy is described in Section 12.4. Laboratory and other safety assessments will continue as in Table 1 and in Section 9.7.

Disease Evaluations

Disease evaluations, including assessment of response, will be conducted by the site, as described in Table 1 and Section 9.4.

9.3. Guidance for Subjects Continuing on Study with Atezolizumab Monotherapy (per Amendment 7)

The third planned DMC review (23 May 2018) determined that the addition of daratumumab to atezolizumab did not result in additional clinical benefit. As a result, further treatment with daratumumab was discontinued (with implementation of Amendment 6) and data collection will cease after locking of the clinical database (with implementation of Amendment 7). For those subjects who are deriving clinical benefit from atezolizumab monotherapy, but do not have access to commercial atezolizumab, treatment may continue under the supervision of treating investigators in accordance with local regulatory approvals and standard of care guidelines.[50,51] Prior to the administration of atezolizumab, investigators will be required to submit documentation of subject response and clinical status to the Sponsor, either electronically or via facsimile.

Data from these safety and efficacy evaluations will no longer be collected with the exception of serious adverse events that are to be reported and entered in the Sponsor safety repository. Study drug accountability must continue to be monitored and documented by the study site.

9.4. Efficacy Evaluations

Beginning with the implementation of Amendment 7, efficacy evaluations will be performed by the investigator according to local regulatory approvals and standard of care guidelines.[50,51] These data will no longer be collected by the Sponsor.

Efficacy evaluations will be performed at shown in the Time and Events Schedule (Table 1), per RECIST 1.1 (Attachment 5) and irRECIST (Attachment 6). Results will be evaluated by the investigator and recorded in the CRF. Subjects will undergo tumor assessments until radiographic disease progression, or withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. For subjects who discontinue treatment for reasons other than progression (eg, adverse event), disease assessments may be discontinued. Subjects who have documented disease progression should discontinue study therapy.

9.4.1. Disease Assessments

Screening Tumor Assessments

Screening tumor assessments will include CT scans (with IV contrast unless contraindicated) or MRIs of the chest, abdomen, head, and pelvis. For subjects with known bone lesions, CT, or MRI scan of the affected area of bone will be required at Screening. Additionally, CT scans of the neck should also be performed at Screening if clinically indicated. Subjects who are intolerant to IV contrast agents or in whom IV contrast is contraindicated may have CT scans performed with oral contrast; the reason for not using IV contrast must be noted in the source documents. At the investigator's discretion, other methods of assessment of measurable disease (eg, physical examination) as per RECIST 1.1 may be used.

Magnetic resonance imaging may be used to evaluate sites of disease that cannot be adequately imaged using CT or if IV and oral contrast for CT scan are contraindicated. In any case where an MRI is performed, it must be the imaging technique used to assess disease at Screening and at all subsequent response evaluations.

Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. All known sites of active disease must be documented at Screening.

Subsequent Tumor Assessments

At each subsequent tumor evaluation, chest and abdomen CT scans or MRIs, in addition to any other known sites of active disease, will be performed. The same radiographic procedure used to assess disease sites at Screening should be used throughout the study (eg, the same contrast protocol for CT scans). Response will be assessed by the investigator using RECIST 1.1; irRECIST will also be used for exploratory purposes.

Deterioration of health status requiring discontinuation of study treatment without objective evidence of progressive disease should be reported as "clinical disease progression". Every effort should be made to document objective progression via radiographic confirmation.

Subjects in Arm A who crossed over to Arm B after confirmed disease progression should be carefully evaluated to determine whether they will benefit from treatment with atezolizumab monotherapy.

9.4.2. Treatment After Initial Disease Progression

Anti-tumor response patterns seen with immunotherapeutic agents may extend beyond the typical time course of responses seen with cytotoxic agents. Therefore, the investigator may decide to continue a treatment with study drug beyond tumor progression determined on the basis of the RECIST 1.1 criteria. Any treatment beyond disease progression requires prior discussion with and approval by the Sponsor's Study Responsible Physician.

Once the specific criteria of RECIST 1.1 defined disease progression are met, a repeat efficacy evaluation should be performed at the next per protocol scheduled assessment timepoint or earlier, if clinically necessary, but no sooner than 4 weeks from the previous assessment, in order to confirm disease progression. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy but develop subsequent disease response. Subjects should continue study treatment at the discretion of the treating physician while waiting for confirmation of disease progression if they are clinically stable as defined by the following criteria:

- Absence of clinical signs and symptoms indicating disease progression
- Clinical disease progression not requiring immediate therapeutic intervention
- No decline in ECOG performance status
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

Subjects that are deemed clinically unstable are not required to have imaging assessments and can be taken off study treatment.

Table 12 provides guidelines to continue or discontinue study drug based on the initial and subsequent assessments of the tumor and the clinical status.

Table 12: Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable	Clinically Unstable
	Additional Imaging and Treatment	**Additional Imaging and Treatment**
1st radiologic evidence of PD by RECIST 1.1	Any treatment beyond first disease progression requires prior discussion with and approval by the Sponsor's Study Responsible Physician. If continued treatment is approved by Sponsor's Study Responsible Physician, imaging should be repeated ≥4 weeks later (or the next protocol specified timepoint) to confirm PD.	Repeat imaging at ≥4 weeks to confirm PD per investigator's discretion only and subject should discontinue study treatment
Repeat tumor imaging confirms PD by RECIST 1.1	No additional imaging required if the subject discontinues study treatment. Regularly scheduled imaging should be performed if the subject continues on study treatment (exception to continue study treatment is possible upon consultation with Sponsor).	No additional imaging required and subject should discontinue study treatment
Repeat tumor imaging does not show PD by RECIST 1.1	Regularly scheduled imaging should be performed while the subject continues on study treatment.	Continue regularly scheduled imaging assessments, per investigator's discretion. Subject may restart study treatment if condition has improved or clinically stable per investigator's discretion, upon consultation with Sponsor.

9.5. Pharmacokinetics and Immunogenicity

Pharmacokinetics/immunogenicity samples will no longer be collected in this study, therefore this section is no longer applicable.

