PROTOCOL

TITLE:	**A RANDOMIZED, MULTICENTER, PHASE Ib/III STUDY TO INVESTIGATE THE PHARMACOKINETICS, EFFICACY, AND SAFETY OF ATEZOLIZUMAB SUBCUTANEOUS COMPARED WITH ATEZOLIZUMAB INTRAVENOUS IN PATIENTS WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	BP40657
VERSION NUMBER:	7
EUDRACT NUMBER:	2018-002328-18
IND NUMBER:	pre-IND 140100
NCT NUMBER	NCT03735121
TEST PRODUCT:	Atezolizumab (RO5541267/F06, RO5541267/F03, RO5541267/F01, RO5221651)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
7	See electronic stamp on the final page of this document
6	25 February 2022
5	10 February 2021
4	28 August 2020
3	30 March 2020
2	1 June 2019
1	5 August 2018

PROTOCOL AMENDMENT, VERSION 7:
RATIONALE

Protocol BP40657 (IMscin001) has been amended primarily to align with the Atezolizumab Investigator's Brochure, Version 19. Changes to the protocol, along with a rationale for each change, are summarized below:

- The medical term "Wegener granulomatosis" has been replaced by the term "granulomatosis with polyangiitis" to align with the updated preferred term in MedDRA (Section 4.1.2.1 and Appendix 8).
- The list of identified risks for atezolizumab has been revised to include pericardial disorders (Section 5.1.1 and Appendix 10).
- The list of identified risks for atezolizumab has been revised to include myelitis and facial paresis (Section 5.1.1 and Appendix 10).
- Hemophagocytic lymphohistiocytosis has been updated from a potential risk to an identified risk associated with atezolizumab and language has been revised accordingly (Section 5.1.1).
- The list of adverse events of special interest has been revised to include myelitis and facial paresis (Section 5.2.3).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section CPT A1-4 Data Protection / Legacy 8.4 Confidentiality.
- Appendix 8 has been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a pericardial disorder while receiving another immunostimulatory anti-cancer agent.
- Appendix 8 has been revised to include autoimmune myelitis.
- The adverse event management guidelines have been updated to align with the Addendum 1 and the Addendum 2 to the Atezolizumab Investigator's Brochure, Version 19 (Appendix 10).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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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 as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, MULTICENTER, PHASE Ib/III STUDY TO INVESTIGATE THE PHARMACOKINETICS, EFFICACY, AND SAFETY OF ATEZOLIZUMAB SUBCUTANEOUS COMPARED WITH ATEZOLIZUMAB INTRAVENOUS IN PATIENTS WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC NON–SMALL CELL LUNG CANCER**
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PHASE:	Phase Ib/III
INDICATION:	Non–small cell lung cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics, safety, and efficacy of atezolizumab SC compared with atezolizumab IV in patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) who have not been exposed to cancer immunotherapy (CIT) (i.e., "CIT-naive") and for whom prior platinum-based therapy has failed. The study is comprised of two parts, as follows:

- Part 1 (Phase Ib, dose finding) will aim to identify the dose of atezolizumab SC that yields drug exposure that is comparable to that of atezolizumab IV
- Part 2 (Phase III, randomized, dose confirmation) will aim to demonstrate the non-inferiority of observed drug exposure following treatment with atezolizumab SC at the identified dose compared with drug exposure following treatment with atezolizumab IV

OBJECTIVES AND ENDPOINTS FOR PART 1

Pharmacokinetic Objectives for Part 1

The primary pharmacokinetic (PK) objective for Part 1 is to determine the dose of atezolizumab SC that is predicted to yield drug exposure that is comparable to that of atezolizumab IV on the basis of the following endpoint:

- Serum atezolizumab trough concentration (C_{trough}) at Cycle 1 (i.e., predose Cycle 2)

The secondary PK objective for Part 1 is to characterize the PK profile of atezolizumab SC on the basis of the following endpoint:

- Serum atezolizumab concentration at specified timepoints during SC administration

The exploratory PK objective for Part 1 is to characterize the PK profile of rHuPH20 on the basis of the following endpoint:

- Plasma rHuPH20 concentration at specified timepoints during SC administration

Safety Objective for Part 1

A secondary objective for Part 1 is to evaluate the safety of atezolizumab SC on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0)
- Incidence and severity of targeted vital signs
- Incidence and severity of clinical laboratory abnormalities

Immunogenicity Objective for Part 1

The exploratory immunogenicity objective for Part 1 is to evaluate the immune response to atezolizumab SC and rHuPH20 on the basis of the following endpoints:

- Incidence of anti-drug antibodies (ADAs) to atezolizumab after SC administration relative to the prevalence of ADAs at baseline
- Incidence of ADAs to rHuPH20 after SC administration relative to the prevalence of ADAs at baseline

OBJECTIVES AND ENDPOINTS FOR PART 2

Pharmacokinetic Objectives for Part 2

The primary PK objective for Part 2 is to demonstrate non-inferiority of exposure to atezolizumab SC compared with atezolizumab IV on the basis of the following co-primary endpoints:

- Observed serum C_{trough} at Cycle 1 (predose Cycle 2)
- Model-predicted area under the concentration-time curve (AUC) from 0 to 21 days ($AUC_{0\text{-}21\ d}$) at Cycle 1

A secondary PK objective for Part 2 is to evaluate exposure following administration of atezolizumab SC compared with atezolizumab IV on the basis of the following endpoints, as appropriate and as data allow:

- Model-predicted C_{trough} at Cycle 1 ($C_{trough\ Cycle\ 1}$), model-predicted C_{trough} at steady state ($C_{trough,ss}$), and model-predicted AUC at steady state (AUC_{ss})

The exploratory PK objective for Part 2 is to evaluate potential relationships between atezolizumab exposure and efficacy and safety.

Safety Objectives for Part 2

A secondary objective for Part 2 is to evaluate the safety of atezolizumab SC compared with atezolizumab IV on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0
- Overall patient-reported adverse event burden over time, as assessed by the patient global impression of cancer treatment side effects burden item from the European Organisation for Research and Treatment of Cancer (EORTC) IL57

Efficacy Objectives for Part 2

A secondary objective for Part 2 is to evaluate the efficacy of atezolizumab SC 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), as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
- Progression-free survival (PFS), defined as the time from study entry 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
- Overall survival (OS), defined as the time from study entry to death from any cause

- Duration of response (DOR), defined as the time from 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

An additional secondary objective for Part 2 is to evaluate patient experience with atezolizumab SC compared with atezolizumab IV, on the basis of the following endpoints:

- Functioning and global health status over time, as assessed by the physical functioning, role functioning, and global health status/quality of life scales of the EORTC IL57
- Overall satisfaction with treatment, as assessed by the modified satisfaction with therapy (SWT) scale of the Cancer Therapy Satisfaction Questionnaire (CTSQ)

Immunogenicity Objectives for Part 2

A secondary objective for Part 2 is to evaluate the incidence of ADAs to the tested molecules on the basis of the following endpoint:

- Incidence of ADAs to atezolizumab after SC administration or IV administration relative to the prevalence of ADAs at baseline
- Incidence of ADAs to rHuPH20 after SC administration relative to the prevalence of ADAs at baseline

The exploratory immunogenicity objective for Part 2 is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between post-baseline ADA status and PK, safety, or efficacy endpoints

