Official Title: A Single Arm, Phase II Study of Atezolizumab (MPDL3280A, Anti-PD-L1 Antibody) in Combination With Bevacizumab in Patients With EGFR Mutation Positive Stage IIIB-IV Non-Squamous Non-Small Cell Lung Cancer Pretreated With Epidermal Growth Factor Receptor Tyrosine-Kinase Inhibitors

NCT Number: NCT04426825

Document Date: Protocol Version 3: 11-January-2021

PROTOCOL

TITLE:	**A SINGLE ARM, PHASE II STUDY OF ATEZOLIZUMAB (MPDL3280A, ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH BEVACIZUMAB IN PATIENTS WITH EGFR MUTATION POSITIVE STAGE IIIB-IV NON-SQUAMOUS NON-SMALL CELL LUNG CANCER PRETREATED WITH EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE-KINASE INHIBITORS**
PROTOCOL NUMBER:	ML41256
VERSION NUMBER:	3
EUDRACT NUMBER:	Not Applicable
IND NUMBER:	Not Applicable
TEST PRODUCT:	Atezolizumab (RO5541267) Bevacizumab（RO4876646）
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	2021-1-11

PROTOCOL AMENDMENT APPROVAL

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PROTOCOL AMENDMENT, VERSION 3 RATIONALE

Protocol ML41256 has been amended primarily for the following reasons:

1. The primary endpoint has been revised from PFS rate at 6 month to Objective Response Rate (ORR). Simon's minimax two-stage design will be used to re-design this trial. The expected ORR=0.5 versus poor ORR=0.3. 19 subjects will be enrolled in the first stage, and if ≤6 people get ORR, the study will be terminated; otherwise, 20 more subjects will be enrolled into the second stage. Finally, if more than 16 of 39 subjects occur ORR events, this study will meet its primary endpoint. Reasons: A. A Simon's two stage-designed ORR could allow the investigators to assess the patient's benefits after first stage enrollment, it is more in line with the benefits of subjects, and ethical for subject at the same time. B. China Clinical trial of anti-tumor drug combination therapy Technical guidelines announced by Center for Drug Evaluation and Research of China in July 2020 suggested the clinical trials with PFS as primary endpoint should set a control arm. Although ML41256 had PFS rate at 6 month as its primary endpoint, it is suitable to have this change currently.

2. The sample size has been revised from 60 patients to 44 patients. Considering that the primary endpoint changed from PFS rate at 6 month to a Simon`s two stage designed ORR. (Simon's two stage design: Poor ORR = 0.3, expected ORR = 0.5, 19 patients would be enrolled in the first stage, if less than 6 patient with ORR, the study would be terminated; Otherwise, 20 more people would be recruited. Finally, if we have > 16 patients in 39 patients with ORR, the endpoint is reached) as showed below:

Mathod	Poor ORR	Target ORR	Stage I	Probability of ending in stage I	Stage II	Sample Size (10% cencensored)
Minmax	0.3	0.5	>6/19	0.666	>16/39	44

3. Patients with stage IIIC (according to UICC/AJCC 8th version) will be allowed into this study, for the reasons summarized below: A. The rationale of this study is to evaluate the efficacy and safety of atezolizumab in combination with bevacizumab in patients with advanced or metastatic Non-Squamous Non-Small Cell Lung Cancer (NSCLC) harbored EGFR mutation after treatment failure of EGFR TKI. All patients will be selected on the basis of PD-L1 expression ≥ 1% on tumor cells (TC) and/or immune cells (ICs) using a centrally performed immunohistochemistry (IHC) test. Patients with stage IIIC (UICC/AJCC 8th Version) were also included into advanced or metastatic Non-Squamous Non-Small Cell Lung Cancer (NSCLC). B. Patients

with stage IIIC NSCLC shared same systemic treatment with stage IIIB and stage IV patients. The prognosis of these patients is between stage IIIB and stage IV regardless of the molecular type and treatment.

4. Addition of “severe cutaneous adverse reactions” in Risks associated with Atezolizumab (section 5.1.1) and updated related contents in Appendix 6 and Appendix 9.
5. Updated SAE and AESI reporting period from 6 months to 90 days to reflect protocol template change (section 5.3.1, section 5.4.2.2, section 5.6 and Appendix 1).
6. Addition of “Cytokine-Release Syndrome” in section 5.3.5.1 Infusion-Related Reactions to align with management guidelines for IRR and CRS inTable 7, Appendix 9 and updated content in Table 7 footnote, Appendix 9.
7. Clarified that all special situations with atezolizumab and bevacizumab should be reported to the Sponsor within 30 calendar days (Section 5.3.5.13).
8. Clarified spontaneous abortions, therapeutic or elective abortion in reporting requirements for pregnancies (section 5.4.3.3).
9. Updated management guidelines for suspected HLH or MAS in Table 14, Appendix 9.

PROTOCOL AMENDMENT, VERSION 3:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

TITLE:

A SINGLE ARM, PHASE II STUDY OF ATEZOLIZUMAB (MPDL3280A, ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH BEVACIZUMAB IN PATIENTS WITH EGFR MUTATION POSITIVE STAGE IIIB~~/~~-IV NON-SQUAMOUS NON-SMALL CELL LUNG CANCER PRETREATED WITH EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE-KINASE INHIBITORS

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus bevacizumab in the evaluable population on the basis of the following endpoint (evaluable population: it includes all enrolled patients who receive any amount of atezolizumab or bevacizumab, and have at least one post-baseline efficacy measurement):

- ~~PFS rate at 6 months, defined as the proportion of patients who have not experienced disease progression or death from any cause at 6 months after enrollment, as determined by the investigator according to RECIST v1.1.~~*Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ⩾4 weeks apart, as determined by the investigator according to RECIST v1.1.*

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus bevacizumab in the evaluable population on the basis of the following endpoints:

- ~~Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ⩾4 weeks apart, as determined by the investigator according to RECIST v1.1.~~
- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause whichever occurs first, as determined by the investigator according to RECIST v1.1.
- Time to response (TTR), defined as the time from the start of the treatment to the first objective tumor response observed for patients who achieved CR or PR, as determined by the investigator according to RECIST v1.1.
- Disease control rate (DCR), defined as the proportion of patients who have a best overall response of CR or PR or stable disease (SD), as determined by the investigator according to RECIST v1.1

- Overall survival (OS) after enrollment, defined as the time from enrollment to death from any cause.
- Progression-free survival (PFS), defined as the time from enrollment to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1
- PFS rate at ***6*** and 12 months, defined as the proportion of patients who have not experienced disease progression or death from any cause at ***6*** months and 12 months, as determined by the investigator according to RECIST v1.1.
- OS rate at 1 and 2 years, defined as the proportion of patients who have not experienced death from any cause at 1 and 2 years.
- ~~The above endpoints will also be summarized in PD-L1 expression high vs. low population.~~
- ~~The consistency among in SP 142 and SP 263.~~
- ~~Exploratory analyses ORR, DOR, PFS,PFS rate at 12m,by investigator according to Modified RECIST V1.1(iRECIST)~~
- Expression of PD-L1 defined by the SP142 and SP263 assay.
- Analyses ORR, DOR, PFS,PFS rate at 12m,by investigator according to Modified RECIST V1.1(iRECIST)

2.2 SAFETY OBJECTIVE

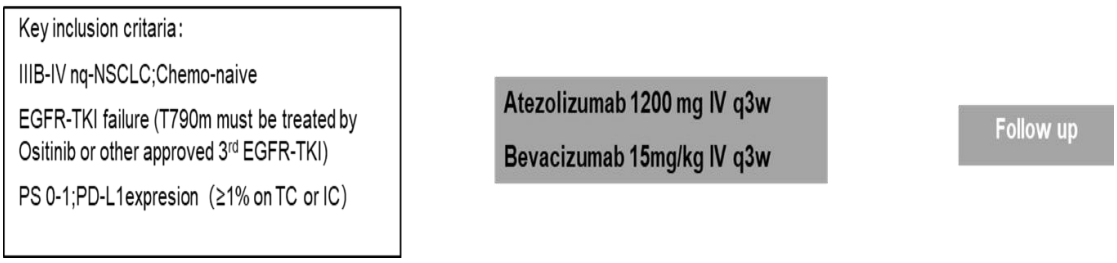
- Incidence of serious and non-serious immune-~~related~~mediated adverse events ~~(irAEs)~~ related to atezolizumab treatment

3.1.1 Overview of Study Design

This is an open-label, single-arm, phase II, multicenter study designed to evaluated the efficacy and safety of atezolizumab in combination with bevacizumab in PD-L1-selected patients with Stage IIIB/~~–~~IV Non-Squamous NSCLC harbored EGFR mutation after EGFR TKI therapy. Patients should have received at least one EGFR TKI and have disease progressed before enrollment.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



IV = intravenous; NSCLC = non–small cell lung cancer;

3.3.5 Rationale for Objective response rate as Primary Endpoint

In this study, the primary efficacy endpoint will be investigator ~~-assessed 6m PFS rate~~ confirmed objective response rate. Phase II studies are limited because they lack a control arm. Objective response rate directly measures the efficacy of initial therapy, unaffected by treatment at progression.

4.1 Patients

Approximately ~~60~~ 44 patients with PD-L1-expression ⩾1%,Stage IIIB~~/~~ -IV Non-Squamous NSCLC harbored EGFR mutation after EGFR TKI therapy will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Histologically or cytologically confirmed stage IIIB ~~or~~ -IV non-squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 8th edition)

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, ~~and~~ myositis and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Refer to Appendix 9 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.3.1 Adverse Event Reporting Period

After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until ~~6 months~~ 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

5.3.5.1 Infusion-Related Reactions and Cytokine-Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and cytokine-release syndrome (CRS). While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "cytokine-release syndrome") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Cases of late-onset CRS should be reported as "cytokine-release syndrome" on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient

experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 9.

5.3.5.13 Cases of Accidental Overdose or Medication Error

In addition, all special situations associated with atezolizumab and bevacizumab, regardless of whether they result in an adverse event, should be reported to the Sponsor within 30 calendar days and recorded on the Adverse Event eCRF as described below:

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All sites

Medical Monitor{Roche Medical Responsible}: [redacted](Primary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until ~~6 months~~ 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF on the electronic data capture (EDC) system, generate, and submit the report to Sponsor.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A report should be downloaded from EDC system and sent the report to Sponsor.

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as ~~6 months~~ 90 days) after the final dose of study treatment or until initiation of

new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN.

This is an open-label, single-arm study. A Simon's Minimax two-stage design will be used (Simon. 1989).

6.1 Determination of Sample Size

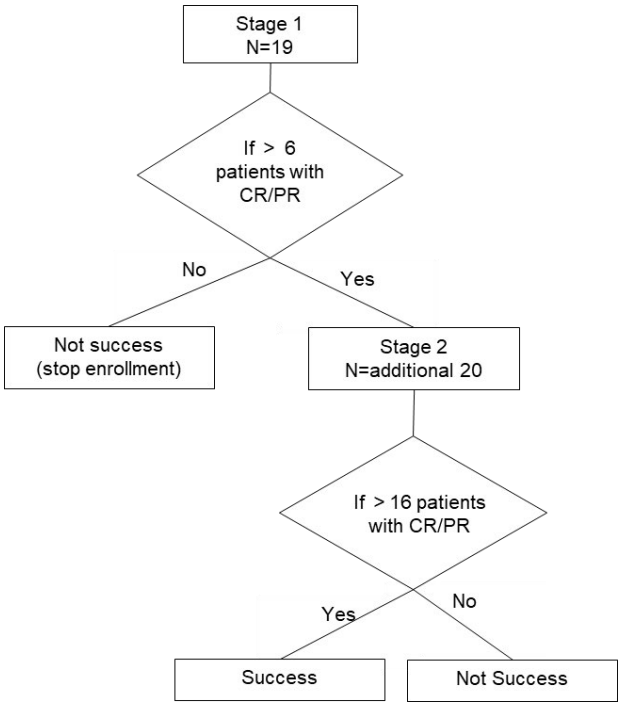
The sample size estimation is based on having sufficient sample in the FAS population to show that the ORR is higher than 30%. Simon's minimax two-stage design will be used (Simon, 1989). The null hypothesis that the true ORR is at least 50% will be tested against a one-sided alternative.

The sample size calculation was based on a Simon two-stage design, and the primary end point was ORR (H0 = 30%, H1 = 50%). Two-sided alpha is set to be 0.1 and statistical power is set to be 80%.

19 fully evaluable patients will be included at the first stage. If there are 6 or fewer responders (CR/PR) in these 19 patients, enrollment will be stopped. Otherwise, additional 20 fully evaluable patients will be included into the second stage. Finally, if we have more than 16 patients in 39 patients have objective response, the endpoint is reached. Thus, considering a drop-out rate of 10%, a total number of 22 patients (if stops at the first stage) or 44 patients (if runs into the second stage) will need to be finally enrolled in this study.

Figure 2 presents an overview of the sample size allocation.

Figure 2 Sample size allocation



~~The purpose of this study is to estimate the effect of atezolizumab plus bevacizumab on the primary endpoint, PFS rate at 6 months. Objective response rate. Point and interval estimates of the true underlying hazard rate will be obtained.~~

~~It is assumed that the median duration of PFS in the atezolizumab plus bevacizumab group is about 8 months, thus the hazard rate is 0.0866 under the exponential distribution. At the time of 6 months after the last patient enrollment, about 40% patients will experience disease progression or death. Assuming the percent censoring (includeing those that are lost to follow up, and those patient who does not experience disease progression of death at the time of 6 months after enrollmen) at 6 months is 65%, so the number of events at 6 months is estimated to be 21. A total of 21 events produces a two-sided 95% confidence interval for hazard rate with a width equal to 0.074 when the estimate of λ (the hazard rate) is 0.0866, see the table below. Relatively, the 95% CI for the estimate PFS rate at 6 months, 60%, will be (46.6%, 72.5%). The estimation accuracy is acceptable clinically.~~

~~Numeric Results for Two-Sided Confidence Intervals for an Exponential Hazard Rate~~

		Expected				
	Number of	Sample		Hazard	C.I.	C.I.
Confidence	Events	Size		Rate	Lower	Upper
Level	E	N	Width	λ	Limit	Limit
0.950	21	60	0.074	0.0866	0.0536	0.1274

6.2 SUMMARIES OF CONDUCT OF STUDY

~~Descriptive statistics will be used in evaluating the conduct of the study.~~

Enrollment, study treatment administration and discontinuation ~~(including reasons)~~ from the study will be summarized ~~with ITT population~~. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized.