Serum samples from venous blood collections will be used to evaluate the pharmacokinetics and immunogenicity (generation of anti-drug antibodies) of atezolizumab and daratumumab. Serum collected for pharmacokinetic and immunogenicity analyses may additionally be used to evaluate safety and efficacy questions, drug characteristics, or certain biomarkers for future research. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

9.5.1. Evaluations

Samples will be collected for measurement of serum concentrations of atezolizumab and daratumumab and the assessment of anti-atezolizumab and anti-daratumumab antibodies (immunogenicity). Serum samples should be collected at the final visit from subjects who are discontinued from treatment or withdrawn from the study. Subjects who discontinue treatment will also be asked to return for immunogenicity evaluation during the Follow-up Phase. These samples will be tested by the Sponsor or Sponsor's designee.

The exact dates and times of blood sampling must be recorded. Refer to the Laboratory Manual for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the Laboratory Manual. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

9.5.2. Analytical Procedures

Serum samples will be analyzed to determine concentrations of daratumumab, concentrations of atezolizumab, or the generation of antibodies to daratumumab and atezolizumab using validated immunoassay methods.

All samples collected for detection of anti-atezolizumab and daratumumab antibodies will also be evaluated for serum concentration to enable interpretation of the antibody data. For the atezolizumab and daratumumab immunogenicity assessments, serum samples will be screened for antibodies binding to atezolizumab or daratumumab and serum titer will also be determined from confirmed positive samples. Other immunogenicity analyses (eg, assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated. Neutralizing antibody assessments may also be performed to further characterize immune responses that are generated.

9.5.3. Pharmacokinetic Parameters

The PK parameters are defined as:

C_{max} = Maximum observed concentration

C_{min} = Minimum observed concentration

For both atezolizumab and daratumumab, the PK evaluations include C_{min} and C_{max}. If sufficient data are available, other PK parameters may be calculated. The C_{min} and C_{max} will be summarized by descriptive statistical method for Arm A and Arm B. If there are sufficient data, then a population PK analysis of serum concentration-time data of daratumumab and atezolizumab may be performed and may include data from other clinical studies. If performed, details will be provided in a population-PK analysis plan and the results of the analysis will be presented in a separate report.

9.5.4. Immunogenicity Assessments

When both serum concentration and immunogenicity analyses are specified, they will be performed on aliquots from the same blood draw and no additional sampling is required.

No unscheduled samples need to be collected for IRRs associated with the first administration of daratumumab. Daratumumab serum concentration will also be determined from the daratumumab IRR sample for interpreting immunogenicity data. If the IRR results in treatment discontinuation, then subjects should undergo all scheduled safety and efficacy evaluations. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the Laboratory Manual or equivalent document.

Subjects who discontinue treatment or withdraw from the study before confirmation of PD should have samples collected at the time of early discontinuation. Subjects who discontinue treatment will also be asked to return for immunogenicity evaluation during the Follow-up Phase.

9.6. Biomarker Assessments

Biomarker samples will no longer be collected in this study.

In this study, mandatory archival or fresh tumor specimens from subjects at Screening will be evaluated for expression of PD-L1^{+}, CD38^{+}, [redacted]
Published results suggest that the expression of PD-L1 in tumors correlates with response to anti-PD-L1 therapy (Horn 2015; Spira 2015).[23,45] Evaluation of CD38^{+} expression will be performed to determine if elevated expression of CD38^{+} correlates with responses to daratumumab therapy.

Fresh biopsies at Cycle 3 and at progressive disease are mandatory, if clinically feasible, to evaluate biomarkers related to the clinical benefit of atezolizumab + daratumumab. Additionally, if a biopsy is taken at any other time while a subject is on study, a sample is also requested for biomarker analysis. Evaluation of biopsies by IHC and IF may include PD-L1 and CD38 expression in addition to other markers and cell populations [redacted] to identify changes in inflammatory populations in response to treatment. Collection of a tumor biopsy, at the time of radiographic progression will be evaluated for immune infiltrate, PD-L1, and CD38 expression by IHC and is required in order to distinguish pseudoprogression/tumor-immune infiltration from true progression. Anti-tumor immune responses such as those potentially associated with atezolizumab + daratumumab may result in objective responses that are preceded by initial apparent radiological progression as a result of robust tumor-immune infiltration with a concomitant increase in tumor size in 8 to 10% of patients treated with PD-1 inhibitors (Dronca 2016).[13] DNA or RNA extraction may be performed to enable next-generation sequencing (NGS) to identify biomarkers associated with disease progression or acquired resistance to atezolizumab + daratumumab and to increase understanding of disease pathobiology.

Evaluation of blood biomarkers may provide evidence for biomarkers of biologic activity of atezolizumab + daratumumab in subjects with NSCLC. Flow cytometry will be performed to immunophenotype [redacted] response to treatment. These samples may be used to evaluate specific subsets of immune cells [redacted] by CyTOF. Proteomic analysis may also be used to evaluate potential biomarkers of response and resistance.

9.6.1. Tumor Tissue Samples

As of 25 May 2018, scheduled tumor biopsies are no longer required. However, if a subject has an unscheduled tumor biopsy, tissue samples may be submitted as per protocol.

Archival and freshly collected tumor tissue samples for screening

Tumor tissue should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status). An archival tumor specimen can be submitted if available. Archival tumor biopsies are acceptable at baseline as long as the biopsy was collected after completion of the most recent prior therapy and is less than one year old. If an archival specimen is not available, the subject may still be eligible, with the assumption that the subject is willing to consent to and undergo a pretreatment biopsy or resection of the tumor. For subjects enrolled in the crossover arm, if a biopsy was taken at the time of disease progression while enrolled in Arm A of this protocol, a new biopsy is not required at Cycle 1X Day 1 predose.

For freshly collected biopsy specimens, acceptable samples include:

- Core needle biopsy sample collection for deep tumor tissue: At least 3 cores, embedded into a single paraffin block, should be submitted for evaluation.
- Excisional, incisional, punch, or forceps biopsy sample collection for cutaneous, subcutaneous, or mucosal lesions
- Fine-needle aspiration, brushing, cell pellets (eg, from pleural effusion), and lavage samples are not acceptable.

For archival samples, the remaining tumor tissue block for all subjects enrolled will be returned to the site upon request or 18 months after final closure of the study database, whichever is sooner. Tissue samples from subjects who are deemed ineligible to enroll in the study will be returned promptly after eligibility determination.