Biomarker Objective for Part 2

The exploratory biomarker objective for Part 2 is to evaluate biomarkers that may be predictive of response to atezolizumab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to atezolizumab, can provide evidence of atezolizumab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology. They will be evaluated on the basis of the following endpoint:

- Relationship between biomarkers in tumor tissue and efficacy, or other biomarker endpoints

Health Care Professional-Reported Experience Utility Objective for Part 2

The secondary utility objective for Part 2 is to evaluate health care professional (HCP)-reported experience with administration of atezolizumab SC and atezolizumab IV, on the basis of the following endpoints:

- Convenience, potential time savings, and overall satisfaction with atezolizumab SC compared with atezolizumab IV, as assessed by the HCP SC versus IV Perspective Questionnaire
- Convenience, ease of administration, and overall satisfaction with atezolizumab SC, as assessed by the HCP Subcutaneous Perspective Questionnaire

STUDY DESIGN

DESCRIPTION OF STUDY

This is a two-part, open-label, multicenter Phase Ib/III study in patients with locally advanced or metastatic NSCLC who are CIT-naive and for whom prior platinum therapy has failed. The two parts of the study are as follows:

Part 1 of the study will consist of three single-arm cohorts and will determine the dose of atezolizumab SC that yields comparable exposure to atezolizumab IV on the basis of serum C_{trough} at Cycle 1 (predose Cycle 2). Atezolizumab SC co-mix will be used for Cohort 1 of Part 1. A ready-to-use formulation of atezolizumab with rHuPH20 (atezolizumab SC) may be used for Cohorts 2 and 3 of Part 1, subject to review and approval from relevant Health Authorities and Sponsor decision.

Part 2 of the study will consist of a two-arm, randomized, multicenter study of atezolizumab SC compared with atezolizumab IV. The aim of Part 2 is to demonstrate non-inferiority of PK exposure of the SC formulation versus the IV formulation based on the co-primary endpoints, Cycle 1 observed serum C_{trough} (predose Cycle 2) and model-predicted AUC from 0 to 21 days

($AUC_{0-21\ d}$). The ready-to-use SC formulation of atezolizumab co-formulated with rHuPH20 (atezolizumab SC) will be used in Part 2.

Safety will be monitored throughout the study by the Sponsor Internal Monitoring Committee (IMC) for Part 1 and by a Joint Monitoring Committee (JMC) for Part 2.

Part 1: Dose Finding

Part 1 will be composed of three cohorts: Cohorts 1 and 2 will consist of approximately 12 evaluable patients each and Cohort 3 will consist of approximately 20–30 evaluable patients. Patients will receive one (Cohort 1) or more (Cohorts 2 and 3) administrations of atezolizumab SC co-mix or atezolizumab SC (see below for details) followed by treatment with atezolizumab IV 1200 mg every 3 weeks (Q3W), as indicated, for subsequent cycles until disease progression, loss of clinical benefit, unacceptable toxicity, or withdrawal of consent.

The following cohorts are planned:

- Cohort 1: Patients will receive 1800 mg atezolizumab SC co-mix for one cycle (21 days), followed by 1200 mg atezolizumab IV Q3W for subsequent cycles.
- Cohort 2: Patients will receive 1200 mg atezolizumab SC co-mix or atezolizumab SC every 2 weeks (14 days) for 3 cycles, followed by 1200 mg atezolizumab IV Q3W for subsequent cycles.
- Cohort 3: Patients will receive 1800 mg atezolizumab SC co-mix or atezolizumab SC Q3W (21 days) for 3 cycles, followed by 1200 mg atezolizumab IV Q3W for subsequent cycles.

In Cohorts 1 and 2, all SC injections will be administered in the thigh. In Cohort 3, the first subcutaneous dose of atezolizumab will be administered in the lower part of the abdomen and the following 2 doses will be administered in the thigh.

The doses specified for Cohorts 2 and 3 are projected doses. The actual doses will depend on the results from Cohort 1. Additional dose-finding cohorts may be opened if the doses from planned cohorts result in atezolizumab exposure outside of the expected exposure obtained with atezolizumab IV or if the variability in C_{trough} is too high to determine a dose for Part 2 of the study.

All patients must report any symptoms and adverse events immediately to the investigator, particularly during the first 72 hours after the first injection. Enrollment of the first 6 patients in Cohort 1 will be staggered in order to closely monitor the safety and tolerability resulting from the first atezolizumab SC co-mix administration. This will allow for a 72-hour interval during which safety will be assessed by the investigator and communicated to the Sponsor. Safety of the first 72 hours in these patients will be evaluated by the Sponsor before enrollment of the next patient. For Cohorts 2 and 3, enrollment of only the second patient will be dependent on the outcome of the safety assessment of the 72 hours from the first patient. Further enrollment in Cohorts 2 and 3 will be completed without staggering.

Data from all cohorts will be analyzed to determine the optimal atezolizumab SC dose to be tested in Part 2.

Patients will be followed until 90 days after the final dose of study treatment, initiation of new systemic anti-cancer therapy, withdrawal from the study, or study termination by the Sponsor, whichever occurs first.

Part 1 will be conducted at up to approximately 20 sites globally.

Part 2: Dose Confirmation

Part 2 will be initiated once a dose has been identified based on the cumulative data collected from Part 1. In Part 2, patients will be randomized in a 2:1 ratio to receive monotherapy with either 1875 mg of atezolizumab SC Q3W or 1200 mg of atezolizumab IV Q3W, respectively, starting on Day 1 of each 21-day cycle.

Part 2 of this study will initially randomize approximately 327 patients across approximately 150 sites in a global enrollment phase.

To ensure a patient population representative of standard clinical practice, the Sponsor will periodically evaluate the prevalence of *EGFR* mutation and limit the number of patients with *EGFR*-positive mutation to a maximum of approximately 10% of all randomized patients if required. The Sponsor may also monitor other biomarkers such as PD-L1 expression levels

and, if considered appropriate, carry out actions to ensure a balanced distribution in the study population.

A structured evaluation of safety data will be conducted after the first 24 patients (approximately 16 patients in the atezolizumab SC arm and another 8 patients in the atezolizumab IV arm) have completed at least one cycle to ensure that the safety of atezolizumab SC (provided as a ready-to-use mixture of atezolizumab and rHuPH20) is comparable to that of the atezolizumab SC co-mix formulation administered in Part 1. A blinded sample-size re-estimation will be conducted once approximately 210–250 patients have been randomized.

Atezolizumab SC Cycle 1 observed serum C_{trough} (predose Cycle 2) and model-predicted area under the concentration-time curve (AUC) from 0 to 21 days ($AUC_{0–21\ d}$) at Cycle 1 will be measured and compared with atezolizumab IV Cycle 1 C_{trough} and model-predicted $AUC_{0\text{-}21\ d}$, respectively, to confirm non-inferiority between atezolizumab SC and atezolizumab IV (co-primary PK endpoints). Efficacy and safety information will be collected on a regular basis to assess secondary efficacy and safety endpoints.

Patients will receive atezolizumab SC or atezolizumab IV, as indicated, until disease progression, loss of clinical benefit, or unacceptable toxicity. Crossover is not allowed.

NUMBER OF PATIENTS

A total of approximately 60 patients with locally advanced or metastatic NSCLC will be enrolled in Part 1 of the study. Part 2 of the study is expected to randomize approximately 327 patients during the global enrollment phase of this study.