6.4 EFFICACY ANALYSES

~~The efficacy analyses will be performed on the FAS population, defined as all enrolled patients who receive any amount of study treatment and evaluable for efficacy endpoints.~~

The analysis population for the efficacy analyses will consist of all enrolled patients who receive any amount of study treatment and evaluable for efficacy endpoints. ORR and DCR will be analyzed using all enrolled patients who have measureable disease at baseline. DOR will be assessed in patients who have an objective response.

6.4.1Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus bevacizumab on the basis of the following endpoint:

- ~~PFS rate at 6 months, defined as the proportion of patients who have not experienced disease progression or death from any cause at 6 months after enrollment, as determined by the investigator according to RECIST v1.1~~

~~The primary efficacy analysis will be performed in FAS population, of which consists all enrolled patients who receive any amount of study treatment and evaluable for efficacy endpoints.~~
~~PFS will be summarized descriptively using the Kaplan-Meier (KM) product-limit method. Median values of PFS, if available, along with two-sided 95% CIs (based on the log-log transformation), will also be calculated. The source of progression (death vs. progression) will be summarized.~~
~~The status of subjects who are censored in the PFS Kaplan Meier analysis will be tabulated using the following three categories:~~
~~• Received another kind of anti-cancer therapy before progression~~
~~• Still on treatment and progression free at the time of analysis~~
~~• Off-study: (lost to follow-up, withdrew consent, other).~~
~~Patients who are alive and have not experienced disease progression at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the time of initiation of study treatment plus 1 day.~~
~~KM curve of PFS will be generated. PFS rates 6 and 12 months will be estimated using KM estimates on the PFS curve. Associated two-sided 95% CIs will be calculated.~~
~~Further detailed discussion will be found in the Statistical Analysis Plan~~

- ORR defined as the proportion of patients with a CR or PR on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1. Patients not meeting these criteria, including patients without any post-baseline tumor assessment, will be excluded from the primary analysis.

Number and percentage of responders with corresponding Clopper-Pearson 90% and 95% confidence intervals will be provided.

The ORR will be the basis for decision whether the study would be continued when Stage 1 is completed. Refer to section 66.1 Determination of sample size for details.

6.4.2 Secondary Efficacy Endpoints

~~The secondary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus bevacizumab in the evaluable population on the basis of the following endpoints and the analysis will be performed in FAS population. :~~

● Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1. Patients without any post-baseline tumor assessments will be considered non-responders. An estimate of ORR will be provided along with the corresponding 95% CIs calculated using the Clopper-Pearson method. ORR will be summarized by estimated response rate and its corresponding 95% Pearson-Clopper confidence interval.

● For patients who have experienced an objective response (CR or PR) during the study, duration of objective response (DOR) is defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause whichever occurs first, as determined by the investigator according to RECIST v1.1.

Patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the time of the last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a complete or partial response, DOR will be censored at the date of the first occurrence of a complete or partial response plus 1 day.

The analysis population will be FAS that have experienced an objective response (CR or PR).

● Time to response (TTR), defined as the time from the start of the treatment to the first objective tumor response observed for patients who achieved CR or PR, as determined by the investigator according to RECIST v1.1.

Patients who are alive and who have not experienced the response at the time of analysis will be censored at the date of data cutoff.

● Overall survival (OS) after enrollment, defined as the time from enrollment to death from any cause.

Patients who do not have post-baseline information will be censored at the date of initiation of study treatment plus 1 day.

● Progression-free survival (PFS), defined as the time from enrollment to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (RECIST v1.1).

Patients who are alive and have not experienced disease progression at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the time of initiation of study treatment plus 1 day.

● PFS rate at 12 months, defined as the proportion of patients who have not experienced disease progression or death from any cause at 12 months, as determined by the investigator according to RECIST v1.1. The analysis method is similar with PFS rate at 6 months.

● OS rate at 12 and 24 months, defined as the proportion of patients who have not experienced death from any cause at 12 and 24 months. The analysis method is similar with PFS rate at 6 months. The above endpoints will also be summarized in PD-L1 expression high vs. low population.

The consistency among in SP 142 and SP 263.

Exploratory analyses ORR, DOR, PFS,PFS rate at 12m,by investigator according to Modified RECIST V1.1(iRECIST)

6.4.2.1 Duration of Response

DOR will be assessed in patients who had an objective response as determined by the investigator using RECIST v1.1. DOR is defined as the time interval from the date of the first occurrence of a documented objective response until the first date of disease progression or

death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1.

Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a documented objective response, DOR will be censored at the date of the first occurrence of a documented objective response plus 1 day. The KM approach will be used to estimate median DOR. The Brookmeyer-Crowley methodology (Brookmeyer and Crowley 1982) will be used to construct the 95% CI for the median DOR.

6.4.2.2 Time to Response

TTR, defined as the time from the start of the treatment to the first objective tumor response observed for patients who achieved CR or PR, as determined by the investigator according to RECIST v1.1.

Patients who are alive and who have not experienced the response at the time of analysis will be censored at the date of data cutoff.

The methodologies detailed for the DOR analysis will be used for the TTR analysis.

6.4.2.3 Disease Control Rate

DCR, defined as the proportion of patients who have a best overall response of CR or PR or SD, as determined by the investigator according to RECIST v1.1.

Number and percentage of patients with DCR with corresponding Clopper-Pearson 95% confidence intervals will be provided.

6.4.2.4 Progression-free Survival

PFS defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of initiation of study treatment plus 1 day.

The methodologies detailed for the DOR analysis will be used for the PFS analysis.

6.4.2.5 Overall Survival

OS, defined as the time from initiation of study treatment to death from any cause. Patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Patients with no post-baseline information will be censored at the date of initiation of study treatment plus 1 day. Methods for OS analyses are similar to those described for the DOR endpoint.

6.4.2.6 Landmark Analysis on Progression-free Survival and Overall Survival

PFS rate at 6 months and 1 year, defined as the proportion of patients who have not experienced disease progression or death from any cause at 6 months and 1 year separately, as determined by the investigator according to RECIST v1.1. OS rate at 1 year and 2 years, defined as the proportion of patients who have not experienced death from any cause at 1 year and 2 years.

The PFS rates at 6 months and 1 year after initiation of treatment will be estimated using Kaplan-Meier methodology, along with 95% CIs calculated using the standard error derived from Greenwood's formula.

Similar analyses will be performed for the OS rates at 1 year and 2 years after initiation of treatment.

6.4.2.7 ORR, DCR, DOR, and PFS per Modified RECIST

Analyses using modified RECIST criteria (see Appendix 5) for ORR, DCR, DOR, and PFS as determined by the investigator will be conducted. The methods outlined for the primary and secondary efficacy endpoint analyses will be used for these analyses.

6.4.2.8 Expression of PD-L1 defined by the SP142 and SP263 IHC Assay

Expression of PD-L1 defined by the SP142 and SP263 IHC assay will be investigated. The proportions of the patients with PD-L1+ tested by SP142 and SP263 in all patients will be presented respectively, with their 95% Clopper-Pearson CI. The consistency between SP142 and SP263 IHC assay will be investigated using Chisq-square Test if applicable.

6.4.2.9 Patent-Reported Outcomes (PROs)

TTD using EORTC is defined as the time from baseline to the first time the patient's score shows a ≥10 points increase above baseline in any of the following EORTC-transformed symptom subscale scores (whichever occurs first): cough, dyspnea (single item), dyspnea (multi-item subscale), chest pain, or arm/shoulder pain, whichever occurs first. The linear transformation gives each individual symptom subscale a possible score of 0-100. In order for the symptoms to be considered "deteriorated", acore increase of ≥ 10 points above baseline must be held for at least two consecutive assessment or an initial score increase of ≥ 10 points is followed by death within 3 weeks from the last assessment. A "≥10 point" change in the symptoms subscale score is perceived by patients as clinically significant (Osoba et al. 1998). Patients will be censored at the last time when they complete an assessment if they have not deteriorated. If no post-baseline assessment is performed, patients will be censored at the randomization date plus 1 day. TTD using the EORTC scale will be analyzed using the same methods as for PFS. The analysis populations for TTD will be all randomized patients with a non-missing baseline PRO assessment.

PROs of HRQoL, lung cancer related symptoms, and health status will be measured using the EORTC QLQ-C30 and EORTC QLQ-LC3. Summary statistics (mean, SD, median, 25th and 75th percentiles, minimum and maximum) and mean change from baseline of linear-transformed scores will be reported for all of the items and subscales of EORTC QLQ-C30 questionnaire and the QLQ-LC13 according to the EORTC scoring manual guidelines. Completion and compliance

rates will be summarized at each timepoint by treatment arm. The analysis populations for PRO changes will be all randomized patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment.

6.5 Safety Analyses

~~The safety objective for this study is to evaluate the safety of atezolizumab plus bevacizumab on the basis of the following endpoints:~~

- ~~Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0~~
- ~~Incidence of serious and non-serious immune-related adverse events (irAEs) related to atezolizumab treatment~~

~~These safety endpoints will be summarized by incidence rates and 95% Pearson-Clopper confidence intervals if applicable.~~
~~Verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0.~~

The safety analysis population will consist of all enrolled patients who received at least one dose of study treatment.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature), physical examination and ECG data will be displayed by time, with grades identified where appropriate. Changes from baseline in vital signs and ECGs will be summarized.

~~6.6 BIOMARKER ANALYSES~~

~~Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.~~

6.~~7~~ INTERIM ANALYSES

~~No interim analyses were planned for efficacy endpoints in this study. However, to address information that may emerge during the course of this study, the Sponsor may choose to conduct one interim analysis for reporting of safety and efficacy result.~~

One interim analysis is planned. The interim analysis will be performed for futility at the time of 19 patients completing ORR evaluation. According to preplanned stopping rules of Simon 2-stage design, further testing of Atezolizumab and Bevacizumab would be halted if the number of patients that respond in the first evaluable 19 patients (stage 1) is less or equal than 6. This study has probability of 66.6% terminate at the first stage.

When the study runs into the second stage, in the end of the study, if more than 16 patients out of 39 patients have responses, we can recommend this treatment in IIIB-IV Non-squamous NSCLC to go to the next step in the clinical trial phase, otherwise, the treatment is rejected.

9.4 Administrative Structure

~~Approximately 8 sites globally will participate to randomize~~ Approximately ~~60~~ 44 patients from China will be enrolled into this study.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses~~, and PK analyses~~), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

Appendix 1 Schedule of Activities

Footnote “u”: After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest, regardless of relationship to study treatment, will be reported until ~~6 months~~ 90 days after the last dose of study treatment or initiation of new non-protocol systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the investigator should report any serious adverse event or adverse events of special interest that is believed to be related to prior exposure to study treatment.

Appendix 6
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering

atezolizumab for patients who have previously experienced a severe or life–threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent. Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Appendix 9

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

[e] There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

~~f~~[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit–risk ratio.

~~g~~[f] Refer to Riegler et al. (2019) for information on experimental treatments for CRS.

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. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • 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 patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, 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 Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]
Stevens Johnson syndrome or toxic epidermal necrolysis, (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant), and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • Permanently discontinue atezolizumab for confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis.

Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

- If event does not ~~improve within 48 hours after initating corticosteroids, consider adding an immunosuppressive agent~~ respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A SINGLE ARM, PHASE II STUDY OF ATEZOLIZUMAB (MPDL3280A, ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH BEVACIZUMAB IN PATIENTS WITH EGFR MUTATION POSITIVE STAGE IIIB-IV NON-SQUAMOUS NON-SMALL CELL LUNG CANCER PRETREATED WITH EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE-KINASE INHIBITORS**
PROTOCOL NUMBER:	ML41256
VERSION NUMBER:	3
EUDRACT NUMBER:	NA
IND NUMBER:	NA
TEST PRODUCT:	Atezolizumab (RO5541267) Bevacizumab（RO4876646）
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A SINGLE ARM, PHASE II STUDY OF ATEZOLIZUMAB (MPDL3280A, ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH BEVACIZUMAB IN PATIENTS WITH EGFR MUTATION POSITIVE STAGE IIIB-IV NON-SQUAMOUS NON-SMALL CELL LUNG CANCER PRETREATED WITH EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE-KINASE INHIBITORS**
PROTOCOL NUMBER:	ML41256
VERSION NUMBER:	3
EUDRACT NUMBER:	Not Applicable
IND NUMBER:	Not Applicable
TEST PRODUCT:	Atezolizumab (RO5541267) Bevacizumab（RO4876646）
PHASE:	Phase II
INDICATION:	Non-squamous NSCLC
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of atezolizumab in combination with bevacizumab in patients with stage IIIB/IV Non-Squamous Non-Small Cell Lung Cancer (NSCLC) harbored EGFR mutation after treatment failure of EGFR TKI. All patients will be selected on the basis of PD-L1 expression ≥ 1% on tumor cells (TC) and/or immune cells (ICs) using a centrally performed immunohistochemistry (IHC) test. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of atezolizumab and bevacizumab assigned to patients as part of this study.

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus bevacizumab in the evaluable population on the basis of the following endpoint (evaluable population: it includes all enrolled patients who receive any amount of atezolizumab or bevacizumab, and have at least one post-baseline efficacy measurement):

- *Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1.*

The secondary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus bevacizumab in the evaluable population on the basis of the following endpoints:

- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause whichever occurs first, as determined by the investigator according to RECIST v1.1.
- Time to response (TTR), defined as the time from the start of the treatment to the first objective tumor response observed for patients who achieved CR or PR, as determined by the investigator according to RECIST v1.1.
- Disease control rate (DCR), defined as the proportion of patients who have a best overall response of CR or PR or stable disease (SD), as determined by the investigator according to RECIST v1.1

- Overall survival (OS) after enrollment, defined as the time from enrollment to death from any cause.
- Progression-free survival (PFS), defined as the time from enrollment to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1
- PFS rate at 6 and 12 months, defined as the proportion of patients who have not experienced disease progression or death from any cause at 6 months and 12 months, as determined by the investigator according to RECIST v1.1.
- OS rate at 1 and 2 years, defined as the proportion of patients who have not experienced death from any cause at 1 and 2 years.
- Expression of PD-L1 defined by the SP142 and SP263 assay.
- Analyses ORR, DOR, PFS,PFS rate at 12m,by investigator according to Modified RECIST V1.1(iRECIST)

Safety Objective

The safety objective for this study is to evaluate the safety of atezolizumab plus bevacizumab on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0
- Incidence of serious and non-serious immune-mediated adverse events related to atezolizumab treatment

Study Design

Description of Study

This is an open-label, single-arm, phase II, multicenter study designed to evaluated the efficacy and safety of atezolizumab in combination with bevacizumab in PD-L1-selected patients with Stage IIIB-IV Non-Squamous NSCLC harbored EGFR mutation after EGFR TKI therapy. Patients should have received at least one EGFR TKI and have disease progressed before enrollment.

This study will consist of a screening period (Day -28 to Day -1), a treatment period, a treatment discontinuation visit period (≤30 days after last dose) and a follow-up period. It is anticipated that this study will enroll about 60 patients at multiple sites in China.