Tumor samples at Cycle 3 and at the time of confirmed radiographic progression

Subjects in all treatment arms will undergo a tumor biopsy to obtain a mandatory tumor sample, unless not clinically feasible, at Cycle 3, Cycle 3X, and at the time of radiographic disease progression.

Note: The Cycle 3 biopsy may be collected within 7 days prior to or up to 21 days after the Cycle 3 Day 1 dose but must be done prior to Cycle 4 Day 1. In addition, this biopsy must be performed following the first radiologic tumor assessment.

Acceptable samples include:

- Core needle biopsy sample collection for deep tumor tissue; at least three cores, embedded into a single paraffin block, should be submitted for evaluation.
- Excisional, incisional, punch, or forceps biopsy sample collection for cutaneous, subcutaneous, or mucosal lesions

Tumor tissue resection

The status of immune-related, tumor type–related, and other exploratory biomarkers (including, but not limited to, T-cell markers and non-inherited biomarkers identified through NGS on extracted DNA or RNA) in tumor tissue samples may be evaluated.

9.6.2. Biomarker Assays in Blood Samples

Blood samples will be obtained for biomarker evaluation (including but not limited to biomarkers that are related to NSCLC or tumor immune biology) from all eligible subjects. Samples will be processed to obtain plasma and serum for the determination of changes in blood-based biomarkers. Whole blood samples may be processed to obtain their derivatives (eg, RNA and DNA) and evaluated for immune-related, tumor type–related, and other exploratory biomarkers (eg, alterations in gene expression or clonal T-cell expansion). Also, based on emerging scientific evidence, the Sponsor may request additional blood samples for biomarker evaluation. In this case, such analyses will be limited to research related to the study drug(s) or diseases being investigated.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

Additional Collections

If it is determined at any time before study completion that additional material is needed from a FFPE tumor sample for the successful completion of the protocol-specified analyses, the Sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the Sponsor may request additional material from previously collected tumor samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study drug(s) or diseases being investigated.

9.7. Safety Evaluations

Beginning with the implementation of Amendment 7, safety evaluations will be performed by the investigator according to local regulatory approvals and standard of care guidelines.[50,51] These data will no longer be collected by the Sponsor with the exception of serious adverse events that are to be reported and entered in the Sponsor safety repository.

Safety will be assessed by the incidence and severity of adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, ECOG performance status score, and other evaluations as described in the Time and Events Schedule (Table 1). Toxicities will be graded according to the NCI-CTCAE Version 4.03. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Based on the previous human experience with daratumumab, in vitro studies, and animal toxicological findings, infusion-related reactions/allergic reactions, hemolysis, and thrombocytopenia will be closely monitored. As daratumumab and atezolizumab are both

biologic agents, immunogenicity also will be monitored. Any of the safety monitoring assessments may be performed more frequently, and adverse events should be evaluated by the investigator according to the standard practice, if clinically indicated.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples for clinical laboratory evaluation will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents. The following tests will be performed by the local laboratory, unless otherwise specified:

Hematology	
– Hemoglobin	– White blood cell (WBC) – Absolute neutrophil count (ANC) – Absolute lymphocyte count (ALC) – Platelet count
Coagulation[a]	
– Prothrombin time/International Normalized Ratio	– Activated partial thromboplastin time
Chemistry	
– Sodium – Potassium – Creatinine – Aspartate aminotransferase (AST) – Alanine aminotransferase (ALT)	– Total bilirubin[b] – Alkaline phosphatase – Lactic acid dehydrogenase (LDH) – Calcium[a] – Amylase, lipase
Urinalysis[a]	
Standard Urine Dipstick	
Other Tests	
Thyroid panel[a] – Thyroid stimulating hormone (TSH) – Triiodothyronine (T3; total or free) – Free thyroxine (T4)	Serology (hepatitis B, hepatitis C) and HCV Viral Load: [a] – Hepatitis B: HBsAg, anti-HBc – Hepatitis C: anti-HCV; HCV RNA PCR, if necessary
Pregnancy Test (for women of childbearing potential only) – serum (<5 IU/mL) β-hCG at Screening; serum or urine thereafter as clinically indicated	

a. Not performed for subjects who crossover from Arm A to Arm B, except as clinically indicated.
b. Direct bilirubin if Gilbert disease.

Indirect Antiglobulin Test (IAT) results

This test no longer needs to be performed since daratumumab treatment is discontinued.

Blood Type, Rh, and Indirect Antiglobulin Test (IAT) should be done before the first dose of daratumumab. Subject red blood cell (RBC) phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab infusion.

Daratumumab interferes with the IAT, which is a routine pretransfusion test performed to identify a subject's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015, 2016).[10,9]

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

a. Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units
b. Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies. For additional details, refer to the Daratumumab Investigator's Brochure.

Pulmonary Function Test

Subjects with known or suspected COPD must have a FEV1 test during Screening. Refer to Section 6.2.1.1 of the protocol for details on subjects with higher risk of respiratory complications.

Electrocardiogram:

A 12-lead ECG will be performed at Screening and at End-of-Treatment.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Clinically significant abnormalities will be recorded as adverse events in the appropriate CRF.

Vital Signs

Temperature, pulse/heart rate, blood pressure will be performed as specified in the Time and Events Schedule (Table 1). Clinically significant abnormalities will be recorded as adverse events in the appropriate CRF.

Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Physical Examination and ECOG performance status

A complete physical examination should be performed during the Screening Phase and at crossover eligibility assessment. Thereafter, only a symptom directed physical examination is required. Height will be measured at Screening only; weight will be measured regularly at Screening and preinfusion, as specified in Time and Events schedule. Abnormalities will be recorded in the appropriate section of the CRF. ECOG performance status will be used to evaluate the effect of the disease status on the activities of daily living (Attachment 3). When scheduled, ECOG assessments should be obtained prior to any other study procedures planned for the same day.

9.8. Sample Collection and Handling

Beginning with the implementation of Amendment 7, samples will no longer be collected in this study.

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed study treatment if he or she has completed all planned administrations of the study drug(s) in the assigned treatment arm. A subject will be considered to have completed the study if he or she has finished all protocol-specified procedures before the end of the study, has died before the end of the study, has not been lost to follow up, and has not withdrawn consent for study participation before the end of the study.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if he or she has to discontinue treatment. The End-of-Treatment Visit and Follow-up visit assessments should continue as specified in the Time and Events Schedules.