TARGET POPULATION

Inclusion Criteria

General inclusion criteria applicable to both Parts 1 and 2 are described. Additional inclusion criteria applicable to either Part 1 or Part 2 are also described.

General Inclusion Criteria Applicable to Both Parts 1 and 2 (All Patients)

All patients must meet all the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Measurable disease as defined by RECIST v1.1

  Previously irradiated lesions can only be considered as measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of disease.
- Eastern Cooperative Oncology Group Performance Status of 0 or 1
- Life expectancy ≥ 12 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC ≥ 1.5×10^9/L (1500/μL) without granulocyte colony-stimulating factor support
  - Lymphocyte count ≥ 0.5×10^9/L (500/μL)
  - Platelet count ≥ 100×10^9/L (100,000/μL) (without transfusion)
  - Hemoglobin ≥ 90 g/L (9 g/dL)

    Patients may be transfused to meet this criterion.
  - AST, ALT, and ALP ≤ 2.5 × upper limit of normal (ULN), with the following exceptions:

    Patients with documented liver metastases: AST and ALT ≤ 5 × ULN

    Patients with documented liver or bone metastases: ALP ≤ 5 × ULN
  - Total bilirubin ≤ 1.5 × ULN with the following exception:

    Patients with known Gilbert disease: total bilirubin level ≤ 3 × ULN
  - Serum creatinine ≤ 1.5 × ULN

  - Serum albumin ≥ 25 g/L (2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 × ULN
- 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 patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, 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.

  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.
- Patients must have recovered (i.e., improvement to Grade 1 or better) from all acute toxicities from previous therapy, excluding alopecia

  For peripheral neuropathy, improvement to Grade ≤2 is acceptable.
- Intact normal skin without potentially obscuring tattoos, pigmentation, or lesions in the area for intended injection
- Histologically or cytologically documented NSCLC that is currently locally advanced or metastatic (i.e., Stage IIIB not eligible for definitive chemoradiotherapy, Stage IV, or recurrent) NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 8th edition)

  Pathological characterization may be from tumor specimens collected at a time when the NSCLC was at an earlier stage but must be sufficient to define patients as having either squamous or non-squamous histology.
- Disease progression during or following treatment with a platinum-containing regimen for locally advanced, unresectable/inoperable or metastatic NSCLC or disease recurrence within 6 months of treatment with a platinum-based adjuvant/neoadjuvant regimen or combined modality (e.g., chemoradiation) regimen with curative intent

  Patients may have received one additional cytotoxic chemotherapy regimen provided no interval disease progression has occurred. Chemotherapy regimens will be counted based on interval disease progression and not the number of agents or switches in agents (e.g., a first-line therapy that consists of several cycles of a platinum doublet and subsequent maintenance therapy that introduces or switches to

a new chemotherapy agent without interval disease progression will all be considered one chemotherapy regimen).

Adjuvant/neoadjuvant chemotherapy or chemoradiation counts as a prior chemotherapy regimen if < 6 months have elapsed between the last dose and the date of recurrence. Combined treatment with chemotherapy and radiation constitutes a single regimen; surgery is not considered a regimen.

Patients with advanced lung cancer and a sensitizing EGFR mutation will additionally be required to have experienced disease progression (during or after treatment) or intolerance with one or more EGFR TKIs appropriate for the treatment of EGFR-mutant NSCLC as outlined below:

– 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 (for example: erlotinib, gefitinib, afatinib, dacomitinib) and who have no evidence of the EGFR T790M mutation in the tumor tissue after TKI therapy are eligible. Patients whose T790M mutational status is unknown are also eligible if this is in accordance to local standard practice.
– Patients who have progressed on or were intolerant to first- or second-generation EGFR TKIs and who have evidence of the EGFR T790M mutation in the tumor tissue after TKI therapy must also have progressed on, were intolerant to, or lack access to third-generation TKIs such as osimertinib or others.

Patients with a previously detected ALK fusion oncogene must additionally have experienced disease progression (during or after treatment) or intolerance to treatment with one or more ALK inhibitors (e.g., alectinib, crizotinib, brigatinib, ceritinib, lorlatinib, or others) appropriate for the treatment of NSCLC in patients having an ALK fusion oncogene.

The last dose of prior systemic anti-cancer therapy must have been administered ≥ 21 days prior to enrollment/randomization, with the exception being TKIs approved for treatment of NSCLC have to be discontinued ≥ 7 days prior to Cycle 1, Day 1. The baseline scan must be obtained after discontinuation of prior TKIs (washout not required prior to obtaining the scan).

The last dose of treatment with any investigational agent or participation in another interventional study must have ended ≥ 28 days prior to enrollment/randomization.

Anti-cancer agents used for pleurodesis are not counted as a line of therapy.

Prior radiation therapy is allowed provided the patient has recovered from any toxic effects thereof.

Additional Inclusion Criteria Applicable to Part 1 Only

Patients in Part 1 must also meet the following additional criteria for study entry:

- A body mass index (BMI) between 18 and 32 kg/m^2 inclusive

Additional Inclusion Criteria Applicable to Part 2 Only

Patients in Part 2 must also meet the following additional criteria for study entry:

- For patients whose tumor may harbor a sensitizing *EGFR* mutation, known *EGFR* test results at the time of randomization

  Patients who may harbor a sensitizing EGFR mutation are defined as having non-squamous histology (including those with a mixed histology that includes any non-squamous component), and without any other known driver mutation (e.g., KRAS status wild-type/unknown, BRAF status wild-type/unknown, or ALK fusion oncogene negative/unknown).

  EGFR tests may be assessed locally or submitted for central laboratory testing. If available, EGFR status assessed locally should be performed on tissue samples using a validated health authority–approved test that detects mutations in exons 18–21. Patients recruited in China are required to be tested centrally, even if local results are available.

If patients are recruited in China or if no local results are available, tissue is required for central testing as promptly as possible and always prior to randomization

Patients with a sensitizing *EGFR* mutation will be excluded once approximately 10% of the total target sample size has been reached.

- Availability of a pre–study treatment representative formalin-fixed paraffin-embedded (FFPE) tumor specimen in paraffin block (preferred) or at least six slides containing unstained, freshly cut, serial sections from an FFPE tumor specimen for exploratory biomarker analysis (e.g., PD-L1)

  For patients recruited in China, availability of nine slides (including six for exploratory biomarker testing) containing unstained, freshly cut, serial sections from a pre–study treatment representative formalin-fixed paraffin embedded (FFPE) tumor specimen.

  For both patients recruited in China and ex-China, if fewer slides are available at baseline, additional slides may be requested in case of testing failure.

Exclusion Criteria

General exclusion criteria applicable to both Parts 1 and 2 are described. Additional exclusion criteria applicable to either Part 1 or Part 2 are also described.

General Exclusion Criteria Applicable to Both Parts 1 and 2 (All Patients)

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

Cancer-Specific Exclusions

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

- Symptomatic, untreated, or actively progressing CNS metastases

  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.

  Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to enrollment, if all other criteria are met.

- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for $\geq$ 2 weeks prior to enrollment
- History of leptomeningeal disease
- 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 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 have 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 or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected serum calcium > ULN)
- History of malignancy other than NSCLC within 5 years prior to screening, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated with curative intent, or ductal carcinoma in situ treated surgically with curative intent)

General Medical Exclusions

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

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

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- History of severe anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or any component of the atezolizumab formulation
- 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, *granulomatosis with polyangiitis*, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, 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.
  – There is 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

- Current treatment with anti-viral therapy for HBV
- 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, or any active infection that, in the opinion of the investigator, could impact patient safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to initiation of study treatment, unstable arrhythmias, or unstable angina

  Patients with a known left ventricular ejection fraction (LVEF) $<$40% will be excluded.