At screening, tumor specimens (either fresh or archival) from each potentially eligible patient will be tested for PD-L1 expression by a central laboratory using an IHC assay. The patients will be tested T790M by blood or re-biospy tissue sample.

All eligible enrollees will receive atezolizumab by intravenous (IV) infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Bevacizumab will be administered by IV infusion at 15 mg/kg on Day 1 of each 21-day cycle. Patients will continue treatment until progressive disease, unacceptable toxicity, or death. Patients may continue treatment beyond radiographic progression by RECIST v1.1, provided they are experiencing clinical benefit as assessed by investigator (i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status (see below). Patients who temporarily or permanently discontinue either atezolizumab or bevacizumab may continue on single-agent therapy until disease progression (i.e., patients temporarily withdrawn from bevacizumab due to adverse events may continue atezolizumab monotherapy and vice versa).

Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudoprogression) with atezolizumab treatment, radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving atezolizumab will be permitted to continue atezolizumab if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data

- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Patients will undergo tumor assessments at baseline and every 6 weeks (±7days) for the first 36 weeks following Cycle 1, Day 1, regardless of dose delays. After 36 weeks, tumor assessment will be required every 9 weeks (±7days). Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab treated patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. Patients who discontinue treatment for reasons other than radiographic disease progression (e.g., toxicity) will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab treated patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first, even if patient starts another anti-cancer therapy after study treatment discontinuation, unless consent is withdrawn.

Number of Patients

Approximately *44* patients will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Male or female, Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Life expectancy ≥ 10 months
- Histologically or cytologically confirmed stage IIIB, IIIC, IV non-squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 8th edition)

  Patients with tumors of mixed histology (i.e., squamous and non-squamous) are eligible if the major histological component appears to be non-squamous.
- No prior treatment for Stage IIIB,IIIC, IV non-squamous NSCLC, with the following exceptions:

  Patients with a sensitizing mutation in the EGFR gene must have experienced disease progression (during or after treatment) or were intolerant to treatment with one or more EGFR TKIs, such as erlotinib, gefitinib, icotinib, afatinib, osimertinib, or another EGFR TKI appropriate for the treatment of EGFR-mutant NSCLC.

  Patients who have progressed on or were intolerant to first-line osimertinib or other third-generation EGFR TKIs are eligible.

  Patients who have progressed on or were intolerant to first- or second-generation EGFR TKIs, such as erlotinib, gefitinib, afatinib, dacomitinib, and who have no evidence of the EGFR T790M mutation after TKI therapy are eligible.

  Patients who have progressed on or were intolerant to first- or second-generation EGFR TKIs and who have evidence of the T790M mutation must have also progressed on or were intolerant to osimertinib to be eligible.
- TKIs approved for treatment of NSCLC discontinued ＞7 days prior to enrollment.
- Measurable disease per RECIST v1.1

  PD-L1 expression of ≥1% as documented through central testing of a representative tumor tissue specimen either from previously obtained archival tumor tissue or tissue obtained from a biopsy at screening (see Section 4.5.6 for details)
- ECOG Performance Status of 0-1

- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥90 g/L (9 g/dL)

    Patients may be transfused to meet this criterion.
  - AST, ALT, and alkaline phosphatase (ALP) $\leqslant 2.5 \times$ upper limit of normal (ULN), with the following exceptions:

    Patients with documented liver metastases: AST and ALT $\leqslant 5 \times$ ULN

    Patients with documented liver or bone metastases: ALP $\leqslant 5 \times$ULN
  - Bilirubin $\leqslant 1.5 \times$ULN with the following exception:

    Patients with known Gilbert disease: bilirubin level $\leqslant 3 \times$ULN
  - Creatinine clearance ≥50 mL/min (calculated using the Cockcroft-Gault formula)
  - Albumin ≥ 25 g/L (2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leqslant 1.5 \times$ULN

    For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- Negative HIV test at screening
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

  The HBV DNA test will be performed only for patients who have a positive total HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<$ 1% per year during the treatment period and for 5 months after the final dose of atezolizumab and/or 6 months after the last dose of bevacizumab, whichever is later. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of contraceptive methods with a failure rate of $<$ 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<$ 1% per year during the

treatment period and for 6 months after the final dose of bevacizumab. Men must refrain from donating sperm during this same period.

With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of bevacizumab to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases as determined by CT or MRI evaluation during screening and prior radiographic assessments

  Asymptomatic patients with treated CNS lesions are eligible, provided that all of the following criteria are met:

  - Measurable disease, per RECIST v1.1, must be present outside the CNS.
  - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
  - The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment.
  - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.
  - Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
  - There is no evidence of interim progression between completion of CNS-directed therapy and initiation of study treatment.

  Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain
- History of leptomeningeal disease
- Prior chemotherapy or other systemic therapy for stage IIIB/IV disease
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$12 mg/dL or corrected calcium $>$ ULN)
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis

(see Appendix 6 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

- Rash must cover < 10% of body surface area
- Disease is well controlled at baseline and requires only low-potency topical corticosteroids
- No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Active tuberculosis
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina

  Patients with known coronary artery disease, arrhythmias, congestive heart failure not meeting the above criteria must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. Baseline evaluation of left ventricular ejection fraction (LVEF) should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease or where low LVEF is suspected

  Patients with known LVEF < 40%
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- History of malignancy other than NSCLC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Prior allogeneic stem cell or solid organ transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Current treatment with anti-viral therapy for HBV
- Treatment with investigational therapy within 28 days prior to initiation of study treatment

- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti−CTLA-4, anti−PD-1, and anti−PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

  Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor approval has been obtained.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or bevacizumab formulations
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of atezolizumab, 6 months after the final dose of bevacizumab

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Inadequately controlled hypertension (defined as systolic blood pressure $>$150 mmHg and/or diastolic blood pressure $>$100 mmHg)

  Anti-hypertensive therapy to achieve these parameters is allowable.
- Prior history of hypertensive crisis or hypertensive encephalopathy
- Patients with a baseline ECG demonstrating a QTc > 460 msec
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment
- History of Grade ≥ 2 hemoptysis (defined as ≥ one-half teaspoon of bright red blood per episode (approximately 2.5ml)) within 1 month prior to enrollment
- Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation) Current or recent (within 10 days of initiation of study treatment) use of aspirin ($>$ 325 mg/day), clopidogrel ($>$ 75mg/day) or treatment with dipyramidole, ticlopidine, or cilostazol
- Current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that has not been stable for $>$ 2 weeks prior to enrollment

  The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been on a stable dose of anticoagulants for at least 2 weeks prior to enro

  llment

  Prophylactic anticoagulation for the patency of venous access devices is allowed, provided the activity of the agent results in an INR $<$ 1.5 × ULN and aPTT is within normal limits within 14 days prior to enrollment.

  Prophylactic use of low-molecular-weight heparin (i.e., enoxaparin 40 mg/day) is permitted.
- History of stroke or transient ischemic attack within 6 months prior to enrollment

- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to the first dose of bevacizumab
- History of abdominal or tracheosphageal fistula or gastrointestinal perforation within 6 months prior to enrollment
- History of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including but not limited to active peptic ulcer disease, diverticulitis,or colitis
- Clinical signs of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Serious, non-healing wound, active ulcer, or untreated bone fracture
- Proteinuria, as demonstrated by urinalysis or ＞1.0 g of protein in a 24-hour urine collection

  All patients with ≥ 2 ＋ protein on urinalysis at baseline must undergo a 24 hour urine collection and must demonstrate ≤ 1 g of protein in 24 hours.
- Clear tumor infiltration into the thoracic great vessels is seen on imaging
- Clear cavitation of pulmonary lesions is seen on imaging

End of Study

The end of this study is defined as the date when all the patients have either died, withdraw from study, are lost to follow up, or have been followed for 24 months since the last patient is enrolled, whichever occurs first.

Length of Study

The total length of the study, from first patients recruited to the end of the study, is expected to be approximately 3 years.

Investigational Medicinal Products

Test Product (Investigational Drug)

Atezolizumab (1200 mg IV) will be administered by IV infusion on Day 1 of each 21–day cycle.

Bevacizumab (15 mg/kg IV) will be administered by IV infusion on Day 1 of each 21-day

Statistical Methods

Primary Analysis

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab on the basis of the following endpoint:

- ORR defined as the proportion of patients with a CR or PR on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1. Patients not meeting these criteria, including patients without any post-baseline tumor assessment, will be excluded from the primary analysis.

Number and percentage of responders with corresponding Clopper-Pearson 90% and 95% confidence intervals will be provided.

The ORR will be the basis for decision whether the study would be continued when Stage 1 is completed. Refer to section 6.1 Determination of sample size for details.

Determination of Sample Size

The sample size estimation is based on having sufficient sample in the FAS population to show that the ORR is higher than 30%. Simon's minimax two-stage design will be used (Simon, 1989). The null hypothesis that the true ORR is at least 50% will be tested against a one-sided alternative.

The sample size calculation was based on a Simon two-stage design, and the primary end point was ORR (H0 = 30%, H1 = 50%). Two-sided alpha is set to be 0.1 and statistical power is set to be 80%.

19 fully evaluable patients will be included at the first stage. If there are 6 for fewer responders (CR/PR) in these 19 patients, enrollment will be stopped. Otherwise, additional 20 fully evaluable patients will be included in the second stage. Finally, if we have more than 16 patients in 39 patients have objective response, the endpoint is reached. Thus, considering a drop-out rate of 10%, a total number of 22 patients (if stops at the first stage) or 44 patients (if runs into the second stage) will need to be finally enrolled in this study.

Interim Analyses

One interim analysis is planned. The interim analysis will be performed for futility at the time of 19 patients completing ORR evaluation. According to preplanned stopping rules of Simon 2-stage design, further testing of Atezolizumab and Bevacizumab would be halted if the number of patients that respond in the first evaluable 19 patients (stage 1) is less or equal than 6. This study has probability of 66.6% terminate at the first stage.

When the study runs into the second stage, in the end of the study, if more than 16 patients out of 39 patients have responses, we can recommend this treatment in IIIB-IV Non-squamous NSCLC to go to the next step in the clinical trial phase, otherwise, the treatment is rejected.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
BFI	Brief Fatigue Inventory
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DOR	duration of response
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQol 5-Dimension Questionnaire, 5-level version
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IC	tumor-infiltrating immune cell
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRF	independent review facility
IV	intravenous
LPLV	last patient, last visit
MDASI	MD Anderson Symptom Inventory
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic
PRO	patient-reported outcome
Q3W	every 3 weeks
QLQ-C30	quality-of-life questionnaire for cancer
RBR	Research Biosample Repository
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors

TC	tumor cell
ULN	upper limit of normal
VAS	visual analogue scale

1. BACKGROUND

1.1 BACKGROUND ON LUNG CANCER

Lung cancer remains the leading cause of cancer deaths worldwide; it is the most common cancer in both men and women and accounted for approximately 13% of all new cancers in 2008 (Jemal et al. 2011). In 2012, it was estimated that there were 313,000 new cases of lung cancer and 268,000 lung cancer deaths in Europe (GLOBOCAN 2012). In the United States, there were an estimated 221,200 new cases of lung cancer and 158,040 lung cancer deaths in 2015 (Siegel et al. 2015).

Non–small cell lung cancer (NSCLC) is the predominant subtype of lung cancer, accounting for approximately 85% of all cases (Howlader et al. 2015). NSCLC can be divided into two major histologic types: adenocarcinoma and squamous cell carcinoma (Travis et al. 2011). Adenocarcinoma histology accounts for more than half of all NSCLC, while squamous cell histology accounts for approximately 25% of NSCLC (Langer et al. 2010). The remaining cases of NSCLC are represented by large cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and poorly differentiated histology.

The overall 5-year survival rate for advanced disease is 2%–4%, depending on geographic location (Cetin et al. 2011). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status, and a history of unintentional weight loss. More than half of the patients with NSCLC are diagnosed with distant disease, which directly contributes to poor survival prospects.

Genetic changes that have prognostic and/or predictive significance in NSCLC include mutations in the EGFR gene and rearrangement in the ALK gene. The rates of these mutations differ between squamous cell carcinoma and adenocarcinoma. For example, EGFR mutations have been reported in 10%–40% of patients with adenocarcinoma NSCLC but are infrequently observed in squamous NSCLC (Herbst et al. 2008). Rearrangement in the ALK gene is very rare in the squamous histology but observed in approximately 7% of patients with adenocarcinoma (Herbst et al. 2008; Langer et al. 2010).

1.2 FIRST-LINE TREATMENT FOR NON-SQUAMOUS NSCLC

1.2.1 Patients with an EGFR Mutation

Genotype-directed therapy has the potential to dramatically improve the balance of benefit and toxicity for selected patients with NSCLC (mainly non-squamous histology) characterized by alterations of driver oncogenes, including sensitizing EGFR mutations and ALK rearrangements. Randomized Phase III trials of the EGFR inhibitors gefitinib, erlotinib, and afatinib showed

significant improvement of PFS and objective response rate (ORR) compared with platinum doublet chemotherapy (Fukuoka et al. 2011; Rosell et al. 2012; Yang et al. 2012).

Despite the high initial response rate, patients treated with first line EGFR TKIs develop acquired resistance after 9–14 months. About half of these resistance conditions are caused by EGFR T790M mutation (8) and respond well to third-generation EGFR TKIs such as osimertinib targeting EGFR T790M (Janne PA et al 2015). Unfortunately, almost all patients treated with EGFR TKIs ultimately develop resistance to targeted therapies. Salvage treatment with platinum-based doublet chemotherapy gives response rate of ~10-20% only(Yang CJ et al 2016, Tseng Y-H et al 2016). Hence novel treatment strategies are urgently warranted.

1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma, the treatment of non−small cell lung cancer ,the treatment of Triple-Negative Breast Cancer and for small cell lung cancer.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.4 BACKGROUND ON BEVACIZUMAB

Vascular endothelial growth factor (VEGF) is the most important pro-angiogenic factor and a key regulator of physiological angiogenesis. It is also implicated in pathological angiogenesis such as that associated with tumor growth. Increased levels of VEGF have been found in most tumors examined to date, including tumors of the lung where, in addition, overexpression is associated with a poorer prognosis (Giatromanolaki 2001;Brattstrom et al. 2004).

AVASTIN® (bevacizumab) is a recombinant humanized monoclonal antibody to VEGF that recognizes all isoforms of VEGF. It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor environment. Additional anti-tumor activity may be on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).Bevacizumab has been tested in Phase II and III studies in a variety of solid tumors in combination with chemotherapy. Bevacizumab is registered in over 40 countries worldwide for the first-line treatment of metastatic colorectal

cancer (CRC) in combination with chemotherapy, as second-line CRC treatment, and first-line treatment of advanced NSCLC, metastatic breast cancer, advanced renal cell carcinoma (RCC), ovarian cancer, and glioblastoma (Reck and Crino 2009).