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject (or the subject's legally acceptable representative) withdraws consent for administration of study treatment
- The subject experiences unacceptable toxicity, including IRRs described in Section 6.3
- The subject missed more than 2 consecutive planned doses due to daratumumab-related AEs
- The subject missed more than 105 consecutive treatment days due to atezolizumab-related AEs
- The subject experiences confirmed disease progression (per RECIST 1.1), see Table 12.
- A subject who experiences a second primary malignancy that cannot be treated by surgery alone must be withdrawn from the study. However, a subject who develops a malignancy that can be cured surgically may continue to receive the assigned study treatment and should continue to be followed for subsequent progression of NSCLC.

The primary reason for discontinuation of study treatment is to be recorded in the CRF.

Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent to study participation
- Pregnancy
- Second primary malignancy (see Discontinuation of Study Treatment for additional details)
- Death
- The study investigator, for any reason, stops the subject's participation in the study
- Sponsor terminated the study

Before a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject discontinues from treatment, end-of-treatment assessments should be obtained.

10.3. Withdrawal From the Use of Research Samples

A subject who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the subject's original informed consent for optional research samples.
- The subject may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the Sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The Sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the Sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The subject may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

11. STATISTICAL METHODS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

11.1. Subject Information

The primary analysis population for the efficacy endpoint will be the intent-to-treat population in the randomized phase of the study. The subjects in the safety run-in cohort will also be included in the efficacy analyses and listed separately. Safety will be evaluated for all subjects who have received at least 1 dose of study drug (atezolizumab or daratumumab). The pharmacokinetic analyses will be performed on the population described in Section 11.4.

11.2. Sample Size Determination

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. In the event that 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 (see Section 11.3). 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 (ie, a positive signal in favor of the combination).

11.3. Efficacy Analyses

The primary endpoint will be evaluated after approximately 90 subjects have been enrolled. The DMC will perform additional interim analyses after approximately 40 subjects and 60 subjects have had at least 1 disease assessment, respectively. These analyses will include an evaluation of efficacy as a function of PD-L1 expression. Based on these results, the DMC may recommend restricting enrollment of subjects in PD-L1 subgroups in whom clinical benefit is not demonstrated or expanding enrollment by a maximum of 100 subjects in PD-L1 subgroups without adequate enrollment (see Section 11.2) in accordance with the product label of the Ventana SP-142 assay. Study sites will be notified in writing of any changes to enrollment based on DMC recommendations.

Number and percent of subjects in each response category will be tabulated, along with those for subjects who achieve overall response (CR or PR) and who achieve disease control (ie, CBR: CR, PR, or SD with duration of at least 16 weeks). Odds ratio and its 95% confidence interval will be provided as a measure of treatment effect. Descriptive summaries (mean, standard deviation, median, and range) will be provided for time to response among those subjects who have CR or PR.

For time-to-event endpoints (PFS, OS, and duration of response), Kaplan-Meier estimates of the survival functions will be presented. For PFS and OS, Cox's regression will be performed to obtain the hazard ratio estimate and the corresponding 95% CI, which will be used as a measure for treatment effect. Additional Cox's regression may be performed to include appropriate baseline prognostic variables. Furthermore, exploratory analyses for OS may be performed to adjust for the effect of crossover. Analysis of duration of response will be performed descriptively among those subjects who achieve CR or PR.

11.4. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed on the PK-evaluable population, defined as subjects who have received at least 1 dose of daratumumab or atezolizumab and have at least 1 postinfusion sample.

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. The number of subjects and samples excluded from the analysis will be clearly documented.

Descriptive statistics will be used to summarize daratumumab and atezolizumab serum concentrations at each sampling time point. C_{min} is defined as the minimal concentration observed immediately before infusion and C_{max} is defined as the maximum concentration observed at the end of infusion, as presented in the summary of serum concentration by sampling time point and route of administration. Other PK parameters, if available, may also be summarized.

If sufficient data are available, population-PK analysis of serum concentration-time data of daratumumab or atezolizumab may be performed and may be combined with data from other studies. If the population-PK analysis is conducted, details will be given in a population-PK analysis plan and the results of the analysis will be presented in a separate report.

11.5. Immunogenicity Analyses

The incidence of anti-atezolizumab and daratumumab antibodies will be summarized for all subjects who receive at least 1 dose of atezolizumab and daratumumab and have appropriate samples for detection of antibodies to atezolizumab and daratumumab (ie, subjects with at least 1 sample obtained after their first dose). In addition, subjects who are positive for antibodies to atezolizumab or daratumumab will be listed.

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

11.6. Biomarker Analyses

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab and atezolizumab. Analyses will be stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate, analysis of variance, or survival analysis, depending on the endpoint). Correlation of baseline expression levels or changes in expression levels with response to time-to-event endpoints will identify responsive (or resistant) subgroups in addition to genes and pathways attenuated following treatment with daratumumab and atezolizumab.

Any pharmacodynamic measures will be listed, tabulated, and where appropriate, plotted. Subjects may be grouped by cohort, dose schedule, or clinical response. As this is an open-label study with an observation control arm, statistical analyses will be done to aid in the understanding of the results.

Results of biomarker and pharmacodynamic analyses may be presented in a separate report. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

11.7. Pharmacokinetic/Pharmacodynamic Analyses

If sufficient data are available, then other PK/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of atezolizumab and daratumumab and endpoints of clinical efficacy and safety. If performed, details and results of the analysis will be presented in a separate report.

11.8. Safety Analyses

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are AEs with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled timepoint. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables.

Electrocardiogram

Electrocardiogram data will be summarized based on categories of normal, abnormal either clinically significant or not clinically significant and listed.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled timepoint. The percentage of subjects with values beyond clinically important limits will be summarized.