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF $<$ 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
- 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 course of the study
- Prior allogeneic stem cell or solid organ transplantation
- 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
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, or that may affect the interpretation of the results, or may render the patient at high risk from treatment complications

<u>Exclusion Criteria Related to Medications</u>

- Prior treatment with CD137 agonists or immune checkpoint blockade therapies including anti-TIGIT, anti−PD-1, and anti−PD-L1 therapeutic antibodies

  Patients who have had prior anti−CTLA-4 treatment may be enrolled, provided the following requirements are met:

  – Last dose of anti−CTLA-4 at least 6 weeks prior to enrollment
  – No history of severe immune-mediated adverse effects from anti−CTLA-4 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 3 or 4)
- 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

  Prior treatment with cancer vaccines is allowed.
- 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 enrollment

  Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study.

  The use of corticosteroids (≤ 10 mg oral prednisone or equivalent) for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency is allowed.
- Known allergy or hypersensitivity to hyaluronidase, bee or vespid venom, or any other ingredient in the formulation of rHuPH20

Additional Exclusion Criteria Applicable to Part 1 Only

Patients in Part 1 who meet the following additional criterion will be excluded from study entry:

- Pathology (e.g., lower extremity edema, cellulitis, lymphatic disorder or prior surgery, preexisting pain syndrome, previous lymph node dissection, etc.) that could interfere with any protocol-specified outcome assessment (e.g., PK)

Additional Exclusion Criteria Applicable to Part 2 Only

Patients in Part 2 who meet any of the following additional criteria will be excluded from study entry:

- Tested tumor PD-L1 expression status with an intention to treat the patient if positive. This implies that:
  - Patients who had access to PD-1 or PD-L1 first line therapies and were tested for PD-L1 expression status are not eligible, irrespective of the test result
  - Patients who had no access to PD-1 or PD-L1 first line therapies but were tested anyway as part of a testing routine despite lack of access are eligible, irrespective of the test result

END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or when the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 33 months after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

LENGTH OF STUDY

The total duration of the study, from screening of the first patient to the end of the study, is expected to be approximately 5.3 years.

INVESTIGATIONAL MEDICINAL PRODUCTS

TEST PRODUCT (INVESTIGATIONAL DRUG)

The investigational medicinal products (IMPs) for this study are atezolizumab SC for co-mix, atezolizumab SC, atezolizumab IV, and rHuPH20; IMPs will be supplied by the Sponsor.

Atezolizumab SC for co-mix will be manually mixed with rHuPH20 at a concentration of 2000 U/mL.

Atezolizumab SC will be co-formulated with rHuPH20 in the atezolizumab SC formulation at a concentration of 2000 U/mL.

In Part 1 of the study, patients will receive one (Cohort 1) or three (Cohorts 2 and 3) administrations of atezolizumab SC co-mix or atezolizumab SC. After treatment with atezolizumab co-mix or atezolizumab SC is concluded, patients will receive atezolizumab 1200mg IV Q3W for subsequent cycles until disease progression, loss of clinical benefit, unacceptable toxicity, or withdrawal of consent.

In Part 2, patients will be randomized in a 2:1 ratio to receive monotherapy with either 1875 mg of atezolizumab SC Q3W or 1200 mg of atezolizumab IV Q3W, respectively, starting on Day 1 of each 21-day cycle. The dose level of atezolizumab SC proposed to be tested in this phase will be derived from the results obtained in Part 1 of the study. Patients will receive atezolizumab SC or atezolizumab IV until disease progression, loss of clinical benefit, or unacceptable toxicity.

STATISTICAL METHODS

PRIMARY ANALYSIS

PK analyses of Part 1 will be performed on data from all PK-evaluable patients enrolled in Part 1. A PK-evaluable patient is defined as one who has received at least one dose of atezolizumab (atezolizumab SC co-mix, atezolizumab SC, or atezolizumab IV) and has at least one evaluable postdose PK sample, and who does not have protocol deviations that could affect PK results.

Specific criteria for exclusion from the primary analysis will be defined prior to the analysis and documented in the Statistical Analysis Plan.

The Part 1 safety analysis population is defined as all patients who received at least one dose of atezolizumab (atezolizumab SC co-mix, atezolizumab SC, or atezolizumab IV).

In Part 2, the primary analysis will be performed in the per protocol PK analysis population. This population will include patients in the atezolizumab SC and atezolizumab IV treatment arms who do not have protocol deviations that could affect PK results.

DETERMINATION OF SAMPLE SIZE

The sample size for Part 1 was determined by using simulation methods. Cohorts 1 and 2 are planned to enroll approximately 12 eligible patients each and Cohort 3 is planned to enroll approximately 20–30 eligible patients for a total of approximately 60 patients in Part 1. Based on the known PK profile of atezolizumab IV, such a sample size should allow estimation of the PK parameters with sufficient precision.

A total of 327 patients are planned to be randomized in Part 2 of the study. This sample size will provide sufficient power for the statistical hypothesis test for the primary endpoint, based on the following assumptions:

- 2:1 randomization ratio
- True GMR $\geq$ 0.95 for Cycle 1 C_{trough}
- True GMR $\geq$ 0.95 for Cycle 1 $AUC_{0–21\ d}$
- One-sided significance level 0.05
- Coefficient of variation (CV%) of geometric mean C_{trough} in Cycle 1 is $<$55%; this value is based on the results observed after atezolizumab SC co-mix administration in Part 1 of the study (clinical cutoff date 10 March 2020)
- CV% of geometric mean Cycle 1 $AUC_{0–21\ d}$ is $<$ 45%; this value is based on the results observed after atezolizumab SC co-mix administration in Part 1 of the study (CCOD 10 March 2020)
- Positive correlation between Cycle 1 $AUC_{0–21\ d}$ and Cycle 1 C_{trough} $>$ 0.8; this value is based on the results observed after atezolizumab SC co-mix administration in Part 1 of the study (CCOD 10 March 2020)

The total number of patients to be enrolled in Part 2 of the study may be increased or decreased, after taking into account the actually observed PK variability during the blinded sample-size re-estimation (once approximately 210–250 patients have been randomized). For example, for a coefficient of variation of 70% for Cycle 1 C_{trough}, the number of patients enrolled in Part 2 would be increased to 477 in order to ensure sufficient power for the non-inferiority test.

SAFETY ANALYSES

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. Laboratory toxicities will be defined based on local laboratory normal ranges and NCI CTCAE, v5.0.

INTERIM ANALYSES

No formal interim statistical analysis is planned in the study.

During Part 1, PK data will be analyzed on an ongoing basis. In addition, data will be reviewed by an Internal Monitoring Committee (IMC) at regular intervals. All required analyses will be performed by the study team and provided to the IMC. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRBs/ECs.