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, RCC, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-related causes consistent with an immunotherapeutic agent, including rash, influenza-like illness endocrinopathies, hepatitis or transaminitis, pneumonitis colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment or interruption of atezolizumab treatment.

Bevacizumab is a recombinant, humanized therapeutic antibody directed against VEGF. In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggest that in the tumor microenvironment, VEGF may reduce lymphocyte adhesion to vessel walls, thus contributing to decreased immune-cell recruitment to the tumor site (Bouzin et al. 2007).

Some immunosuppressive activities of VEGF can be reversed by inhibition of VEGF signaling. Thus, mice exposed to pathophysiologic levels of VEGF exhibited impaired dendritic cell function,

which could be restored by blockade of VEGFR2 (Huang et al. 2007). In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010).

Synergistic effects have also been observed in a clinical study of melanoma patients combining an immunomodulatory antibody (anti−CTLA-4; ipilimumab) and bevacizumab (Hodi et al. 2011). In this study of an immunomodulatory agent and bevacizumab, best overall responses were PR in 8 of 22 patients (35%) and stable disease in 6 of 22 patients (27%). All responses were durable for > 6 months. Therefore, the combined treatment with atezolizumab and bevacizumab may augment the antitumor immune response, resulting in improved and more durable clinical benefit. In phase III trial IMpower 150, stage IV NSCLC patients received atezolizumab plus carboplatin plus paclitaxel(ACP), bevacizumab plus carboplatin plus paclitaxel (BCP), or atezolizumab plus BCP(ABCP) every 3 weeks for four or six cycles, followed by maintenance therapy with atezolizumab, bevacizumab, or both. The ABCP followed by maintenance therapy group showed mPFS 8.3m, mOS 19.2m, ORR 63.5%.（Socinski MA et al. 2018）

The IMmotion 151 was the front-line, phase III trail of the atezolizumab combination with bevacizumab in RCC. The result of IMmotion 151 showed atezolizumab + bevacizumab demonstrated a clinically meaningful and statistically significant improvement in PFS (as evaluated by the investigators) versus sunitinib in the PD-L1+ population (HR = 0.74 [95% CI: 0.57, 0.96]). This significant improvement in HR translated into improved median PFS values of 11.2 months for atezolizumab + bevacizumab compared to 7.7 months for sunitinib. In the ITT population, median PFS was 11.2 versus 8.4 months, respectively (HR = 0.83 [95% CI: 0.70, 0.97]).(Brian I Rini et al. 2019)

In the analysis of safety data from Study GO30140 (clinical cutoff date of 7 June 2017) in 20 patients with HCC (median treatment duration of 2.8 months [range: 1-11 months]), the combination of atezolizumab +bevacizumab was generally safe and well tolerated; no new safety signals related to the combination therapy were identified beyond the established safety profile for each individual agent. There is a global phase III YO40245 is on going, which evaluate the efficacy and safety of atezolizumab + bevacizumab versus sorafenib in patients with locally advanced or metastatic HCC who have received no prior systemic treatment.

Several steps will be taken to ensure the safety of participants in ML41256. First, administration of atezolizumab and bevacizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies (Section 4.3). Second, identified and potential risks associated with study treatment will continue to be closely monitored throughout this study (Section 5.1.1 and Section 5.1.2). Third, the study contains protocol-specified study treatment interruption criteria designed to ensure safety.

This trial will enroll patients with stage IIIB/IV Non-Squamous Non-Small Cell Lung Cancer (NSCLC) harbored EGFR mutation after treatment failure of EGFR TKI. All patients will be selected on the basis of PD-L1 expression ⩾ 1%. Given the relatively poor prognosis and limited

treatment options for these patients, this population is considered appropriate for trials of novel therapeutic candidates.

With the above safety precautions in place, combined with the efficacy, safety evidence from previous studies, the current assessment of the expected benefits of atezolizumab + bevacizumab combination therapy outweigh the risks in this study, especially given the potential of the combination in this setting.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of atezolizumab in combination with bevacizumab in patients with stage IIIB/IV Non-Squamous Non-Small Cell Lung Cancer (NSCLC) harbored EGFR mutation after treatment failure of EGFR TKI. All patients will be selected on the basis of PD-L1 expression $\geqslant$ 1% on tumor cells (TC) and/or immune cells (ICs) using a centrally performed immunohistochemistry (IHC) test. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of atezolizumab and bevacizumab assigned to patients as part of this study.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus bevacizumab in the evaluable population on the basis of the following endpoint (evaluable population: it includes all enrolled patients who receive any amount of atezolizumab or bevacizumab, and have at least one post-baseline efficacy measurement):

- Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions $\geqslant$4 weeks apart, as determined by the investigator according to RECIST v1.1.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus bevacizumab in the evaluable population on the basis of the following endpoints:

- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause whichever occurs first, as determined by the investigator according to RECIST v1.1.
- Time to response (TTR), defined as the time from the start of the treatment to the first objective tumor response observed for patients who achieved CR or PR, as determined by the investigator according to RECIST v1.1.
- Disease control rate (DCR), defined as the proportion of patients who have a best overall response of CR or PR or stable disease (SD), as determined by the investigator according to RECIST v1.1

- Overall survival (OS) after enrollment, defined as the time from enrollment to death from any cause.
- Progression-free survival (PFS), defined as the time from enrollment to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1
- PFS rate at 6 and 12 months, defined as the proportion of patients who have not experienced disease progression or death from any cause at 6 months and 12 months, as determined by the investigator according to RECIST v1.1.
- OS rate at 1 and 2 years, defined as the proportion of patients who have not experienced death from any cause at 1 and 2 years.
- Expression of PD-L1 defined by the SP142 and SP263 assay.
- Analyses ORR, DOR, PFS,PFS rate at 12m,by investigator according to Modified RECIST V1.1(iRECIST)

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of atezolizumab plus bevacizumab on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0
- Incidence of serious and non-serious immune-mediated adverse events related to atezolizumab treatment

2.3 HEALTH STATUS UTILITY OBJECTIVE

The patient-reported outcome (PRO) objectives are to evaluate the impact of atezolizumab plus bevacizumab from the patient's perspective, on the basis of the following endpoints:

- PROs of lung cancer symptoms, patient functioning, and health-related quality of life (HRQoL) as measured by the European Organization for Research and treatment of Cancer (EORTC) Quality-of-life Questionnaire Core 30 (QLQ C30) and its Lung Cancer Module (QLQ LC13).

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

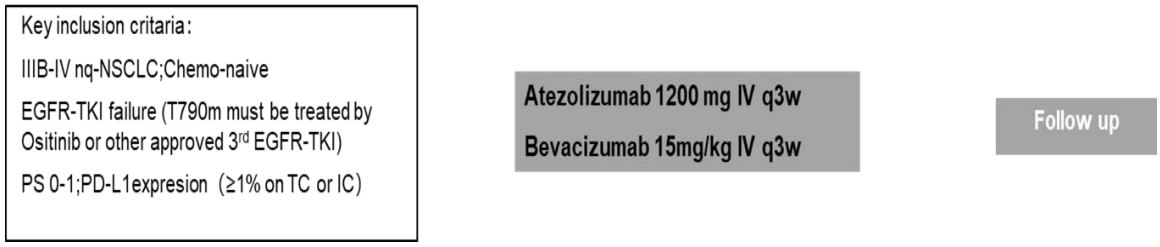
This is an open-label, single-arm, phase II, multicenter study designed to evaluated the efficacy and safety of atezolizumab in combination with bevacizumab in PD-L1-selected patients with Stage IIIB-IV Non-Squamous NSCLC harbored EGFR mutation after EGFR TKI therapy. Patients should have received at least one EGFR TKI and have disease progressed before enrollment.

This study will consist of a screening period (Day -28 to Day -1), a treatment period, a treatment discontinuation visit period (≤30 days after last dose) and a follow-up period. It is anticipated that this study will enroll about 60 patients at multiple sites in China.

At screening, tumor specimens (either fresh or archival) from each potentially eligible patient will be tested for PD-L1 expression by a central laboratory using an IHC assay. The specimens will be tested PD-L1 expression by Ventana SP142 and SP 263.The patients will be tested T790M by blood or re-biospy tissue sample. Tumor EGFR mutation status will also be confirmed by central laboratory using either tissue or blood samples.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



IV = intravenous; NSCLC = non–small cell lung cancer;

All eligible enrollees will receive atezolizumab by intravenous (IV) infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Bevacizumab will be administered by IV infusion at 15 mg/kg on Day 1 of each 21-day cycle. Patients will continue treatment until progressive disease, unacceptable toxicity, or death. Patients may continue treatment beyond radiographic progression by RECIST v1.1, provided they are experiencing clinical benefit as assessed by investigator (i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status (see below). Patients who temporarily or permanently discontinue either atezolizumab or bevacizumab may continue on single-agent therapy until disease progression (i.e., patients temporarily withdrawn from bevacizumab due to adverse effects may continue atezolizumab monotherapy and vice versa). Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudoprogression) with atezolizumab treatment, radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving atezolizumab will be permitted to continue atezolizumab if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease

- Absence of decline in ECOG Performance Status that can be attributed to disease progression

- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Patients will undergo tumor assessments at baseline and every 6 weeks (±7days) for the first 36 weeks following Cycle 1, Day 1, regardless of dose delays. After 36 weeks, tumor assessment will be required every 9 weeks (±7days). Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab treated patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. Patients who discontinue treatment for reasons other than radiographic disease progression (e.g., toxicity) will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab treated patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first, even if patient starts another anti-cancer therapy after study treatment discontinuation, unless consent is withdrawn.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when all the patients have either died, withdraw from study, are lost to follow up, or have been followed for 24 months since the last patient is enrolled, whichever occurs first. In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no DLTs were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

3.3.2 Rationale for bevacizumab Dose and Schedule

Bevacizumab will be administered at a fixed dose of 15 mg/kg Q3W on Day 1 of each 21-day cycle which is the approved dosage for bevacizumab. This dose schedule aligns with the atezolizumab dose schedule highlighted above and is the dose used in combination with atezolizumab in Study GO30140. In this study, the combination of atezolizumab and

bevacizumab was generally safe and well tolerated and no new safety signals related to the combination therapy were identified beyond the established safety profile for each individual agent.

3.3.3 Rationale for Patient Population

This study will enroll patients with advanced NSCLC who have PD-L1 expression defined as PD-L1 ⩾1% expression, determined by SP142 and SP 263 IHC assay .

Phase II trial BIRCH was designed to assess the efficacy and safety of single-agent atezolizumab in patients with PD-L1–selected stage IIIB/IV NSCLC, across multiple lines of therapy. In the EGFR mutation subgroup analyses, ORR 23%, PFS 5.5m 95%CI (2.6-8.3), OS 20.1m 95%CI (NE-NE). The safetyprofile was similar across cohorts and consistent with previous atezolizumab monotherapy trials (Solange Peters et al 2017).

PD-L1 prevalence in IMpower150 using the SP142 and SP263 IHC assays was similar and substantial overlap was observed. The majority (~76%) of the PD-L1 positive patients by SP142 were also positive by SP263 and vice versa. A similar percentage of patients was positive by one assay but not another (13% for SP142 and 14% for SP263) (Kowanetz M et al. 2018).

In one retrospective study explore the immunophenotypic signature of patients with de novo resistance to EGFR-TKIs, and the results suggested that this population may be benefit from programmed death 1 (PD-1) blockade therapy. It suggests the existence of immune mechanisms of resistance to targeted therapy（ShanSu et al. 2018）.

In IMpower 150, EGFR+/ALK+ subgroup, atezolizumab+bevzcizumab+ carboplatin + paclitaxel mPFS 9.7m, bevacizumab+CP 6.1m,HR 0.59(95% CI 0.37.0.94).(Martin Reck et al 2019)

Inhibition of PD-L1/PD-1 signaling has been shown to produce durable responses in some patients, and expression of PD-L1 correlates with response to therapy in several tumor types (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016).

Data from Study PCD4989g suggest that tumor PD-L1 status as determined by IHC correlates with response to atezolizumab in patients with NSCLC. In a Phase II study (GO28753), patients with NSCLC whose tumors expressed PD-L1 (TC1/2/3 or IC1/2/3) had an improvement in OS when treated with atezolizumab compared with docetaxel in the second- or third-line setting. These data provide a rationale for evaluating the efficacy of atezolizumab in patients with advanced NSCLC selected on the basis of tumor PD-L1 expression.

3.3.4 Rationale for Open-Label Study

The primary objective of this study is to assess the efficacy and safety profile of atezolizumab + bevacizumab in a non-comparative fashion. The study will have an open-label, single-arm and non-randomized design.

3.3.5 Rationale for Objective response rate as Primary Endpoint

In this study, the primary efficacy endpoint will be investigator confirmed objective response rate. Phase II studies are limited because they lack a control arm. Objective response rate directly measures the efficacy of initial therapy, unaffected by treatment at progression.

3.3.6 Rationale for Atezolizumab Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response has been termed pseudoprogression (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed ICs and no viable cancer cells. Because of the potential for a response after pseudoprogression, this study will allow patients to continue treatment after apparent radiographic progression per RECIST v1.1, provided the benefit-risk ratio is judged to be favorable by the investigator (see criteria in Section 3.1.). Patients should be discontinued for unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1.1 for details).

3.3.7 Rationale for the Use of Modified Response Criteria

Increasing clinical experience indicates that traditional response criteria (e.g., RECIST v1.1) may not adequately assess the activity of immunotherapeutic agents because initial radiographic evidence of disease progression does not necessarily reflect therapeutic failure. Patients can experience a response in the presence of new lesions or after an increase in tumor burden. Thus, this study will employ tumor response criteria modified for unconventional tumor change patterns associated with cancer immunotherapy: modified RECIST v1.1 for immune-based therapeutics (iRECIST; Seymour et al. 2017; see Appendix 3).

iRECIST was developed by the RECIST working group in an effort to create a common set of criteria that the cancer immunotherapy field could apply to clinical trials (Seymour et al. 2017).

iRECIST account for responses that may occur following transient radiographic progression caused by immune-cell infiltration in tumors (leading to a transient increase in the size of existing lesions, including those that were previously undetectable and consequently appear as new lesions). iRECIST rely on collection of tumor assessment data after initial disease progression per RECIST v1.1.

Given the proposed immunomodulatory mechanism of action of atezolizumab and the possibility of observing delayed responses, exploratory efficacy endpoints will include analyses based on iRECIST. These analyses will allow for evaluation of iRECIST as improved measures of the efficacy of immunotherapies relative to standard RECIST v1.1(see Appendix 2).