11.9. Data Monitoring Committee

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, including but not limited to future subject enrollment (see Section 11.3). The DMC may request additional ad-hoc reviews as data accumulate to monitor safety or efficacy in certain PD-L1 subgroups. Additional details will be specified in a separate DMC charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The Sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important.*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject

or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For atezolizumab and daratumumab, the expectedness of an adverse event will be determined by whether or not it is listed within the Reference Safety Information in the Investigator's Brochures.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using the NCI-CTCAE Version 4.03 Any adverse event or serious adverse event not listed in the NCI- CTCAE Version 4.03 will be graded according to investigator clinical judgment by using the standard grades as follows:

Grade 1 (Mild): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities

Grade 2 (Moderate): Sufficient discomfort is present to cause interference with normal activity

Grade 3 (Severe): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities

Grade 4: Life-threatening or disabling adverse event

Grade 5: Death related to the adverse event

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a Sponsor study drug that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a Sponsor study drug
- Suspected abuse/misuse of a Sponsor study drug
- Accidental or occupational exposure to a Sponsor study drug
- Medication error involving a Sponsor product (with or without subject/patient exposure to the Sponsor study drug, eg, name confusion)
- Exposure to a Sponsor study drug from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study drug (or 90 days for serious adverse events), or until start of subsequent anticancer therapy or the subject withdraws consent

for study participation, if earlier, which may include contact for follow-up of safety. For subjects who have received subsequent treatment with therapeutic intent for NSCLC during the adverse event reporting period, only adverse events that are considered to be possibly, probably, or definitely related to atezolizumab or daratumumab need to be reported. Serious adverse events, including those spontaneously reported to the investigator, must be reported using the Serious Adverse Event Form. The Sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1). Death should not be recorded as an adverse event or serious adverse event, but as the outcome of an adverse event. The adverse event that resulted in the death should be reported as a serious adverse event. All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 4.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

The Sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The Sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events the Sponsor will make a determination of relatedness in addition to and independent of the investigator’s assessment. The Sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the Sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the institute).

The investigator (or Sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) will be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local Sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Blood type and IAT (as described in Section 9.7).

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate Sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the Sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the Sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- If the subject has not experienced a significant medical event but is hospitalized overnight only for observation following infusion of atezolizumab or daratumumab, then the hospitalization should not be reported as a serious adverse event
- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

12.4. Safety Reporting for Atezolizumab Monotherapy Subjects (per Amendment 6)

Following implementation of Amendment 6, all adverse events and special reporting situations (with the exception of Grade 1 to 2 events and non-immune-mediated events) will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study drug (or 90 days for serious adverse events), or until withdrawal of consent for study participation. For subjects who have received subsequent treatment with therapeutic intent for NSCLC during the adverse event reporting period, only adverse events that are considered to be possibly, probably, or definitely related to atezolizumab need to be reported; all other Grade 1 to 2 AEs, including laboratory abnormalities, do not need to be recorded in the CRF, but should be recorded in the source documentation.

Beyond 90 days after the last dose of study drug, SAEs, considered possibly, probably, or definitely related to study drug will continue to be collected and reported into the Sponsor's global safety database, using the SAE Form (paper form) faxed to Sponsor's Local Operational Company/Local Safety Officer. These should be reported until the subject discontinues the study (per the definitions in Section 10.2). SAEs (see Section 12.3.2) should include information on study agent administration and concomitant medications and other treatments associated with the SAE.

12.5. Safety Reporting for Atezolizumab Monotherapy Subjects (per Amendment 7)

Beginning with the implementation of Amendment 7, data from safety evaluations performed according to local regulatory approvals and standard of care guidelines[50,51] will no longer be collected with the exception of serious adverse events that are to be reported and entered in the Sponsor safety repository.

12.6. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the Sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.7. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the Sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the Sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Atezolizumab is a colorless to yellow liquid and sterile concentrate of 60 mg/mL in a vial for IV administration. Refer to the respective Investigator's Brochures for a list of excipients.

14.2. Packaging

Atezolizumab is supplied in glass vials containing atezolizumab at a concentration of 60 mg/mL.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. Each vial will contain a study-specific label with a unique identification number.

14.4. Preparation, Handling, and Storage

Atezolizumab

Atezolizumab must be stored in the original carton in a refrigerator at controlled temperatures ranging from 2°C to 8°C.

Study drug must not be utilized after the expiry date printed on the label. The drug product must be protected from light and must not be frozen. Atezolizumab do not contain preservatives; therefore, any unused portion remaining in the vial must be discarded.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the Sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the Sponsor's study site monitor during monitoring visits. The return to the Sponsor of unused study drug will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes, and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be administered only to subjects participating in the study. Returned study drug must not be dispensed again,

even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the Sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochures for daratumumab and atezolizumab
- Site Investigational Product Procedures Manual and IPPI
- Laboratory manual
- IWRS manual
- CRF completion guidelines
- Sample ICF
- Subject wallet card indicating blood type and IAT
- Other manuals and guidance documents as needed.

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This is the first clinical evaluation of daratumumab in combination with atezolizumab in NSCLC subjects; hence, the benefits and risks in the NSCLC population are unknown. However, as described in Section 1, clinical studies in NSCLC have demonstrated that atezolizumab and daratumumab have manageable safety profiles with monitoring and rapid intervention for immune-related AEs and infusion reactions. Subjects will be closely monitored throughout the study, as discussed throughout this protocol, for both safety and clinical benefit. Subjects in both arms will receive atezolizumab, which has been studied in clinical trials of NSCLC subjects (see Section 1.2 for an overview of the efficacy and safety results). As discussed in Section 1.4, based on the known data regarding the response to atezolizumab in NSCLC and the mechanism of action of both study drugs, there is adequate justification, including significant unmet clinical need, for evaluating these drugs in combination for the treatment of NSCLC in subjects who are eligible for this study.

Additionally, all subjects will undergo periodic CT or MRI scans to monitor the underlying disease. The frequency of such scans (as well as radiation exposure) is similar to standard practice for patients outside of clinical trials and the overall risk is low. Subjects will have a pre- and posttreatment biopsy. In general, these procedures are routinely performed during a subject's diagnostic workup and follow-up care. Although biopsy collection is associated with risk, the complication rate for these procedures is low. The data obtained from these biopsies will

generate valuable scientific data on the pharmacodynamic effect of the combination of these study drugs in NSCLC subjects.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be informed that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The blood volume collection for a subject is estimated at approximately 35 mL/month. This blood volume is not burdensome and falls within the normal range of a single blood donation.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or Sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)

- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects

- Any other documents that the IEC/IRB requests to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or Sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct)

- Revision(s) to ICF and any other written materials to be provided to subjects

- If applicable, new or revised subject recruiting materials approved by the Sponsor

- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable

- New edition(s) of the Investigator's Brochures and amendments/addenda

- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)

- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug

- New information that may adversely affect the safety of the subjects or the conduct of the study

- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects

- Report of deaths of subjects under the investigator's care

- Notification if a new investigator is responsible for the study at the site

- Development Safety Update Report and Line Listings, where applicable

- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions

must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or Sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject or a legally acceptable representative must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the Sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized Sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining

all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained.