During Part 2, a JMC will be set up to evaluate PK and safety data on an ongoing basis. All analyses for this review will be prepared by the study team, who will maintain the blind of treatment allocation.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody, also known as an anti-therapeutic antibody
AUC	area under the concentration–time curve
CCOD	clinical cutoff date
CIT	cancer immunotherapy
C_{max}	maximum serum concentration observed
COVID-19	coronavirus disease 2019
CR	complete response
CRS	cytokine-release syndrome
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CTSQ	Cancer Therapy Satisfaction Questionnaire
CV	coefficient of variation
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
ER	exposure-response
FAS	Full Analysis Set
FFPE	formalin-fixed paraffin-embedded
GMR	geometric mean ratio
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	health care professional
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICH	International Council for Harmonisation
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)

Abbreviation	Definition
IRB	Institutional Review Board
IRR	infusion-related reaction
FAS	Full Analysis Set (population)
IxRS	interactive voice or web-based response system
JMC	Joint Monitoring Committee
Ln	natural logarithm
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic
popPK	population PK
PR	partial response
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
rHuPH20	recombinant human hyaluronidase
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SmPC	Summary of Product Characteristics
SWT	Satisfaction with Cancer Therapy (scale)
T3	triiodothyronine
T4	thyroxine
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum serum concentration
TPS	tumor proportion score
UCC	urothelial cell carcinoma
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON NON–SMALL CELL LUNG CANCER

Lung cancer remains the leading cause of cancer deaths worldwide; it is the most common cancer in both men and women and accounts for 12%–14% of all new cancer cases in the United States. In 2019 in the United States, it was estimated that there were 228,150 new cases of lung cancer (116,440 in men and 111,710 in women) and 142,670 lung cancer deaths (American Cancer Society 2019). Similar data from Europe estimate that in 2018 there were 387,900 lung cancer deaths (267,300 in men and 120,600 in women) (Ferlay et al. 2019).

In China in 2015, there were approximately 733,300 new cases of lung cancer and 610,200 lung cancer deaths (Chen et al. 2016).

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.

Despite recent advances in the treatment options for patients with metastatic NSCLC, the majority of patients will ultimately relapse and die from their disease: 5-year survival rates are still disappointingly low (Detterbeck et al. 2017). Continued research into new drugs and combination therapies is therefore required to expand the clinical benefit to a broader patient population and to improve outcomes in NSCLC. Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, distant metastases, poor performance status, and a history of unintentional weight loss. Notably, more than half of the patients with NSCLC are diagnosed with distant disease.

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 TREATMENT FOR NON–SMALL CELL LUNG CANCER

1.2.1 First-Line Non–Small Cell Lung Cancer

The discovery of treatable oncogenic alterations has led to the recommendation that molecular testing should be included as a standard approach to further classify NSCLC. Genotype-directed therapy has the potential to dramatically improve the balance of benefit and toxicity for selected patients with NSCLC characterized by alterations of driver oncogenes, including sensitizing *EGFR* mutations and *ALK* rearrangements. However, these mutations are more prevalent in adenocarcinoma NSCLC and are very rare in squamous NSCLC.

For patients with a targetable oncogenic driver mutation, randomized Phase III studies have demonstrated clinical efficacy and manageable toxicity of *EGFR* and *ALK* inhibitors versus chemotherapy (Fan et al, 2018; Ayati et al. 2020).

Patients with previously untreated NSCLC that does not harbor a targetable oncogenic driver mutation have been typically treated with platinum-based chemotherapy. The standard-of-care chemotherapy in the first-line setting often involves either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab for non-squamous NSCLC, and cisplatin or carboplatin and gemcitabine for squamous NSCLC. However, the benefit conferred by platinum-based doublets appeared to have reached a plateau in objective response rate (ORR; approximately 15%–22%) and median survival (7 to 10 months). The addition of bevacizumab to carboplatin and paclitaxel in the treatment of non-squamous NSCLC resulted in an increase in response rate from 15% to 35% and an increase in median overall survival (OS) from 10 to 12 months.

Immune checkpoint inhibitors, including PD-L1/PD-1–blocking antibodies, have emerged as a new therapeutic option for the first-line treatment of metastatic NSCLC (Xia et al, 2019). In the randomized Phase III study GO29436 (IMpower150), OS and progression-free survival (PFS) were significantly prolonged with atezolizumab, bevacizumab, paclitaxel, and carboplatin relative to bevacizumab, paclitaxel, and carboplatin in patients with advanced non-squamous NSCLC without an activating *EGFR* mutation or *ALK* gene rearrangement independent of the PD-L1 expression level (Socinski et al. 2018). The randomized Phase III study GO29537 (IMpower130) found that the addition of atezolizumab to carboplatin plus nab-paclitaxel significantly improved overall and progression-free survival in first-line treatment of Stage IV non-squamous NSCLC with no *ALK* or *EGFR* mutations. A benefit in OS and PFS in the atezolizumab group was observed, regardless of PD-L1 expression (West et al. 2019). In the KEYNOTE-189 study, OS and PFS were also significantly improved with pembrolizumab, pemetrexed, and carboplatin relative to pemetrexed and carboplatin in patients with advanced non-squamous NSCLC (Gandhi et al. 2018; Gadgeel et al. 2019). In the CHECKMATE-9LA study, nivolumab, given in combination with ipilimumab and two cycles of chemotherapy, demonstrated superior efficacy when compared to chemotherapy-only (Reck et al, 2020).

Results from these studies have led to the approval in the United States and other countries of atezolizumab, nivolumab in combination with ipilimumab and pembrolizumab, with the corresponding chemotherapy regimens, as first-line therapy for patients with advanced non-squamous NSCLC without an activating *EGFR* mutation or *ALK* gene rearrangement.

Chemotherapy-based regimens are associated with substantial toxicities and are generally poorly tolerated by elderly patients and by patients with poor performance status. Therefore, novel therapies that deliver an improved therapeutic index are needed for NSCLC. Pursuing personalized cancer immunotherapy (CIT), several Phase III trials have been conducted to investigate chemotherapy-free regimens involving anti–PD-L1/PD-1 inhibitors versus standard cytotoxic chemotherapy in treatment-naive patients with PD-L1–positive NSCLC.

The KEYNOTE-024 study demonstrated significant improvement in survival with pembrolizumab monotherapy over standard platinum-based doublets in advanced NSCLC with high PD–L1 expression (tumor proportion score [TPS] ≥50% (Reck et al. 2016; Reck et al. 2019).

In the KEYNOTE-042 study in which patients with a TPS ≥ 1% were enrolled, survival outcomes of pembrolizumab compared with chemotherapy doublets in the two primary patient populations with a TPS ≥ 50% and a TPS ≥ 1% were statistically significant and clinically meaningful in favor of pembrolizumab. However, patients in a prespecified exploratory subgroup with TPS 1%–49% appeared to have similar OS in the two arms (Mok et al. 2019). Based on results from these studies, pembrolizumab is approved for first-line treatment in patients with metastatic NSCLC without an activating *EGFR* mutation or *ALK* gene rearrangement, in the United States in patients whose tumors express PD-L1 (TPS ≥ 1%) and in the European Union in patients whose tumors express high PD-L1 (TPS ≥ 50%).

At the time of the interim OS analysis (clinical cutoff date, 10 September 2018) in Study GO29431 (IMpower110), of atezolizumab monotherapy compared with platinum-based doublet chemotherapy as first-line treatment of metastatic NSCLC that expresses high PD-L1, atezolizumab monotherapy showed a statistically significant and clinically meaningful improvement in OS compared with chemotherapy in patients with high PD-L1 expression (TC3/IC3-WT). Because the OS statistical testing boundary was not crossed in the TC2/3 or IC2/3-WT or TC1/2/3 or IC1/2/3-WT subgroups at this interim analysis, the study will continue to the OS final analysis for these subgroups (Spigel et al. 2019).