3.3.8 Rationale for Biomarker Assessments

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 and anti-PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In the current study, archival or baseline tumor specimens will be collected from patients and tested for PD-L1 expression by a central laboratory during the screening period. Only patients with tumor PD-L1 expression categorized as ⩾ 1% by SP142 and SP 263 assay , will be enrolled in the study.

The data form IMpower 150 showed the EGFR mutation patients will get benefit from atezolizumab+bevacizumab + CP, The type of EGFR mutation and T790M will confirm duiring screening.

3.3.9 Rationale for Patient-Reported Outcome Assessments

PROs provide an understanding of the impact a treatment has on a patient. The QLQ-C30 is a validated instrument that has been widely used in assessing quality of life in patients with cancer. The core instrument assesses global health status/quality of life, functions (physical, role, emotional, cognitive, and social), and general cancer symptoms. The EORTC QLQ-LC13 is a lung cancer-specific module that can provide information on disease and treatment-related symptoms and functional interference that are specific to this patient population.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 44 patients with PD-L1-expression ⩾1%,Stage IIIB-IV Non-Squamous NSCLC harbored EGFR mutation after EGFR TKI therapy will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Male or female, Age ⩾ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Life expectancy ⩾ 10 months
- Histologically or cytologically confirmed stage IIIB - IV non-squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 8th edition)

  Patients with tumors of mixed histology (i.e., squamous and non-squamous) are eligible if the major histological component appears to be non-squamous.
- No prior treatment for Stage IIIB or IV non-squamous NSCLC, with the following exceptions:

  Patients with a sensitizing mutation in the EGFR gene must have experienced disease progression (during or after treatment) or were intolerant to treatment with one or more EGFR TKIs, such as erlotinib, gefitinib, icotinib, afatinib, osimertinib, or another EGFR TKI appropriate for the treatment of EGFR-mutant NSCLC.

  Patients who have progressed on or were intolerant to first-line osimertinib or other third-generation EGFR TKIs are eligible.

  Patients who have progressed on or were intolerant to first- or second-generation EGFR TKIs, such as erlotinib, gefitinib, afatinib, dacomitinib, and who have no evidence of the EGFR T790M mutation after TKI therapy are eligible.

Patients who have progressed on or were intolerant to first- or second-generation EGFR TKIs and who have evidence of the T790M mutation must have also progressed on or were intolerant to osimertinib to be eligible.

- TKIs approved for treatment of NSCLC discontinued $>$7 days prior to enrollment.
- Measurable disease per RECIST v1.1
- PD-L1 expression of $\geqslant$1% as documented through central testing of a representative tumor tissue specimen either from previously obtained archival tumor tissue or tissue obtained from a biopsy at screening

  Archival or newly collected tumor tissue sample obtained at baseline for determination of PD-L1 expression and EGFR mutation test.

  Optional biopsy at screening is the preferred method to collected the tumor specimens for PD-L1 expression at screening and T790M mutation.

  A representative FFPE tumor specimen from in a paraffin block (preferred) or at least 10 slides containing unstained, freshly cut, serial sections must be submitted, 5 slides for PD-L1 testing (SP 263 and SP142),5 slides for T790M test. The associated pathology report must be submitted prior to study enrollment. If the patient onlyhave archival tumor tissue sample, 5 slides must be submietted for PD-L1 expression test (SP 263 and SP142). If less than 5 slides are available, the patient may still be eligible for the study, after Medical Monitor approval has been obtained, The slides is preferred to do PD-L1 expression test with SP263 assay. PD-L1 expression of $\geqslant$1%, either SP142 or SP263,is eligible.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

  If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria. (see Section 4.5.6 for details)
- ECOG Performance Status of 0-1
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin $\geq$90 g/L (9 g/dL)

    Patients may be transfused to meet this criterion.
  - AST, ALT, and alkaline phosphatase (ALP) $\leqslant$ 2.5 $\times$ upper limit of normal (ULN), with the following exceptions:

    Patients with documented liver metastases: AST and ALT $\leqslant 5 \times$ ULN

    Patients with documented liver or bone metastases: ALP $\leqslant 5 \times$ULN
  - Bilirubin $\leqslant 1.5 \times$ULN with the following exception:

    Patients with known Gilbert disease: bilirubin level $\leqslant 3 \times$ULN
  - Creatinine clearance $\geqslant$50 mL/min (calculated using the Cockcroft-Gault formula)
  - Albumin $\geq$ 25 g/L (2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leqslant 1.5 \times$ULN

    For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- Negative HIV test at screening

- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

  The HBV DNA test will be performed only for patients who have a positive total HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<$ 1% per year during the treatment period and for 5 months after the final dose of atezolizumab and/or 6 months after the last dose of bevacizumab, whichever is later. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geqslant$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of contraceptive methods with a failure rate of $<$ 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<$ 1% per year during the treatment period and for 6 months after the final dose of bevacizumab. Men must refrain from donating sperm during this same period.

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of bevacizumab to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases as determined by CT or MRI evaluation during screening and prior radiographic assessments

  Asymptomatic patients with treated CNS lesions are eligible, provided that all of the following criteria are met:

  - Measurable disease, per RECIST v1.1, must be present outside the CNS.
  - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
  - The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to

initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment.

- The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.
- Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
- There is no evidence of interim progression between completion of CNS-directed therapy and initiation of study treatment.

Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain

- History of leptomeningeal disease
- Prior chemotherapy or other systemic therapy for stage IIIB/IV disease
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium >12 mg/dL or corrected calcium > ULN)
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 6 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  - Rash must cover < 10% of body surface area
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Active tuberculosis

- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina

    Patients with known coronary artery disease, arrhythmias, congestive heart failure not meeting the above criteria must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. Baseline evaluation of left ventricular ejection fraction (LVEF) should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease or where low LVEF is suspected

    Patients with known LVEF < 40%
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- History of malignancy other than NSCLC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>$90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

    Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Prior allogeneic stem cell or solid organ transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Current treatment with anti-viral therapy for HBV
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

    Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor approval has been obtained.

    Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or bevacizumab formulations

- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of atezolizumab, 6 months after the final dose of bevacizumab

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Inadequately controlled hypertension (defined as systolic blood pressure ＞150 mmHg and/or diastolic blood pressure ＞100 mmHg)

  Anti-hypertensive therapy to achieve these parameters is allowable.
- Prior history of hypertensive crisis or hypertensive encephalopathy
- Patients with a baseline ECG demonstrating a QTc > 460 msec
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment
- History of Grade ⩾ 2 hemoptysis (defined as ⩾ one-half teaspoon of bright red blood per episode(approximately 2.5ml)) within 1 month prior to enrollment
- Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation) Current or recent (within 10 days of initiation of study treatment) use of aspirin (＞ 325 mg/day), clopidogrel (＞ 75mg/day) or treatment with dipyramidole, ticlopidine, or cilostazol
- Current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that has not been stable for ＞ 2 weeks prior to enrollment

  The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been on a stable dose of anticoagulants for at least 2 weeks prior to enrollment

  Prophylactic anticoagulation for the patency of venous access devices is allowed, provided the activity of the agent results in an INR ＜ 1.5 × ULN and aPTT is within normal limits within 14 days prior to enrollment.

  Prophylactic use of low-molecular-weight heparin (i.e., enoxaparin 40 mg/day) is permitted.
- History of stroke or transient ischemic attack within 6 months prior to enrollment
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to the first dose of bevacizumab
- History of abdominal or tracheosphageal fistula or gastrointestinal perforation within 6 months prior to enrollment
- History of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including but not limited to active peptic ulcer disease, diverticulitis,or colitis
- Clinical signs of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Serious, non-healing wound, active ulcer, or untreated bone fracture
- Proteinuria, as demonstrated by urinalysis or ＞1.0 g of protein in a 24-hour urine collection

  All patients with ⩾ 2 ＋ protein on urinalysis at baseline must undergo a 24 hour urine collection and must demonstrate ⩽ 1 g of protein in 24 hours.
- Clear tumor infiltration into the thoracic great vessels is seen on imaging
- Clear cavitation of pulmonary lesions is seen on imaging

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label (unblinded) study in which all subjects will be assigned to receive the same study treatment, i.e., atezolizumab + bevacizumab.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is atezolizumab and bevacizumab.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab

The atezolizumab Drug Product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

4.3.1.2 Bevacizumab

Bevacizumab will be supplied by the Sponsor as a clear to slightly opalescent, colorless to pale brown, sterile liquid for IV infusion in single-use vials, which are preservative-free. Bevacizumab will be supplied in 20-mL glass vials with a 16-mL fill (400 mg, 25 mg/mL).

For information on the formulation and handling of bevacizumab, see the pharmacy manual, the Bevacizumab / Avastin® Investigator’s Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimen (atezolizumab + bevacizumab) is summarized in Section 3.1. Atezolizumab will be administered first, followed by bevacizumab, with a minimum of 5 minutes between dosing.

Any dose modification(s) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 8, Appendix 9 and Appendix 10.

4.3.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1.1 for details).

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 7. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (± 15) minutes. • If clinically indicated, vital signs should be measured every 15 (± 5) minutes during the infusion and at 30 (± 10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (± 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (± 10) minutes after the infusion.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 8 and Appendix 11.

Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4.

No dose modification for atezolizumab is allowed.

4.3.2.2 Bevacizumab

Bevacizumab will be administered by IV infusion at a fixed dose of 15 mg/kg on Day 1 of each 21-day Cycle.

Administration of bevacizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 7

Bevacizumab infusions will be administered per the instructions outlined in Table 2. Guidelines for preparation,administration,disposal, dosage modification and treatment interruption or discontinuation because of toxicities are provided in Appendix 10 and Appendix 11 .

Table 2 Administration of First and Subsequent Bevacizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the Bevacizumab infusion •Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Bevacizumab should be infused over 90 (± 15) minutes. • Vital signs should be at the end of infusion and 2 (± 1) hours after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Bevacizumab should be infused over 60 (± 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 90 (± 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (± 15) minutes thereafter. • Vital signs should be at the end of infusion and 2 (± 1) hours after the infusion

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab, bevacizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor using appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Atezolizumab

Currently, the Sponsor does not have any plans to provide Roche IMPs (atezolizumab and bevacizumab) or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing atezolizumab and bevacizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal

Product, available at the following website:
http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated influenza vaccinations
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  After completion of Cycle 1, palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy. Treatment with bevacizumab should be suspended during palliative radiotherapy.
- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment after Medical Monitor approval has been obtained. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard 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 (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 7).

4.4.2 Cautionary Therapy

4.4.2.1 Corticosteroids and TNF-α Inhibitors for Atezolizumab-Treated Patients

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 9 for details).

4.4.2.2 Cautionary Therapy Specific to Bevacizumab

Anticoagulants: The use of full-dose oral or parenteral anticoagulants is permitted during the trial as long as the INR and/or aPTT is within therapeutic limits (according to the medical standard of the treating institution). Prophylactic use of anticoagulation at baseline and during study treatment is permitted. Bevacizumab or anticoagulation treatment will be stopped if there is any evidence of tumor invasion into major blood vessels on any CT scan.

Aspirin: Owing to a possible risk of bleeding during treatment with bevacizumab, patients should not take more than 325 mg of aspirin daily (or more than 75 mg of clopidogrel daily, or equivalent), at least until discontinuation of bevacizumab treatment.

4.4.2.3 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.3) may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section 4.4.1 for details).
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the final dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. A history of pleural or pericardial effusion or ascites requiring intervention should be entered in the medical history. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Cancer history will include an assessment of tumor histology.

Demographic data will include age, sex, and self-reported race/ethnicity .

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature.

Atezolizumab will be administered first, followed by bevacizumab, with a minimum of 5 minutes between dosing. Vital signs should be measured within 60 minutes prior to each atezolizumab infusion and, if clinically indicated, during or after the infusion. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1)

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline and every 6 weeks (±7days) for the first 36 weeks following Cycle 1, Day 1, regardless of dose delays. After 36 weeks, tumor assessment will be required every 9 weeks (±7days). Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1 or (for patients who continue treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1 for details).

In the absence of disease progression, tumor assessments should continue regardless of whether patients start new anti-cancer therapy, until consent is withdrawn, death, or the study is terminated by the Sponsor, whichever occurs first. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening.

Screening assessments must include computed tomography (CT) scans (with oral or IV contrast unless contraindicated) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a noncontrast CT scan of the chest may be performed and MRI scans of the abdomen and pelvis should be performed. If a CT scan with contrast is not contraindicated, it is mandatory to obtain a dual-phase imaging of the liver, and every effort should be made to time the contrast administration so that high-quality arterial-phase imaging is obtained throughout the liver on the first run, and high-quality portal venous-phase imaging is obtained throughout the liver on the second run. A CT scan with contrast or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Patients with a history of irradiated brain metastases and without measurable brain lesion at screening are not required to undergo imaging brain scans at subsequent tumor evaluations, unless scans are clinically indicated. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan. All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). Response will be assessed by the investigator using RECIST v1.1 and iRECIST (see Appendix 3，Appendix 4). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle. At the investigator’s discretion, CT scans should be repeated at any time if progressive disease is suspected.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)

- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, and LDH
- Coagulation: INR, and aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- HIV serology
- HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Archival or newly collected tumor tissue sample obtained at baseline for determination of PD-L1 expression and EGFR mutation test.

  Optional biopsy at screening is the preferred method to collected the tumor specimens for PD-L1 expression at screening and T790M mutation.

  A representative FFPE tumor specimen from in a paraffin block (preferred) or at least 10 slides containing unstained, freshly cut, serial sections must be submitted 5 slides for PD-L1 testing (SP 263 and SP142),5 slides for T790M test. The associated pathology report must be submitted prior to study enrollment. If the patient only

  have archival tumor tissue sample, 5 slides must be submietted for PD-L1 expression test. If less than 5 slides are available , the patient may still be eligible for the study, after Medical Monitor approval has been obtained, The slides is preferred to do PD-L1 expression test with SP263 assay. PD-L1 expression of ⩾1%, either SP142 or SP263,is eligible. The high expression define as TC3 or IC3 for SP142 or TC ⩾50% for SP263.

Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria.

The Informed Consent Form will contain a separate section that addresses this optional screening biopsy. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF

- Optional biopsy is the preferred method to collected the tumor specimens for T790M testing at screening(5 slides, mentioned above), If the tumor tissue is not enough, blood 5 ml sample for EGFR and T790M mutation test.
- Patiens must submit the EGFR mutated pathology report (original or photocopy), If the report is not avealiable, archival tumor tissue is preferred to do EGFR mutation confirm testing. The EGFR mutated pathology report is the final reference for EGFR-mutation status.