When prior consent of the subject is not possible and the subject's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or legally acceptable representative must be informed about the study as soon as possible and give consent to continue.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject or his or her legally acceptable representative includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker research is not conducted under standards appropriate for the return of data to subjects. In addition, the Sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand daratumumab and atezolizumab, to understand NSCLC, to understand differential drug responders, and to develop tests/assays related to daratumumab, atezolizumab, and NSCLC. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the Sponsor will modify this protocol without a formal amendment by the Sponsor. All protocol amendments must be issued by the Sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the Sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate Sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the Sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the Sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the Sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, Prescreening, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the Sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not enrolled or randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries.

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as

the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the Sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Beginning with the implementation of Amendment 7, data collection through the electronic data capture (eDC) will no longer be performed.

eDC will be used for this study. Case report forms (CRF) are provided for each subject in electronic format. Study site personnel must log in eDC via a secure manner (personal password). The individual password must keep confidential for personal use.

The study data will be transcribed by study-site personnel from the source documents onto an CRF according to CRF completion guideline provided by the Sponsor. Data must be entered into CRFs in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit. Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation.

All subjective measurements (eg, pain scale information or other questionnaires) shall be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must address the queries and update the CRF if applicable.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or Sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the Sponsor, and direct transmission of clinical laboratory data from a central laboratory into the Sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The Sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The Sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The Sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first postinitiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the Sponsor and study-site personnel and are accessible for verification by the

Sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The Sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site. Central monitoring will take place for data identified by the Sponsor as requiring central review.

Once Amendment 6 is implemented at a site, monitoring will be limited to on-site monitoring visits and remote contacts for the verification and follow-up of SAEs reported to the Sponsor.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

Study completion will occur when the last subject has discontinued study treatment (atezolizumab monotherapy), completed the End of Treatment assessments, and safety follow-up has completed (ie, last required data collection for the last subject has been captured in the CRF). A CSR will be prepared based on interim analysis data reviewed by the DMC at the third planned DMC review on 23 May 2018 (prior to discontinuation of enrollment and daratumumab dosing).

The final data from the study site will be sent to the Sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development.

17.10. On-Site Audits

Representatives of the Sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the Sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the Sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding atezolizumab and daratumumab or the Sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the Sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the Sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the Sponsor in connection with the continued development of atezolizumab and daratumumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the Sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will

not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the Sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the Sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the investigator. The Sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the Sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The Sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Antihistamine Medications

The following antihistamines may be used for daratumumab preinfusion medication:

- Diphenhydramine
- Cetirizine
- Fexofenadine
- Loratadine
- Clemastine
- Dexchlorpheniramine.

Attachment 2: Conversion Table for Glucocorticosteroid Dose

Glucocorticoid	Approximate Equivalent Dose (mg)	Half-life (Biologic) hours
Intermediate-Acting		
Methylprednisolone	4	18-36
Prednisolone	5	18-36
Prednisone	5	18-36
Triamcinolone	4	18-36
Long-Acting		
Betamethasone	0.6 – 0.75	36-54
Dexamethasone	0.75	36-54

Attachment 3: ECOG Performance Status Scale

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

Source: Oken 1982[35]

Attachment 4: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study, the following events will be considered anticipated events:

- The clinical manifestations from primary tumors, regional spread, metastasis, and paraneoplastic syndromes will be considered as anticipated events. These events include local respiratory events (such as cough, dyspnea, hemoptysis, wheezing, chest pain, pneumonia, bronchitis, plural effusion); metastasis to nervous system events (such as bone pain, spinal cord depression, headache, seizures, meningismus, ataxia, altered mental status) and hepatic events; paraneoplastic syndromes (hypercalcemia, syndrome of inappropriate antidiuretic hormone production, Cushing syndrome).
- Given the mechanism of action of atezolizumab, events associated with immune-mediated adverse events will also be considered as anticipated events, including:
  - Pneumonitis
  - Colitis
  - Endocrinopathies (diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, hypophysitis)
  - Hepatitis
  - Transaminitis Grade $\geq$ 2 (AST or ALT > 3xULN and bilirubin > 2xULN, or AST/ALT > 10xULN)
  - Systemic lupus erythematosus
  - Neurologic: Guillain-Barré syndrome, myasthenia gravis/myasthenic syndrome, meningoencephalitis
  - Nephritis
  - Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome, systemic immune activation, infusion reactions syndrome, immune-mediated myocarditis, vasculitis, severe cutaneous adverse reactions autoimmune hemolytic anemia.

Because this is the first study of daratumumab in NSCLC subjects and with the combination of atezolizumab and daratumumab, other adverse events cannot be anticipated.

Reporting of Anticipated Events

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the Sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets serious adverse event criteria will be reported to the Sponsor as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the Sponsor will report these events in an expedited manner.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