In conclusion, immune checkpoint inhibitor treatment in combination with and without chemotherapy is becoming standard of care in the treatment of patients with first-line NSCLC. However, patient access to immunotherapies in the first-line setting can vary considerably across countries.

1.2.2 Previously Treated Non–Small Cell Lung Cancer

The choice of agent in the second-line setting depends on a number of factors, including prior treatment regimens, tumor histology, comorbidities, toxicity from previous treatments, toxicity profile for a given agent, smoking history, and patient preference. Overall, the benefit profile of second-line therapies has been disadvantaged both by limited survival benefit and significant toxicities such as myelosuppression and neuropathy (docetaxel) and diarrhea (pemetrexed) (Stinchcombe and Socinski 2008).

With the approval of immune checkpoint inhibitors as first-line treatment of patients with advanced NSCLC, the treatment algorithm for this patient population is changing.

Monotherapy with immune checkpoint inhibitors (e.g., nivolumab [PD-1 inhibitor], pembrolizumab [PD-1 inhibitor], and atezolizumab [PD-L1 inhibitor]) have been approved for patients with metastatic NSCLC who experience disease progression during or following platinum-containing chemotherapy. Pembrolizumab is approved for patients whose tumors express PD-L1 (TPS $\geq$ 1%), whereas PD-L1 expression is not a requirement for patients receiving treatment with nivolumab or atezolizumab. For pembrolizumab, the median OS was 10.4 months for patients treated at 2 mg/kg every 3 weeks (Q3W) and 12.7 months for patients treated at 10 mg/kg Q3W (squamous and non-squamous histology combined) versus 8.5 months in the control arm (Keytruda® U.S. Package Insert; Keytruda Summary of Product Characteristics [SmPC]). For nivolumab, the median OS was 9.2 months versus 6 months in the control arm for patients with squamous histology and 12.2 months versus 9.4 months in the control arm for patients with non-squamous histology (Opdivo® U.S. Package Insert; Opdivo SmPC).

Atezolizumab IV monotherapy is approved for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy. This approval is based on results from the Phase III study GO28915 (OAK) demonstrating a statistically significant and clinically meaningful survival improvement with atezolizumab IV in monotherapy versus chemotherapy (docetaxel) in patients with locally advanced or metastatic NSCLC who received prior chemotherapy (HR = 0.73; 95% CI: 0.62 to 0.87; p = 0.0003; median OS 13.8 vs. 9.6 months) (Rittmeyer et al. 2017).

In addition to immune checkpoint inhibitors and platinum-based chemotherapy, docetaxel and pemetrexed are approved for patients with metastatic NSCLC who experience disease progression during or following prior chemotherapy. Docetaxel was associated with an estimated median OS of 6–10 months (Stinchcombe and Socinski 2008; Ramlau et al. 2012). Pemetrexed had a higher impact on PFS and OS compared with docetaxel in patients with non-squamous histologies, thus limiting its approval to patients with these histologies (Scagliotti et al. 2009).

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 patients with cancer and is being investigated as a potential therapy in a wide variety of solid tumors and hematological 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 other cancer immunotherapies.

Atezolizumab IV, as single agent and/or in combination, is approved for the treatment of urothelial carcinoma, non–small cell lung cancer, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

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

1.3.1 Nonclinical Studies with Subcutaneously Injected Atezolizumab

The nonclinical safety of subcutaneously injected atezolizumab has been studied in a Good Laboratory Practice repeat-dose study in cynomolgus monkeys to evaluate the toxicity and toxicokinetics following weekly administration for 8 weeks (nine total doses) and to assess the reversibility or persistence of any effects after a 12-week, treatment-free recovery period. Weekly SC administration of atezolizumab was well tolerated at dose levels up to 50 mg/kg. All animals survived to scheduled necropsy or disposition. Atezolizumab administration had no effects on clinical observations, body weight, food consumption, respiratory rate, heart rate, body temperature, blood pressure, electrocardiograms, pulse oximetry, physical, neurologic, ophthalmologic, or cardiovascular examinations, clinical pathology (hematology, serum chemistry, coagulation, or urinalysis), immunologic endpoints (immunophenotyping via flow cytometry, serum cytokines, anti-nuclear antibodies, or anti-dsDNA antibodies), organ weights, or macroscopic pathology.

At terminal necropsy, microscopic lesions that were considered related to atezolizumab administration included arteritis/periarteritis in various tissues in 1 of 6 animals in the 15 mg/kg SC dose groups and in 2 of 6 animals in the 50 mg/kg SC dose group. Generally, affected vessels were located within the interstitium of parenchymal organs (heart, kidney, liver, pancreas, and epididymis) or within the submucosa or muscularis of tubular organs, such as the gastrointestinal and female reproductive tracts. These observations were characterized primarily by increased thickening of the tunica adventitia and intima of medium-sized arteries by spindle cells with large nuclei and

accompanying mixed inflammatory cell infiltrate. Similar microscopic arterial findings occur spontaneously in cynomolgus monkeys to the same extent (generally subclinical in severity, similar in tissue distribution) (Beach et al. 1974; Chamanza et al. 2006); however, this finding is considered atezolizumab-related as it occurred only in test article–treated groups, appears to be dose-related in incidence (high- and mid-dose groups), and occurred at a higher incidence than historical controls at this test facility (historical incidence of approximately 1%). Arteritis/periarteritis was not present at the recovery necropsy timepoint, indicating either resolution during the recovery period or lack of occurrence in the recovery cohorts due to the relatively low incidence within affected dose levels. In addition, minimal, focal to multifocal, and often perivascular mononuclear cell infiltrates were noted in the SC tissue at the injection sites for 3 of 6 animals and 6 of 6 animals in the 15 and 50 mg/kg SC dose groups, respectively; these findings were also considered related to atezolizumab administration. This injection site change was not present at recovery necropsy, suggesting reversibility. The minimal injection-site findings are consistent with SC administration of heterologous protein and resolved during the recovery period; therefore, they were not considered adverse.

Linear dose-dependent systemic exposures were observed up to Day 7 in all dosed groups. The mean concentration-time profiles for males and females show that exposure to atezolizumab generally increased with the increase in dose level and no sex differences greater than 2-fold were observed in mean maximum serum concentration (C_{max}) or exposure values, with the exception of the 5 mg/kg dose level (Roche Study 13-3278 Clinical Study Report, available on request) that was likely confounded by the presence of anti-drug antibodies (ADAs). Overall, the serum concentration–time profiles of all dose groups exhibited apparent biphasic disposition in which a rapid initial distribution phase was followed by a slower elimination phase. Bioavailability of atezolizumab following SC administration of 15 mg/kg or 50 mg/kg was estimated to be 54.3% and 51.8%, respectively.