4.5.7 Electrocardiograms

An ECG is required at screening and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.8 Patient-Reported Outcomes

To more fully characterize the clinical profile of atezolizumab, PRO data will be obtained through use of the following instruments: European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaires for cancer (EORTC QLQ-C30) and lung cancer (EORTC QLQ-LC13) The questionnaires will be translated as appropriate into the local language.

To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety

by the patient before the patient receives any information on disease status and prior to the performance of non-PRO assessments and the administration of study treatment.

Patients will complete paper versions of the EORTC QLQ-C30, EORTC QLQ-LC13 questionnaires at the clinical site on Cycle 1, Day 1 and every cycle thereafter until the treatment discontinuation visit (included); after treatment discontinuation or disease progression, whichever comes first, questionnaires will be completed every 3 months (for 1 year), unless the patient withdraws consent or the Sponsor terminates the study. Paper PRO questionnaires will be provided and collected by site staff.

Study personnel should review all questionnaires for completeness before a patient leaves the investigational site. Patients for whom PRO questionnaires are not available in their native language or who are deemed by the investigator incapable of completing their PRO assessment may be exempt from all PRO assessments. In the event that PRO questionnaires are not administered, site staff will record the reasons for why the measure was not completed in the eCRF.

The Sponsor will not derive adverse events reports from PRO data

4.5.8.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) (see Appendix 5). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The EORTC QLQ-C30 module takes approximately 10 minutes to complete.

4.5.8.2 EORTC QLQ-LC13

The EORTC QLQ-LC13 is a modular supplement to the EORTC quality-of-life questionnaire for use in lung cancer (see Appendix 4). This module incorporates one multiple-item scale to assess dyspnea and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. The QLQ-LC13 module takes approximately 5 minutes to complete.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event

- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details)

Patients who discontinue one of the two drugs comprising the study treatment—either transiently or permanently—for adverse event or other reason (i.e., discontinue atezolizumab but remain on bevacizumab, or discontinue bevacizumab but remain on atezolizumab) may continue on the remaining study drug until disease progression if the investigator deems that the patient is still deriving clinical benefit.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit ≤ 30 days after the final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments and PRO assessments as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study).

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient’s safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with atezolizumab and bevacizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Section 5.1.1{ and Section 5.1.2}).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab and bevacizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or

discontinuation, are provided in Appendix 8, Appendix 9, and Appendix 10. Refer to Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Refer to Appendix 9 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: GI perforations, hemorrhage, arterial thromboembolic events, fistulae, wound-healing complications, hypertension, venous thromboembolism, and proteinuria, etc.

Refer to the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for Bevacizumab.

5.1.3 Risks Associated with Atezolimab with Bevacizumab

The risk of overlapping toxicities between atezolizumab and bevacizumab is anticipated to be minimal based on the known safety profile of each agent and available data from clinical studies. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hemorrhage, hypothyroidism, and GI toxicity) may be ambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with bevacizumab could be exacerbated by the immunostimulatory activity of atezolizumab.

Toxicities should initially be managed according to the recommendations in Appendix 8 Appendix 9 and Appendix 10 with dose holds and modifications (if applicable) applied to the component of the study treatment judged to be the primary cause. If individual component causality for the toxicity cannot be adequately determined, then the most conservative management recommendation should be applied (in the most recent version of the Atezolizumab and Bevacizumab Investigator's Brochures).

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment.
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

Adverse Events of Special Interest for Atezolizumab

Adverse events of special interest for atezolizumab are as follows:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness.
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia

- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

Adverse Events of Special Interest for Bevacizumab

- Grade ≥ 3 hypertension
- Grade ≥ 3 proteinuria
- Any grade GI perforation, abscesses, or fistulae
- Grade ≥ 3 wound-healing complication
- Hemorrhage

- Any grade CNS bleeding

- Grade ≥2 hemoptysis

- Other Grade ≥ 3 hemorrhagic event

- Any grade arterial thromboembolic event
- Grade ≥ 3 venous thromboembolic event
- Any grade posterior reversible encephalopathy syndrome (PRES; also known as reversible posterior leukoencephalopathy syndrome or RPLS)
- Grade ≥ 3 CHF /left ventricular systolic dysfunction
- Grade ≥ 2 non-GI fistula or abscess

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be

reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (V5.0) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE v 5.0, which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 4):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 4 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions and Cytokine-Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and cytokine-release syndrome (CRS). While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "cytokine-release syndrome") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Cases of late-onset CRS should be reported as "cytokine-release syndrome" on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 9.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.

- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3 \times$ ULN) in combination with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $> 3 \times$ ULN value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the

Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of NSCLC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of NSCLC

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF

5.3.5.13 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see

Section 5.4.2). A report should be downloaded from EDC system and sent the report to Sponsor. For atezolizumab and bevacizumab adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with atezolizumab and bevacizumab, regardless of whether they result in an adverse event, should be reported to the Sponsor within 30 calendar days and recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)

- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All sites

Medical Monitor{Roche Medical Responsible}: [redacted] (Primary)

Telephone No.: [redacted]

Mobile Telephone No. [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the final dose of study treatment or until initiation of new

systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF on the electronic data capture (EDC) system, generate, and submit the report to Sponsor.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered in the EDC system.

Instructions for reporting serious adverse events that occur after the reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 momths after the final dose of study treatment. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. A report should be downloaded from EDC system and sent the report to Sponsor. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the final dose of study treatment. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the

pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A report should be downloaded from EDC system and sent the report to Sponsor.

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A report should be downloaded from EDC system and sent the report to Sponsor.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional

case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 90 days) after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event/adverse event of special interest that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. A report should be downloaded from EDC system and sent the report to Sponsor. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Atezolizumab Investigator's Brochure
- Bevacizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN.

This is an open-label, single-arm study. A Simon’s Minimax two-stage design will be used (Simon. 1989).

Parameters estimates and relevant summary statistics will be reported where appropriate. For continuous variables, summary statistics will include number of subjects, mean, median, standard deviation, minimum and maximum. Categorical endpoints will be summarized using number of

subjects, frequency, and percentages. Missing data will not be imputed. Data analysis will be performed in SAS 9.4.

Analysis Populations

This study will include the following analysis populations:

- Full Analysis Set (FAS) population: defined as all enrolled patients who receive any amount of study treatment and evaluable for efficacy endpoints. The efficacy analyses will be performed on the FAS population.
- Safety population: defined as all enrolled patients who receive any amount at least one dose of any study treatment. The safety analysis will be performed on the safety population.
- ITT population: defined as all enrolled patients regardless of whether they receive any assigned study drug. The ITT population will be used for other analyses (Demography, Baseline Characteristics, etc.).

A per-protocol population will not be defined for this study. However, all major deviations (at study entry and on study) will be summarized and reported.

6.1 DETERMINATION OF SAMPLE SIZE

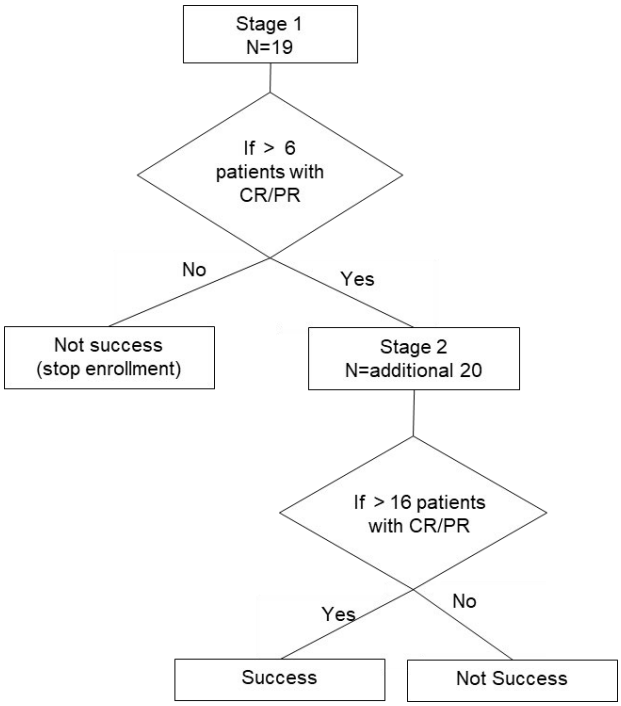
The sample size estimation is based on having sufficient sample in the FAS population to show that the ORR is higher than 30%. Simon's minimax two-stage design will be used (Simon, 1989). The null hypothesis that the true ORR is at least 50% will be tested against a one-sided alternative.

The sample size calculation was based on a Simon two-stage design, and the primary end point was ORR (H0 = 30%, H1 = 50%). Two-sided alpha is set to be 0.1 and statistical power is set to be 80%.

19 fully evaluable patients will be included at the first stage. If there are 6 for fewer responders (CR/PR) in these 19 patients, enrollment will be stopped. Otherwise, additional 20 fully evaluable patients will be included in the second stage. Finally, if we have more than 16 patients in 39 patients have objective response, the endpoint is reached. Thus, considering a drop-out rate of 10%, a total number of 22 patients (if stops at the first stage) or 44 patients (if runs into the second stage) will need to be finally enrolled in this study.

Figure 2 presents an overview of the sample size allocation.

Figure 2 **Sample size allocation**



6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study drug administration, and discontinuation from the study will be summarized. The reasons for study drug discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

List the variables that will be summarized to describe the study population and Demographic and baseline characteristics (including age, sex, medical history and prior treatment, etc.) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented descriptively using the ITT population.

6.4 EFFICACY ANALYSES

The analysis population for the efficacy analyses will consist of all enrolled patients who receive any amount of study treatment and evaluable for efficacy endpoints. ORR and DCR will be analyzed using all enrolled patients who have measureable disease at baseline. DOR will be assessed in patients who have an objective response.

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab on the basis of the following endpoint:

- ORR defined as the proportion of patients with a CR or PR on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1. Patients not

meeting these criteria, including patients without any post-baseline tumor assessment, will be excluded from the primary analysis.

Number and percentage of responders with corresponding Clopper-Pearson 90% and 95% confidence intervals will be provided.

The ORR will be the basis for decision whether the study would be continued when Stage 1 is completed. Refer to section 6.1 Determination of sample size for details.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Duration of Response

DOR will be assessed in patients who had an objective response as determined by the investigator using RECIST v1.1. DOR is defined as the time interval from the date of the first occurrence of a documented objective response until the first date of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1.

Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a documented objective response, DOR will be censored at the date of the first occurrence of a documented objective response plus 1 day. The KM approach will be used to estimate median DOR. The Brookmeyer-Crowley methodology (Brookmeyer and Crowley 1982) will be used to construct the 95% CI for the median DOR.

6.4.2.2 Time to Response

TTR, defined as the time from the start of the treatment to the first objective tumor response observed for patients who achieved CR or PR, as determined by the investigator according to RECIST v1.1.

Patients who are alive and who have not experienced the response at the time of analysis will be censored at the date of data cutoff.

The methodologies detailed for the DOR analysis will be used for the TTR analysis.

6.4.2.3 Disease Control Rate

DCR, defined as the proportion of patients who have a best overall response of CR or PR or SD, as determined by the investigator according to RECIST v1.1.

Number and percentage of patients with DCR with corresponding Clopper-Pearson 95% confidence intervals will be provided.

6.4.2.4 Progression-free Survival

PFS defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of initiation of study treatment plus 1 day.

The methodologies detailed for the DOR analysis will be used for the PFS analysis.

6.4.2.5 Overall Survival

OS, defined as the time from initiation of study treatment to death from any cause. Patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Patients with no post-baseline information will be censored at the date of initiation of study treatment plus 1 day. Methods for OS analyses are similar to those described for the DOR endpoint.

6.4.2.6 Landmark Analysis on Progression-free Survival and Overall Survival

PFS rate at 6 months and 1 year, defined as the proportion of patients who have not experienced disease progression or death from any cause at 6 months and 1 year separately, as determined by the investigator according to RECIST v1.1. OS rate at 1 year and 2 years, defined as the proportion of patients who have not experienced death from any cause at 1 year and 2 years.

The PFS rates at 6 months and 1 year after initiation of treatment will be estimated using Kaplan-Meier methodology, along with 95% CIs calculated using the standard error derived from Greenwood's formula.

Similar analyses will be performed for the OS rates at 1 year and 2 years after initiation of treatment.

6.4.2.7 ORR, DCR, DOR, and PFS per Modified RECIST

Analyses using modified RECIST criteria (see Appendix 5) for ORR, DCR, DOR, and PFS as determined by the investigator will be conducted. The methods outlined for the primary and secondary efficacy endpoint analyses will be used for these analyses.

6.4.2.8 Expression of PD-L1 defined by the SP142 and SP263 IHC Assay

Expression of PD-L1 defined by the SP142 and SP263 IHC assay will be investigated. The proportions of the patients with PD-L1+ tested by SP142 and SP263 in all patients will be presented respectively, with their 95% Clopper-Pearson CI. The consistency between SP142 and SP263 IHC assay will be investigated using Chisq-square Test if applicable.

6.4.2.9 Patent-Reported Outcomes (PROs)

TTD using EORTC is defined as the time from baseline to the first time the patient's score shows a ≥10 points increase above baseline in any of the following EORTC-transformed symptom subscale scores (whichever occurs first): cough, dyspnea (single item), dyspnea (multi-item subscale), chest pain, or arm/shoulder pain, whichever occurs first. The linear transformation gives each individual symptom subscale a possible score of 0-100. In order for the symptoms to be considered "deteriorated", acore increase of ≥ 10 points above baseline must be held for at least two consecutive assessment or an initial score increase of ≥ 10 points is followed by death within 3 weeks from the last assessment. A "≥10 point" change in the symptoms subscale score is perceived by patients as clinically significant (Osoba et al. 1998). Patients will be censored at

the last time when they complete an assessment if they have not deteriorated. If no post-baseline assessment is performed, patients will be censored at the randomization date plus 1 day. TTD using the EORTC scale will be analyzed using the same methods as for PFS. The analysis populations for TTD will be all randomized patients with a non-missing baseline PRO assessment.

PROs of HRQoL, lung cancer related symptoms, and health status will be measured using the EORTC QLQ-C30 and EORTC QLQ-LC3. Summary statistics (mean, SD, median, 25th and 75th percentiles, minimum and maximum) and mean change from baseline of linear-transformed scores will be reported for all of the items and subscales of EORTC QLQ-C30 questionnaire and the QLQ-LC13 according to the EORTC scoring manual guidelines. Completion and compliance rates will be summarized at each timepoint by treatment arm. The analysis populations for PRO changes will be all randomized patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all enrolled patients who received at least one dose of study treatment.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature), physical examination and ECG data will be displayed by time, with grades identified where appropriate. Changes from baseline in vital signs and ECGs will be summarized.