Attachment 5: Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference

RECIST version 1.1	
Measurable Tumor Burden	A maximum of 5 target lesions in total (and up to 2 per organ) can be identified at baseline and measured through the course of therapy.
Minimum Size of Measurable Lesions	≥10 mm in longest diameter (LD) by CT scan of which slice is thickness no greater than 5 mm ≥15 mm in short axis (SA) for nodal lesions by CT scan of which slice is thickness no greater than 5 mm ≥10 mm in LD for clinical lesions (must be measured using electronic calipers) ≥20 mm in LD for chest X-ray (if clearly defined and surrounded by aerated lung); CT is preferable Ultrasound (US) cannot be used to measure lesions
Lymph Nodes	Lymph nodes are considered pathologically enlarged if >10 mm in SA. To be measurable, nodal lesions must be ≥15 mm in SA by CT scan of which slice is thickness no greater than 5 mm. Nodal lesions with SA >10 mm and <15 mm are non- measurable. The sum of the diameters (LD for non-nodal target lesions, SA for nodal lesions) is followed through the course of therapy.
Bone Lesions	A lytic or mixed lytic-blastic bone lesion with a soft tissue component assessed on CT/MRI can be measurable if the minimum size criteria are met. Blastic bone lesions and bone lesions assessed on bone scan, positron emission therapy (PET) or plain films are non-measurable.
Cystic Lesions	Lesions that meet the criteria for radiographically defined simple cysts are not malignant. Cystic lesions thought to be metastases can be measurable if they meet the minimum size criteria. If noncystic lesions are present in the same patient, they are preferred for selection as target lesions.
Lesions with Prior Local Treatment	Lesions in previously irradiated areas (or areas treated with local therapy) are not measurable unless the lesion has progressed since therapy.
Too Small To Measure	If a target lesion becomes too small to measure, a default value of 5 mm is assigned. If the lesion disappears, the measurement is recorded as 0 mm.
Lesions which split or Coalesce	If non-nodal target lesions fragment, the LDs of the fragmented portions are added to calculate the sum. If target lesions coalesce and cannot be distinguished, the LD of the coalesced lesion is added to the sum.
Definition of Complete Response (CR)	CR requires: • The disappearance of all lesions. • All lymph nodes must be non-pathological in size (<10 mm SA). • Normalization of tumor marker level.
Definition of Partial Response (PR)	≥30% decrease in the sum of the diameters of all target lesions compared with baseline, in absence of new lesions or unequivocal progression of non-target lesions
Definition of Stable Disease (SD)	<30% decrease in sum of diameters of all target lesions compared with baseline and <20% increase compared with nadir, in the absence of new lesions or unequivocal progression of nontarget lesions

Definition of Progressive Disease (PD)	PD is assessed if the sum of the diameters has increased by ≥20% and ≥5 mm from nadir (including baseline if it is the smallest sum). Patients with measurable disease: for "unequivocal progression" based on nontarget disease, there must be an overall level of substantial worsening that merits discontinuation of therapy (if target disease is SD/PR). Patients without measurable disease: for "unequivocal progression" of non-target disease, the increase in overall tumor burden must be comparable to the increase required for PD of measurable disease. Furthermore, the appearance of 1 or more new lesions or unequivocal progression of a nontarget lesion is also considered as PD.
Assessment of New Lesions	New lesions should be unequivocal and not attributable to differences in scanning technique or findings which may not be tumor (ie, 'new' bone lesions may be healing or flare of pre-existing lesions). If one is equivocal, repeat scans are needed to confirm. If confirmed, PD is assessed at the date of the initial scan. Lesions identified in anatomic locations not scanned at baseline are considered new. New lesions on US should be confirmed on CT/MRI.
FDG-PET	New lesions can be assessed using FDG-PET: (-) PET at baseline and (+) PET at follow-up is PD based on a new lesion. No PET at baseline and (+) PET at follow-up is PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of the PD is the date of the initial PET scan. No PET at baseline and (+) PET at follow-up corresponding to pre-existing lesion on CT that is not progressing; not PD.
Recurrence of lesions	For a patient with SD/PR, a lesion which disappears and then reappears will continue to be measured and added to the sum. Response will depend upon the status of the other lesions. For a patient with CR, reappearance of a lesion would be considered PD.
Overall Response	One overall response table integrates target, nontarget, and new lesions for subjects with measurable disease; and another table integrates nontarget and new lesions for subjects without measurable disease.
Confirmation of Response	In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. In these trials, subsequent confirmation of PR with one interim time point of SD is acceptable. In randomized trials, confirmation of response is not required.
CR=complete response, CT=computed tomography, FDG-PET=fluorodeoxyglucose positron emission therapy LD=longest diameter, PD=progressive disease, PR=partial response, SA=short axis, SD=stable disease, US=ultrasound	

Source: Eisenhauer 2009 [14]

Attachment 6: Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

	RECIST 1.1	irRECIST
New, measurable lesions	Always represent progressive disease (PD)	Incorporated into tumor burden
New, non-measurable lesions	If unequivocal, represent PD; if equivocal, does not represent PD (but precludes complete response) and should be followed for unequivocal progression at a later timepoint	Same as RECIST 1.1.
Non-target lesions	Changes contribute to defining best overall response (BOR) of CR, PR, SD, and PD	Same as RECIST 1.1.
Response Category		
CR	Disappearance of all lesions	Same as RECIST 1.1.
PR	≥30% decrease in the sum of the diameters of all target lesions compared with baseline, in absence of new lesions or unequivocal progression of non-target lesions	Same as RECIST 1.1.
SD	<30% decrease in sum of diameters of all target lesions compared with baseline and <20% increase compared with nadir, in the absence of new lesions or unequivocal progression of nontarget lesions	Same as RECIST 1.1.
PD	At least 20% increase in the sum of the diameters for target lesions and/or unequivocal progression of nontarget lesions, compared with nadir (at any single time point including baseline). The sum must also demonstrate an absolute increase of at least 5 mm.	Same as RECIST 1.1, with the following exceptions: 1. Increases are observed in 2 consecutive observations at least 4 weeks apart. 2. New target lesions (maximum of 5 new target lesions; maximum of 2 per organ) are included in calculating tumor burden
Handling of lymph nodes	Lymph nodes are considered pathologically enlarged if >10 mm in SA. To be measurable, nodal lesions must be ≥15 mm in SA. Nodal lesions with SA >10 mm and <15 mm are non- measurable. The sum of the diameters (LD for non-nodal target lesions, SA for nodal lesions) is followed through the course of therapy.	Same as RECIST 1.1.
BOR=best overall response, CR=complete response, LD=longest diameter, PD=progressive disease, PR=partial response, SA=short axis, SD=stable disease		

Sources: Henze 2016[19], Nishino 2013[33]

Attachment 7: Management Guidelines for Atezolizumab

Management guidelines for toxicities associated or possibly associated with atezolizumab are provided as follows:

- Pulmonary events, please see Table 13
- Hepatic events, please see Table 14
- Gastrointestinal events, please see Table 15
- Endocrine events, please see Table 16
- Ocular events, please see Table 17
- Pancreatic events, please see Table 18
- Immune-mediated myocarditis, please see Table 19
- Dermatologic events, please see Table 20
- Neurologic disorders and meningoencelphalitis, please see Table 21
- Systemic immune activation events, please see Table 22
- Immune-related Nephritis, please see Table 23.