1.4 BACKGROUND ON RECOMBINANT HUMAN HYALURONIDASE (rHuPH20)

The feasibility and patient acceptability of SC administration of any drug are dependent on the volume of drug that must be administered. The recombinant human hyaluronidase enzyme (rHuPH20) (Hylenex®) is a hyaluronidase for human injection that has been developed by Halozyme Therapeutics, Inc., and is approved in the European Union and United States as a permeation enhancer to improve dispersion and absorption of SC formulations, enabling larger volumes to be administered without reduced tolerability and with improved patient acceptability. Hyaluronidase transiently hydrolyses hyaluronan, a component of the SC matrix, leading to reduced viscosity of the extracellular matrix of the hypodermis and, thus, to an improved delivery of subcutaneously administered drugs to the systemic circulation. rHuPH20,

a recombinant human molecule, has a higher purity and is associated with improved tolerability compared with the animal-derived enzyme (Hylenex U.S. Package Insert).

The safety and efficacy of hyaluronidase products have been widely established. The most significant safety risk identified is hypersensitivity/allergenicity, which is thought to be related to the lack of purity of the animal-derived preparations. The rHuPH20 to be used in the current study is produced from a second generation of the Hylenex process that has improved yield and purity. The concentration of rHuPH20 is guided by data from a mini-pig study in which trastuzumab was administered subcutaneously. In the presence of either 2000 or 6000 U/mL of rHuPH20, there was a more rapid absorption of subcutaneously administered trastuzumab from rHuPH20-containing formulations, while the effect on the absorption rate of trastuzumab was comparable with both rHuPH20 concentrations. Therefore, the lower rHuPH20 concentration of 2000 U/mL was selected.

The highest total rHuPH20 dose administered in a clinical study was 96,000 U (rHuPH20 Investigator's Brochure). This Phase I study investigated the SC injection of adalimumab with different rHuPH20 concentrations in healthy volunteers using different volumes of injection (2, 8, and 16 mL). All injections were well tolerated with no serious adverse events reported. Common injection-site reactions observed were erythema, ecchymosis, pain, and induration. All injection-site reactions, such as erythema, pain, and induration, were mild (98%) or moderate (2%).

To date, four monoclonal antibodies co-formulated with rHuPH20, are approved for SC therapy in oncology in the United States and three in the European Union (Phesgo™ U.S. Package Insert, Darzalex® U.S. Package Insert, Darzalex SmPC, Herceptin® U.S. Package Insert; Herceptin SmPC; Rituxan® U.S. Package Insert; MabThera® SmPC).

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Atezolizumab is available as a concentrated solution for IV infusion. Atezolizumab IV is infused over a period of 60 (±15) minutes. Subsequent infusions are delivered in 30 (±10) minutes if the previous infusion was tolerated without infusion-related reaction or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. For many patients, the atezolizumab IV infusion time may be a taxing experience and disadvantage of the current therapeutic approach. For other patients, such as those with difficult venous access or poor renal or cardiac function, the need for IV infusions may constitute a major challenge. Furthermore, increasing usage of intravenously administered monoclonal antibodies combined with or without chemotherapy has placed a strain on medical centers with respect to time and resources required to prepare and administer the IV infusions that are currently commercially available. The change to the SC route of administration for monoclonal antibodies such as trastuzumab and rituximab has demonstrated a reduction in treatment burden for patients, with improved time and resource utilization at the treatment facility (Pivot et al. 2013; Rummel et al. 2015; De Cock et al. 2016). Furthermore, available data for

subcutaneously administered monoclonal antibodies (daratumumab [Darzalex], trastuzumab [Herceptin], rituximab [MabThera/Rituxan], and trastuzumab plus pertuzumab [Phesgo]) consistently demonstrate that subcutaneous formulations are well tolerated and anti-tumor activity remains the same regardless of administration route (Ismael et al. 2012; Davies et al. 2014; Assouline et al. 2015).

In view of the above aspects, a new formulation of atezolizumab for SC injection is being developed (atezolizumab SC). Atezolizumab SC is a ready-to-use formulation of atezolizumab co-formulated with rHuPH20, a human recombinant hyaluronidase, developed to improve dispersion of large volumes of drugs (i.e., it functions as a permeation enhancer). Atezolizumab SC will be administered with a target delivery time under 10 minutes (depending on bioavailability results).

Results as of the clinical cutoff date (CCOD) of 10 March 2020 from Part 1 of this study (BP40657), with safety of Cycle 1 where all 67 patients received atezolizumab SC administration, demonstrated that although the percentage of patients with adverse events were 69.2% (9 of 13 patients) in Cohort 1, 53.3% (8 of15 patients) in Cohort 2, and 61.5% (24 of 39 patients) in Cohort 3, most adverse events were Grade 1 or 2 in maximum severity. No adverse events in Cycle 1 led to discontinuation of atezolizumab SC. The safety profile of atezolizumab SC was consistent with the known risks of atezolizumab IV. No new safety concerns were identified, and no clinically significant difference in safety profiles among the cohorts was observed.

Based on these considerations, it is expected that SC administration of atezolizumab will result in reduced treatment burden, increased patient satisfaction, and improved cost-effectiveness, while maintaining similar efficacy and safety to the IV formulation of the same product.

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of SARS-CoV-2 infection.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy.

Severe SARS-CoV-2 infection appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN)-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from SARS-CoV-2 infection.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and SARS-CoV-2 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of SARS-CoV-2 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, SARS-CoV-2 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of SARS-CoV-2 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab treatment to receive SARS-CoV-2 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering SARS-CoV-2 vaccines. When administered, SARS-CoV-2 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the SARS-CoV-2 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4.1).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics, safety, and efficacy of atezolizumab SC compared with atezolizumab IV in patients with locally advanced or metastatic NSCLC who have not been exposed to cancer immunotherapy (CIT) (i.e., "CIT-naive") and for whom prior platinum-based therapy has failed. The study is comprised of two parts, as follows:

- Part 1 (Phase Ib, dose finding) will aim to identify the dose of atezolizumab SC that yields drug exposure that is comparable to that of atezolizumab IV
- Part 2 (Phase III, randomized, dose confirmation) will aim to demonstrate the non-inferiority of observed drug exposure following treatment with atezolizumab SC at the identified dose compared with drug exposure following treatment with atezolizumab IV

Specific objectives for each part of the study and corresponding endpoints are outlined in Sections 2.1 and 2.2.

Definitions used in this study are outlined in the following table:

Table 1 Study Definitions

Atezolizumab	Atezolizumab monoclonal antibody as a molecule, irrespective of its formulation
Atezolizumab SC co-mix	SC formulation of atezolizumab for co-mix with rHuPH20, manually mixed at the local pharmacy
Atezolizumab SC	Ready-to-use SC formulation of atezolizumab co-formulated with rHuPH20
Atezolizumab IV	Currently approved formulation of atezolizumab for IV infusion in its 1200 mg vial configuration
Study treatment	Combination of treatments assigned to patients as part of this study (i.e., in Part 1, atezolizumab SC co-mix or atezolizumab SC; in Part 2, atezolizumab SC or atezolizumab IV

IV = intravenous; SC = subcutaneous.