6.6 INTERIM ANALYSES

One interim analysis is planned. The interim analysis will be performed for futility at the time of 19 patients completing ORR evaluation. According to preplanned stopping rules of Simon 2-stage design, further testing of Atezolizumab and Bevacizumab would be halted if the number of patients that respond in the first evaluable 19 patients (stage 1) is less or equal than 6. This study has probability of 66.6% terminate at the first stage.

When the study runs into the second stage, in the end of the study, if more than 16 patients out of 39 patients have responses, we can recommend this treatment in IIIB-IV Non-squamous NSCLC to go to the next step in the clinical trial phase, otherwise, the treatment is rejected.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the CRO, using the CRO's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists,

pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the

country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 44 patients from China will be enrolled into this study.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries of the U.S. National Institutes of Health and the European Medicines Agency, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study, and redacted clinical study reports and other summary reports will be provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 2007;13:1050–9.

Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012;51:119–35.

Bellmunt J, Théodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009;27:4454–61.

Brian I Rini, Thomas Powles, Michael B Atkins et al.Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3,randomised controlled trial Lancet 2019; 393: 2404–15

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739–45.

Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med 2015;373;1627–39.

Bouzin C, Brouet A, De Vrise J, et al. Effects of vascular endothelial growth factor on the lymphocyte-endothelium interactions: identification of caveolin-1 and nitric oxide as control points of endothelial cell anergy. J Immunol 2007;178:1505−11

Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Cetin K, Ettinger DS, Hei YJ, et al. Survival by histologic subtype in stage IV nonsmall cell lung cancer based on data from the Surveillance, Epidemiology and End Results Program. Clin Epidemiol 2011;3:139–48.

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–7.Choueiri TK, Ross RW, Jacobus S, et al. Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer. J Clin Oncol 2012;30:507–12.

Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer 2000;89:1634–46.

DeMets D, Lan KKG. Interim analysis: the alpha spending function approach. Stat Med 1994;13:1341–52.

Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs 2016;8:593–603. doi: 10.1080/19420862.2015.1136043. Epub: 26 February 2016.

Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol 2014;32:1277–80.

European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man [resource on the Internet]. 2012 Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137128.pdf.

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer 1999;35:939–41.

Fozza C, Corda G, Virdis P, et al. Derangement of the T-cell repertoire in patients with B-cell non–Hodgkin's lymphoma. Eur J Haematol 2014:1–12.

Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a Phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non–small-cell lung cancer in Asia (IPASS). J Clin Oncol 2011;29:2866–74.

Galand C, Donnou S, Molina TJ, et al. Influence of tumor location on the composition of immune infiltrate and its impact on patient survival. Lessons from DCBCL and animal models. Front Immunol 2012;3(98):1–8.

Garcia JA, Dreicer R. Systemic chemotherapy for advanced bladder cancer: update and controversies. J Clin Oncol 2006;24:5545–51.

[FDA] U.S. Department of Health and Human Services Food and Drug Administration. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. Rockville (MD): U.S. Department of Health and Human Services Food and Drug Administration; 2007 May.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Galand C, Donnou S, Molina TJ, et al. Influence of tumor location on the composition of immune infiltrate and its impact on patient survival. Lessons from DCBCL and animal models. Front Immunol 2012;3(98):1–8.

GLOBOCAN 2008. Estimated cancer incidence: mortality, prevalence and disability-adjusted life years (DALYs) Worldwide in 2008. Available from: http://globocan.iarc.fr/factsheets/cancers/lung.asp.

Hales RK, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. Ann Oncol 2010;21:1944–51.

Herbst RS, Baas P, Kim D-W, et al. Pembrollizumab versus docetaxel for previously treated PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387;1540–50.

Herbst RS, JV Heymach JV, Lippman SM. Lung Cancer. N Engl J Med 2008;359:1367–80.

Herbst RS, Soria JC, Kowanetz M et al. Predictive correlates of response to the anti-PD-L1 antibody atezolizumab in cancer patients. Nature 2014; 515: 563–7.

Hodi FS, Ballinger M, Lyons B, et al. Immune-modified response evaluation criteria in solid tumors (imRECIST): refining guidelines to assess the clinical benefit of cancer immunotherapy. J Clin Oncol 2018. doi: 10.1200/JCO.2017.75.1644 [published online before print 17 January 2018].

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Hodi FS, Friedlander PA, Atkins MB, et al. A phase I trial of ipilimumab plus bevacizumab in patients with unresectable stage III or stage IV melanoma. J Clin Oncol 2011;29:8511.

Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2012. National Cancer Institute, 2015 [resource on the Internet]. Available from: http://seer.cancer.gov/csr/1975_2012/

Huang Y, Chen X, Dikov MM, et al. Distinct roles of VEGFR-1 and VEGFR-2 in the aberrant hematopoiesis associated with elevated levels of VEGF. Blood 2007;110:624−31.

Janne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. The New England journal of medicine. 2015 Apr 30;372(18):1689-99. PubMed PMID: 25923549. Epub 2015/04/30. eng.

Jemal A, Bray F, Center MM, et al. Global Cancer Statistics. CA Cancer J Clin 2011;61:69–90.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annual Rev Immunol 2008;26:677–704.

Kowanetz M, Socinski M, et al. AACR 2018

Laporte S, Squifflet P, Baroux N, et al. Prediction of survival benefits from progression-free survival benefits in advanced non-small cell lung cancer: evidence from a meta-analysis of 2334 patients from 5 randomized trials. BMJ Open 2013;3:1–6.

Langer CJ, Besse B, Gualberto A, et al. The evolving role of histology in the management of advanced non–small-cell lung cancer. J Clin Oncol 2010;28:5311–20.

Martin Reck, Tony S K Mok, Makoto Nishio et al Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial Lancet Respir Med 2019; 7: 387–401

Merritt RE, Mahtabifard A, Yamada RE, et al. Cisplatin augments cytotoxic T-lymphocyte-mediated antitumor immunity in poorly immunogenic murine lung cancer. J Thorac Cardiovasc Surg 2003;126:1609–17.

Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;12:528–38.

Postow M, Manuel M, Wong P, et al. T cell receptor diversity evaluation to predict patient response to ipilimumab in metastatic melanoma. J Immunother Cancer 2014;2(Suppl 3):08.

Powderly JD, Koeppen H, Hodi FS, et al. Biomarkers and associations with the clinical activity of PD-L1 blockade in a atezolizumab study [abstract]. J Clin Oncol 2013;31:abstract 3001.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Rossille D, Gressier M, Damotte D, et al. High level of soluble programmed cell death ligand 1 in blood impacts overall survival in aggressive diffuse large B-cell lymphoma: results from a French multicenter clinical trial. Leukemia 2014;28(12):2367–75.

Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non–small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239–46.

Shrimali RK, Yu Z, Theoret MR, et al. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. Cancer Res 2010;70:6171−80.

Shan Su, Zhong-Yi Dong, ,Zhi Xie et al J Thorac Oncol. 2018 Nov;13(11):1668-1675

Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012;62:10–29.

Socinski MA, Jotte RM, Cappuzzo F et al Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC N Engl J Med. 2018 Jun 14;378(24):2288-2301.

Sonpavde G, Sternberg CN, Rosenberg JE, et al. Second-line systemic therapy and emerging drugs for metastatic transitional-cell carcinoma of the urothelium. Lancet Oncol 2010;11:861–70.

Solange Peters, Scott Gettinger, Melissa L. Phase II Trial of Atezolizumab As First-Line or Subsequent Therapy for Patients With Programmed Death-Ligand 1–Selected Advanced Non–Small-Cell Lung Cancer (BIRCH) J Clin Oncol 35:2781-2789

Seymour L, Bogaerts J, Perrone A, et al., on behalf of the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143–52.

Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. New Engl J Med 2010;363:733–42.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012;366:2443–54.

Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244–285.

Tseng Y-H, Hung H-Y, Sung Y-C, Tseng Y-C, Lee Y-C, Whang-Peng J, et al. Efficacy of chemotherapy in epidermal growth factor receptor (EGFR) mutated metastatic pulmonary adenocarcinoma patients who had acquired resistance to first-line EGFR tyrosine kinase inhibitor (TKI). Journal of Chemotherapy. 2016 2016/01/02;28(1):50-8.

Yang J, Riella LV, Chock S. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 2011;187:1113–9.

Yang CJ, Tsai MJ, Hung JY, Liu TC, Chou SH, Lee JY, et al. Pemetrexed had significantly better clinical efficacy in patients with stage IV lung adenocarcinoma with susceptible EGFR mutations receiving platinum-based chemotherapy after developing resistance to the first-line gefitinib treatment. OncoTargets and therapy. 2016;9:1579-87.

Appendix 1
Schedule of Activities

	Screening	Treatment [a]	Treatment discontinuation	Survival follow-up
	Days-28 to -1	Every 21 days (±3 Days)	⩽30 days after Final Dose or at initiation of other anti-cancer therapy (whichever occurs first)	Every 3 months after disease progression or loss of clinical benefit
Informed consent	X[b]			
Tumor tissue specimen for PD-L1 and EGFR testing (5 FFPE slides required; blocks preferred) [c] Fresh or archival tissue can be used.	X			
Demographic data	X			
Medical history and baseline conditions	X			
NSCLC Cancer History	X			
Vital Signs[d]	X	X	X	
Weight	X	X	X	
Height	X			
Complete physical examination	X			
Limited physical examination[e]		X	X	
ECOG Performance Status	X	X	X	
12-Lead ECG	X	X[f]	X[f]	
LVEF[g]	X			
Hematology[h]	X	X	X	

Chemistry[i]	X	X	X	
Pregnancy test[j]	X [j]	X [k]	X [k]	
Coagulation test (aPTT or INR)	X		X	
TSH, free T3, free T4	X	X [l]	X [l]	
Viral serology (HIV, HBV, HCV) [m]	X			
Urinalysis [n]	X	X	X	
Blood sample for biomarkers [o]	X			
Tumor response assessments	X [p]	X [q,r]		X [s]
Concomitant medications [t]	X	X	X	
Adverse events [u]	X	X	X	X
Study drugs infusion [v]		X		
Patient-reported outcomes		X [w]		X [x]
Survival and anti-cancer therapy follow-up			X [y]	X [y]

a. Assessments should be performed before study drug infusion unless otherwise noted.

b. Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

c. Optional biopsy at screening is the preferred method to collected the tumor specimens for PD-L1 expression at screening and T790M mutation For PD-L1 testing, if archival tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria.(section 4.5.6)

d. Includes respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

e. Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

f. ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

g. Baseline evaluation of left ventricular ejection fraction (LVEF) should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease or where low LVEF is suspected.

h. Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count.

i. Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total CO2, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.

j. All women of childbearing potential will have a serum pregnancy test within 14 days before Cycle 1, Day 1.

k. Urine pregnancy tests performed at each subsequent visits; if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

l. TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every four cycles thereafter

m. At screening, patients will be tested for HIV, HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. The patient could be enrolled if the HBV DNA is negative (below the lower detection limit of each site). If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

n. Includes pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted.

o. If T790m mutation unknown and re-biopsy tissue sample unavailable，blood sample will be tested for T790M.

p. CT scans (with oral/IV contrast unless contraindicated) or MRI of the chest and abdomen. A CT or MRI scan of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. A CT (with contrast) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. For patient with unknown bone metastases, if ALP ＞2.5xULN and ≤5x ULN and/or have symptom of suspect bone metastases，bone scan should be done at screening.

q. Patients will undergo tumor assessments at baseline and every 6 weeks (±7days) for the first 36 weeks following Cycle 1, Day 1, regardless of dose delays. After 36 weeks, tumor assessment will be required every 9 weeks (±7days). Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab treated patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first.

r. All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

s. If a patient discontinues study treatment for any reason other than disease progression, tumor assessments will continue at the same frequency as would have been followed if the patient had remained on study treatment untilradiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab treated patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first., even if patient starts another anti-cancer therapy after study treatment discontinuation, unless consent is withdrawn.

t. Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days before screening until the treatment discontinuation visit.

u. After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest, regardless of relationship to study treatment, will be reported until 90 days after the last dose of study treatment or initiation of new non-protocol systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the investigator should report any serious adverse event or adverse events of special interest that is believed to be related to prior exposure to study treatment.

v. The initial infusion of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. The initial dose of bevacizumab will be delivered over 90 (± 15) minutes. If the first infusion is tolerated without infusion associated adverse events, the second infusion may be delivered over 60 (± 10) minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or study-related procedures until a final outcome can be reported.w. PRO assessments will be completed before the patient receives any information on disease status and prior to the performance of non-PRO assessments and the administration of study treatment. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site.

x. During survival follow-up, the PRO questionnaires will be completed at 3 and 6 months following disease progression or loss of clinical benefit as determined by the investigator(for patients who continue atezolizumab after radiographic disease progression).

y. After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status

Appendix 2
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval ≤ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

Definition of Non-Measurable Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

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[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions,

documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is $\leq$ 5 mm. When CT scans have slice thickness of $>$ 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation .

<u>ASSESSMENT OF TUMOR BURDEN</u>

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but $<$ 15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$ 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph

node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for

unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

Patients with Non-Measurable Disease Only

For patients with non-measurable disease only, the same general concepts apply as noted above. However, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-measurable disease cannot be easily quantified (by definition, if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

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

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

Table 2 Criteria for Overall Response at a Single Timepoint: Patients with Non-Target Lesions Only

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

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

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned

timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1and Table 2

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

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Appendix 3
Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immunotherapy-specific response criteria adaptations to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; Eisenhauer et al. 2009) have been developed to allow for unconventional response and progression patterns. These include modified RECIST v1.1 for immune-based therapeutics (iRECIST; Seymour et al. 2017), which was developed by the RECIST working group in an effort to create a common set of criteria that the cancer immunotherapy field could apply to clinical trials.

Response evaluation through use of iRECIST requires collection of tumor assessment data after radiographic progression per RECIST v1.1. Details regarding lesion evaluation are described below. When not otherwise specified, RECIST v1.1 conventions will apply.

Criteria for determining overall response at a single timepoint per iRECIST are also summarized below. Of note, overall response per iRECIST will not be captured in the electronic Case Report Form (eCRF), but will instead be calculated programmatically by the Sponsor on the basis of investigator-assessed individual lesion data recorded in the eCRF.

iRECIST response status is not a specific component of treatment discontinuation criteria, including decisions about whether to continue treatment beyond progression per RECIST v1.1. Investigators should instead take into account radiologic data and clinical status in making such decisions, as described in Section 3.1.