Table 13: Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider subject referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer subject to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor.[c]
Pulmonary event, Grade 3 or Grade 4	• Permanently discontinue atezolizumab and contact the Sponsor.[c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL=bronchoscopic alveolar lavage; IVIG=intravenous immunoglobulin

a. Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

Table 14: Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of >5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset.[a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Sponsor.[c] • Consider subject referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function tests.

a. Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.

b. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

Table 15: Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Subject referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer subject to gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab,
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact the Sponsor. [c] • Refer subject to gastrointestinal specialist for evaluation and confirmation biopsy. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

a. Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.
b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

Table 16: Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider subject referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider subject referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Sponsor for life-threatening immune-related hyperthyroidism.[a]
Symptomatic adrenal insufficiency, Grade 2-4	• Withhold atezolizumab for up to 12 weeks after event onset. [b] • Refer subject to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [c] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor. [a]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

Hypophysitis pan-hypopituitarism), Grade 2-3	• Withhold atezolizumab for up to 12 weeks after event onset. [b] • Refer subject to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [c] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor.[a] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact the Sponsor.[a] • Refer subject to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.[b] • Initiate hormone replacement therapy if clinically indicated.

TSH=thyroid-stimulating hormone

a. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

b. Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.

c. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 17: Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Subject referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.[b] • Subject referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab.[a] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor.[c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Sponsor.[c] • Refer subject to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

a. If corticosteroids have been initiated, they must be tapered over ≥1 month to≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
b. Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.
c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

Table 18: Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (eg, > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer subject to gastrointestinal specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor.[c] • For recurrent events, permanently discontinue atezolizumab and contact the Sponsor.[C]
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer subject to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor.[c] • For recurrent events, permanently discontinue atezolizumab and contact the Sponsor.[c]
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact the Sponsor.[c] • Refer subject to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

a. Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.
b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

Table 19: Management Guidelines for Immune-Related Myocarditis

Event	Management
Immune-related myocarditis, Grade 1	• Refer subject to cardiologist • Initiate treatment as per institutional guidelines.
Immune-related myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Sponsor. • Refer subject to cardiologist • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.[a] • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor.[c]
Immune-related myocarditis, Grade 3-4	• Permanently discontinue atezolizumab and contact Sponsor.[c] • Refer subject to cardiologist • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.[a,b] • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device

a. Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

Table 20: Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (eg, antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider subject referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset .[a] • Refer subject to dermatologist. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor.
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact the Sponsor.[c]

a. Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.
b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

Table 21: Management Guidelines for Neurologic Disorders, Including Meningoencephalitis

Event	Management
Immune-related neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-related neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact
Immune-related neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Sponsor.[c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact the Sponsor.[c] • Refer subject to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.
Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact the Sponsor.[c] • Refer subject to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

IV=intravenous

a. Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor.

Table 22: Diagnostic Criteria and Management for Systemic Immune Activation

Systemic Immune Activation		
Systemic immune activation criteria apply only when alternate etiologies have been excluded		
Major Criteria		Minor Criteria
• Fever ≥ 38.5°C (on more than one occasion) • Ferritin > 3000 ng/mL • Cytopenias: ≥ Grade 2 in two or more lineages • ≥ 2 age-adjusted SD elevation soluble IL-2 receptor • Severe multi-organ dysfunction • Decreased fibrinogen		• Splenomegaly • Hemophagocytosis BM, spleen or LN • Elevated GGT or LFTs (AST/ALT/tBili) • Elevated triglycerides • Elevated LDH • Decreased natural killer-cell activity
	Number of Criteria	Management
Consistent with systemic immune activation	4 major criteria	Consider tocilizumab (4 mg/kg IV) and Solumedrol® (methylprednisolone) (1g IV QD). Contact the Sponsor for additional recommendations. Consider HLH-94 protocol if no clinical improvement.
Probable systemic immune activation	3 major criteria OR 2 major criteria AND 3 minor criteria	Depending on clinical severity, subject can be treated as per "Consistent with systemic immune activation" or "Possible systemic immune activation" case definition. Contact the Sponsor for additional recommendations
Possible systemic immune activation	1 major criteria AND 4 minor criteria	Consider Solumedrol® (1g IV QD) Contact the Sponsor for additional recommendations. As per "Consistent with systemic immune activation" recommendations if no improvement or clinically worsening

BM = bone marrow; GGT = gamma-glutamyl transpeptidase; IL-2 = interleukin-2; IV = intravenous; LFT = liver function test; LN= lymph node; QD = once daily; tBili = total bilirubin.

Notes: Criteria adapted from a Delphi Survey of 26 experts regarding helpful criteria in the positive diagnosis of Hemophagocytic Syndrome in adult subjects (Hejblum G. et al PLoS One [Public Library of Science] April 2014; Volume 9, Issue 4). Standard-of-care for systemic immune activation has not been established. Case reports and recommendations have been published for cytokine release syndrome (Lee 2014, Maude 2014, Teachey 2013),[28, 29, 49] and based on etiologic similarities, these practices have been incorporated into the above treatment recommendations.

These recommendations do not replace clinical judgment and are intended as suggested guidance.

Table 23: Management Guidelines for Immune-Related Nephritis

Event	Management
Immune-related nephritis, Grade 2	• Withhold atezolizumab and contact Sponsor. • Refer subject to renal specialist • Initiate treatment as per institutional guidelines and consider renal biopsy and supportive measures. • Corticosteroids and/or additional immunosuppressive agents should be administered as clinically indicated.
Immune-related nephritis, Grade 3-4	• Permanently discontinue atezolizumab and contact Sponsor. • Refer subject to renal specialist • Initiate treatment as per institutional guidelines and and consider renal biopsy and supportive measures. • Corticosteroids and/or additional immunosuppressive agents should be administered as clinically indicated.

INVESTIGATOR AGREEMENT

JNJ-54767414 (daratumumab)
Clinical Protocol 54767414LUC2001; Amendment 7

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Roland Knoblauch MD

Institution: Janssen Research & Development

Signature [redacted] Date: 05 Oct 2018
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the Sponsor, and a protocol amendment will not be required.

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Approved, Date: 4 October 2018