EVALUATION OF LESIONS TO SUPPORT iRECIST RESPONSE ASSESSMENT AFTER DISEASE PROGRESSION PER RECIST V1.1

iRECIST is an extension of RECIST v1.1 that allows for response assessment following disease progression per RECIST v1.1. RECIST v1.1 rules for categorizing lesions as measurable or non-measurable and measuring lesions (see Appendix 2) also apply to iRECIST. After disease progression per RECIST v1.1, the same target and non-target lesions selected at baseline will continue to be followed, along with any new lesions that develop, to support iRECIST response evaluations, as described below and summarized in Table 1. Once a lesion has been categorized as a target, non-target, or new lesion, it will remain classified as such.

TARGET LESIONS

The target lesions selected at baseline should continue to be measured at all tumor assessment timepoints after disease progression per RECIST v1.1, according to RECIST v1.1 conventions.

NON-TARGET LESIONS

Non-target lesions selected at baseline should continue to be followed at all tumor assessment timepoints after disease progression per RECIST v1.1. At each timepoint, non-target lesions

should continue to be categorized as "absent" (complete response [CR]), "unequivocal progression" relative to baseline (progressive disease [PD]), or "present without unequivocal progression" (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous timepoint should be evaluated to determine whether there has been any further increase in size.

NEW LESIONS

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST v1.1 (e.g., non–lymph node lesions must be ≥ 10 mm on the longest diameter; new lymph nodes must be ≥ 15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint should be measured from that point on, if the maximum number of measurable new lesions has not been reached. However, for calculation of the sum of diameters for new lesions, iRECIST excludes measurements from new lesions that were not measurable at first appearance.

All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is ≥ 15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is ≥ 10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is < 10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is ≥ 15 mm. Measurable new lymph node lesions should continue to be measured at all subsequent timepoints, even if the short axis decreases to < 15 mm (or even < 10 mm).

Table 1 Guidelines for Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1

Lesion Type	Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1
Target lesions	• Measurements should be continued according to RECIST v1.1 conventions.
Non-target lesions	• Non-target lesions should continue to be categorized as absent (CR), unequivocal progression (PD), or present without unequivocal progression (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous timepoint should be evaluated to determine whether there has been any further increase in size.
New lesions	• New lesions should be evaluated for measurability per RECIST v1.1. • All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints. • Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint. • All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.

CR = complete response; PD = progressive disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.

SUMMARY OF CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Timepoint response per iRECIST will be calculated programmatically by the Sponsor. A complete description of the iRECIST criteria can be found in a publication by Seymour et al. (2017).

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412–20.

Seymour L, Bogaerts J, Perrone A, et al., on behalf of the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143–52.

Appendix 4
European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire: EORTC QLQ- LC 13

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Appendix 5
European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 6
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent. Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cirrhosis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix 7
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
6. Continue to observe the patient and document observations

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and bevacizumab.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab

Event	Action to Be Taken
IRRs, anaphylaxis, and hypersensitivity reactions	• Guidelines for management of IRRs for atezolizumab are provided in Appendix 9. • Guidelines for management of IRRs for bevacizumab are provided below. • For anaphylaxis precautions, see Appendix 7. • For hypersensitivity reactions and allergic reactions, permanently discontinue the causative agent.
IRR to bevacizumab, Grade 1	• Systemic intervention is not indicated. Continue bevacizumab.
IRR to bevacizumab, Grade 2	• Reduce infusion rate to ≤ 50% or interrupt infusion at the discretion of the investigator per medical judgment. • If the infusion is interrupted, it may be resumed at ≤ 50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.
IRR to bevacizumab, Grade 3 or 4	• Stop infusion and permanently discontinue bevacizumab. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen) if clinically indicated.

IRR = infusion-related reaction.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity	
GI perforation, any grade	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • Initiate treatment per institutional guidelines. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a]
Bowel obstruction, Grade 2	• Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab for partial obstruction requiring medical intervention. • Bevacizumab may be restarted upon complete resolution of event.
Bowel obstruction, Grade 3 or 4	• Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab until complete resolution. • If surgery is necessary, patient may restart bevacizumab after full recovery from surgery and at the investigator's discretion.
Posterior reversible encephalopathy syndrome	
Posterior reversible encephalopathy syndrome, any grade confirmed by magnetic resonance imaging	• Withhold atezolizumab. Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a]

GI = gastrointestinal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit and the Medical Monitor is in agreement.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Hypertension [a]	
General guidance	• Treat with antihypertensive medication as needed.
Hypertension, Grade 1	• Continue atezolizumab and bevacizumab. • Consider inceased BP monitoring.
Hypertension, Grade 2	• Continue atezolizumab. • If asymptomatic, begin or modify baseline anti-hypertensive therapy and continue bevacizumab. • If symptomatic, start or adjust anti-hypertensive therapy.
Hypertension, Grade 3	• Continue atezolizumab. • Modify existing anti-hypertensive therapy (more than one drug or more intensive therapy than previously indicated). • Withold bevacizumab until symptoms resolve AND BP $<$ 160/90 mmHg
Hypertension, Grade 4	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Hemorrhage	
Hemorrhage, Grade 3 or 4 (excluding cerebral hemorrhage)	• Continue atezolizumab. • Permanently discontinue bevacizumab.
CNS hemorrhage, any grade	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Grade $\geq$2 hemoptysis ($\geq$ 2.5 mL of bright red blood per episode)	• Continue atezolizumab. • Permanently discontinue bevacizumab.
Bleeding in patients on full-dose anticoagulant therapy	• Continue atezolizumab. • Permanently discontinue bevacizumab.

BP = blood pressure.

[a] Vascular disorders (including hypertension and hypotension) are possible adverse events of atezolizumab, considering the mechanism of action.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Event	Action to Be Taken
Thromboembolic events	
Venous thromboembolic event, Grade 3	• Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be withheld until the full-dose anticoagulation period is over. The use of direct oral anticoagulants is not recommended. • If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed during full-dose anticoagulation IF all of the criteria below are met: – The patient must not have pathological conditions that carry high risk of bleeding (e.g., tumor involving major vessels or other conditions). – The patient must not have had hemorrhagic events > Grade 2 while on study. – The patient must be on stable dose of heparin, low-molecular-weight heparin, or have an in-range INR (usually 2–3) on a stable dose of warfarin prior to restarting bevacizumab. • If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab.
Venous thromboembolic event, Grade 4	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Arterial thromboembolic event, any grade	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Event	Action to Be Taken
Proteinuria	
Proteinuria, Grade 1 (1+ by dipstick; urinary protein < 1.0 g/24 hours)	• Continue atezolizumab and bevacizumab.
Proteinuria, Grade 2 (2+ and 3 + by dipstick; urinary protein 1.0–3.4 g/24 hours)	• Continue atezolizumab. • For 2+ dipstick: Continue bevacizumab and collect 24-hour urine protein prior to subsequent bevacizumab administration. • For 3+ dipstick: Obtain 24-hour urine prior to administering bevacizumab. • Withhold bevacizumab for urinary protein ≥ 2 g/24 hours. • If bevacizumab is withheld and urine protein improves to < 2 g/24 hours ≤ 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab.
Proteinuria, Grade 3 (4 + by dipstick; urinary protein ≥ 3.5 g/24 hours) with no diagnosis of nephrotic syndrome	• Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab. • If urine protein improves to < 2 g/24 hours ≤ 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab.
Nephrotic syndrome, Grade 3 or 4	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Fistula	
Tracheoesophageal fistula, any grade	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a]
Fistula (non-tracheoesophageal), Grade 4	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit and the Medical Monitor is in agreement.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Event	Action to Be Taken
Wound dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Congestive heart failure	
Congestive heart failure, Grade 3 or 4	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Bevacizumab-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab and bevacizumab.
Grade 3	• Continue atezolizumab. Withhold bevacizumab. • If event resolves to Grade 2 or better ≤ 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]
Grade 4	• Withhold atezolizumab and bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a] • If event resolves to Grade 2 or better ≤ 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 9. • Continue bevacizumab.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 9. • Withhold bevacizumab. • If event resolves to Grade 2 or better ≤ 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit and the Medical Monitor is in agreement.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-related 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-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

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

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Tbale 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • 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 Medical Monitor. [c] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • 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.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

HEPATIC EVENTS

Immune-related hepatitis has been associated with the administration of atezolizumab.–Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Tbale 2.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
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 corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • 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 Medical Monitor. [c]

LFT = liver function tests.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • 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 (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

GASTROINTESTINAL EVENTS

Immune-related colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Tbale 3.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 3 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. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • 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 Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone 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 Medical Monitor. [c]

GI = gastrointestinal.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone 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.

GI = gastrointestinal.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 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 patient 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 patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-related hyperthyroidism. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • 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.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • 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 Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Tbale 5.

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient 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. [a] • Patient 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. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-RELATED MYOCARDITIS

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any patient 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, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated 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.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Tbale 6.

Table 6 Management Guidelines for Immune-Related Myocarditis

Event	Management
Immune-related myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone 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 Medical Monitor. [c]
Immune-related myocarditis, Grade 3-4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone 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.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, anti-pyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 7.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor.[e] • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

Event	Management
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit–risk ratio.

[f] Refer to Riegler et al. (2019) for information on experimental treatments for CRS.

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 workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • 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 Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone 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 Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone 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.

GI = gastrointestinal.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • 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 patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, 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 Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]
Stevens Johnson syndrome or toxic epidermal necrolysis, (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant), and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • Permanently discontinue atezolizumab for confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate

between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

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 Medical Monitor. [c]
Immune-related neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1−2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., $>$ 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of $\leq$ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over $\geq$ 1 month to the equivalent of $\leq$ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-RELATED MENINGOENCEPHALITIS

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any patient 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 patients being considered for meningoencephalitis should be urgently evaluated 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.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Tbale 11.

Table 11 Management Guidelines for Immune-Related Meningoencephalitis

Event	Management
Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone 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] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

RENAL EVENTS

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.

Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • 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 Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • 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 (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Tbale 13.

Table 13 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.

Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • 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 Medical Monitor. [c]

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 13 Management Guidelines for Immune-Mediated Myositis (cont.)

Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); 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, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); 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 (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin <90 g/L (9 g/dL) (<100 g/L [10 g/dL] for infants <4 weeks old)
  - Platelet count $<100\times10^9$/L (100,000/μL)
  - ANC $<1.0\times10^9$/L (1000/μL)
- Fasting triglycerides >2.992 mmol/L (265 mg/dL) and/or fibrinogen <1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin >500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin >684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq181\times10^9$/L (181,000/μL)
  - AST ≥48 U/L

- Triglycerides $>$ 1.761 mmol/L (156 mg/dL)
- Fibrinogen $\leq$ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids and/or an immunosuppressive agent. • If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over $\geq$ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

REFERENCES

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–9.

Adashek ML, Feldman M. Cytokine release syndrome resulting from anti–programmed death-1 antibody: raising awareness among community oncologist. J Oncol Practice 2019;15:502–4.

Lee DW, Santomasso BD, Locke FL et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638.

Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323–35.

Rotz SJ, Leino D, Szabo S, et al. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. Pediatr Blood Cancer 2017;64:e26642.

Appendix 10
Overall Guidelines for Management of Patients Who Experience Adverse Events

DOSE MODIFICATIONS

There will be no dose modifications for atezolizumab in this study. Risks associated with atezolizumab and guidelines for management of adverse events associated with atezolizumab are summarized in Appendix 9.

The bevacizumab dose will be based on the patient's weight at randomization and will remain the same throughout the study, unless there is a weight change of ≥ 10% from baseline. It is not necessary to correct dosing on the basis of ideal weight, unless warranted per institutional guidelines/standard. Management of bevacizumab may be performed according to the label. Risks associated with bevacizumab and guidelines for management of adverse events associated with bevacizumab are summarized in Appendix 8. If adverse events occur that necessitate holding bevacizumab, the weight-based dose in mg/kg will remain unchanged after treatment resumes.

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >12 weeks if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. Patients who develop Grade 4 toxicities related to bevacizumab for > 21 days should permanently discontinue bevacizumab.

Atezolizumab or bevacizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures), with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption. If either study drug is withheld or discontinued, the other study drug can be continued as long as the patient is experiencing clinical benefit, as determined by the investigator per medical judgment.

Appendix 11

Instructions for Preparation, Administration, and Disposal of Bevacizumab

INSTRUCTIONS FOR PREPARATION AND DISPOSAL

Bevacizumab should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute in a total volume of 100 mL of 0.9% sodium chloride injection, United States Pharmacopeia (USP). **Bevacizumab infusions should not be administered or mixed with dextrose or glucose solutions.** In case of administering a total dose exceeding 1000 mg, dilute the calculated dose of bevacizumab with a sufficient amount of 0.9% sodium chloride injection to keep final concentration between 1.4 mg/mL and 16.5 mg/mL. Keep 100 mL as the minimal volume to administer and limit the infusion volume as much as possible. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Diluted bevacizumab should be used within 8 hours.

ADMINISTRATION

Administration will be as a continuous IV infusion. Anaphylaxis precautions should be observed during bevacizumab administration.

The first dose of bevacizumab should be administered over 90 ± 10 minutes. If the first infusion is well tolerated without infusion-associated adverse events (fever or chills), the second infusion may be delivered over 60 ± 10 minutes. If the 60-minute infusion is tolerated all subsequent infusions may be delivered over 30 ± 10 minutes.

Although no data are available specifically on bevacizumab, in general, patients experiencing mild to moderate hypersensitivity/infusion reactions (Grade 1 or 2 of the NCI CTCAE Infusion-Related Reactions), in particular after the first exposure, may tolerate re-administration of the agent at reduced infusion rates and with treatment using antihistamines and corticosteroids after complete resolution of symptoms. Re-challenge is generally discouraged in patients who experienced a severe initial reaction (Grade 3 or 4).

A rate-regulating device should be used for all bevacizumab infusions. When the bevacizumab IV bag is empty, 50 mL of 0.9% sodium chloride solution, USP, will be added to the IV bag or an additional bag will be hung, and the infusion will be continued for a volume equal to that of the tubing to ensure complete delivery of the trial drug. The total infusion time, therefore, should always be either 90, 60, or 30 minutes. If more saline is infused, the extent of saline infusion does not factor into the trial drug infusion time.

Should extravasation of bevacizumab infusion occur, the following steps should be taken: Discontinue the infusion. Treat the extravasation according to institutional guidelines for extravasation of a non-caustic agent. If a significant volume of bevacizumab remains, restart the infusion at a more proximal site in the same limb or on the other side. Treat the infiltration according to institutional guidelines for infiltration of a non-caustic agent.

In the event of a suspected anaphylactic reaction during bevacizumab infusion:

6. Stop the trial drug infusion.
7. Apply a tourniquet proximal to the injection site to slow systemic absorption of bevacizumab. Do not obstruct arterial flow in the limb.
8. Maintain an adequate airway.
9. Administer antihistamines, corticosteroids, epinephrine, or other medications as required.
10. Continue to observe the patient, document observations and administer further treatment as required.
11. Permanently discontinue bevacizumab.

The above events should be reported as adverse events.