2.1 OBJECTIVES AND ENDPOINTS FOR PART 1

2.1.1 Pharmacokinetic Objectives for Part 1

The primary pharmacokinetic (PK) objective for Part 1 is to determine the dose of atezolizumab SC that is predicted to yield drug exposure that is comparable to that of atezolizumab IV on the basis of the following endpoint:

- Serum atezolizumab trough concentration (C_{trough}) at Cycle 1 (i.e., predose Cycle 2)

The secondary PK objective for Part 1 is to characterize the PK profile of atezolizumab SC on the basis of the following endpoint:

- Serum atezolizumab concentration at specified timepoints during SC administration

The exploratory PK objective for Part 1 is to characterize the PK profile of rHuPH20 on the basis of the following endpoint:

- Plasma rHuPH20 concentration at specified timepoints during SC administration

2.1.2 Safety Objective for Part 1

A secondary objective for Part 1 is to evaluate the safety of atezolizumab SC on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0)
- Incidence and severity of targeted vital signs
- Incidence and severity of clinical laboratory abnormalities

2.1.3 Immunogenicity Objective for Part 1

The exploratory immunogenicity objective for Part 1 is to evaluate the immune response to atezolizumab SC and rHuPH20 on the basis of the following endpoints:

- Incidence of ADAs to atezolizumab after SC administration relative to the prevalence of ADAs at baseline
- Incidence of ADAs to rHuPH20 after SC administration relative to the prevalence of ADAs at baseline

2.2 OBJECTIVES AND ENDPOINTS FOR PART 2

2.2.1 Pharmacokinetic Objectives for Part 2

The primary PK objective for Part 2 is to demonstrate non-inferiority of exposure to atezolizumab SC compared with atezolizumab IV on the basis of the following co-primary endpoints:

- Observed serum C_{trough} at Cycle 1 (predose Cycle 2)
- Model-predicted area under the concentration-time curve (AUC) from 0 to 21 days ($AUC_{0–21\ d}$) at Cycle 1

A secondary PK objective for Part 2 is to evaluate exposure following administration of atezolizumab SC compared with atezolizumab IV on the basis of the following endpoints, as appropriate and as data allow:

- Model-predicted C_{trough} at Cycle 1 ($C_{trough\ Cycle\ 1}$), model-predicted C_{trough} at steady state ($C_{trough,ss}$), and model-predicted AUC at steady state (AUC_{ss})

The exploratory PK objective for Part 2 is to evaluate potential relationships between atezolizumab exposure and efficacy and safety.

2.2.2 Safety Objectives for Part 2

A secondary objective for Part 2 is to evaluate the safety of atezolizumab SC compared with atezolizumab IV on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0
- Overall patient-reported adverse event burden over time, as assessed by the patient global impression of cancer treatment side effects burden item from the European Organisation for Research and Treatment of Cancer (EORTC) IL57

2.2.3 Efficacy Objectives for Part 2

A secondary objective for Part 2 is to evaluate the efficacy of atezolizumab SC on the basis of the following endpoints:

- ORR, defined as the proportion of patients with a complete response (CR) or partial response (PR), as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
- PFS, defined as the time from study entry 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
- OS, defined as the time from study entry to death from any cause
- Duration of response (DOR), defined as the time from 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

An additional secondary objective for Part 2 is to evaluate patient experience with atezolizumab SC compared with atezolizumab IV, on the basis of the following endpoints:

- Functioning and global health status over time, as assessed by the physical functioning, role functioning, and global health status/quality of life scales of the EORTC IL57
- Overall satisfaction with treatment, as assessed by the modified satisfaction with therapy (SWT) scale of the Cancer Therapy Satisfaction Questionnaire (CTSQ)

2.2.4 Immunogenicity Objectives for Part 2

A secondary objective for Part 2 is to evaluate the incidence of ADAs to the tested molecules on the basis of the following endpoint:

- Incidence of ADAs to atezolizumab after SC administration or IV administration relative to the prevalence of ADAs at baseline
- Incidence of ADAs to rHuPH20 after SC administration relative to the prevalence of ADAs at baseline

The exploratory immunogenicity objective for Part 2 is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between post-baseline ADA status and PK, safety, or efficacy endpoints

2.2.5 Biomarker Objective for Part 2

The exploratory biomarker objective for Part 2 is to evaluate biomarkers that may be predictive of response to atezolizumab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to atezolizumab, can provide evidence of atezolizumab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology. They will be evaluated on the basis of the following endpoint:

- Relationship between biomarkers in tumor tissue (listed in Section 4.5.7) and efficacy, or other biomarker endpoints

Refer to Section 4.5.7 for details on biomarkers and samples required for exploratory biomarker analysis.

2.2.6 Health Care Professional–Reported Experience Utility Objective for Part 2

The secondary utility objective for Part 2 is to evaluate health care professional (HCP)-reported experience with administration of atezolizumab SC and atezolizumab IV, on the basis of the following endpoints:

- Convenience, potential time savings, and overall satisfaction with atezolizumab SC compared with atezolizumab IV, as assessed by the HCP SC versus IV Perspective Questionnaire
- Convenience, ease of administration, and overall satisfaction with atezolizumab SC, as assessed by the HCP Subcutaneous Perspective Questionnaire

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a two-part, open-label, multicenter Phase Ib/III study in patients with locally advanced or metastatic NSCLC who are CIT-naive and for whom prior platinum therapy has failed. The two parts of the study are as follows:

- Part 1 of the study will consist of three single-arm cohorts and will determine the dose of atezolizumab SC that yields comparable exposure to atezolizumab IV on the basis of serum C_{trough} at Cycle 1 (predose Cycle 2). Atezolizumab SC co-mix will be used for Cohort 1 of Part 1. A ready-to-use formulation of atezolizumab with rHuPH20 (atezolizumab SC) may be used for Cohorts 2 and 3 of Part 1, subject to review and approval from relevant Health Authorities and Sponsor decision.

- Part 2 of the study will consist of a two-arm, randomized, multicenter study of atezolizumab SC compared with atezolizumab IV. The aim of Part 2 is to demonstrate non-inferiority of PK exposure of the SC formulation versus the IV formulation based on the co-primary endpoints, Cycle 1 observed serum C_{trough} (predose Cycle 2) and model-predicted $AUC_{0–21\ d}$. The ready-to-use SC formulation of atezolizumab co-formulated with rHuPH20 (atezolizumab SC) will be used in Part 2.

The study designs of Part 1 and Part 2 are is shown in Figure 1 and Figure 2, respectively. The schedule of activities for Part 1 is provided in Appendix 1 and for Part 2 in Appendix 2. The PK, immunogenicity, and biomarker sampling schedules are presented in Appendix 3 for Part 1 and Appendix 4 and Appendix 5 for Part 2.

After providing informed consent, patients will undergo screening procedures as outlined in the schedules of activities. Patients who do not initially meet all eligibility criteria for participation in this study may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion, provided all initial and subsequent screening assessments are performed within 56 days prior to Day 1. Re-screened patients must meet all eligibility criteria and re-sign the Informed Consent Form prior to re-screening.

A patient may be enrolled only once in this trial. As a general rule, patients enrolled into the study will not be replaced (see Section 4.6.1 for further details).

Safety will be monitored throughout the study by the Sponsor Internal Monitoring Committee (IMC) for Part 1 (see Section 3.1.3.1) and by a Joint Monitoring Committee (JMC) for Part 2 (see Section 3.1.3.2).

3.1.1.1 Part 1: Dose Finding

Part 1 will be composed of three cohorts: Cohorts 1 and 2 will consist of approximately 12 evaluable patients each and Cohort 3 will consist of approximately 20–30 evaluable patients.

Patients will receive one (Cohort 1) or more (Cohorts 2 and 3) administrations of atezolizumab SC co-mix or atezolizumab SC (see below for details) followed by treatment with atezolizumab IV 1200 mg Q3W, as indicated, for subsequent cycles until disease progression, loss of clinical benefit, unacceptable toxicity, or withdrawal of consent (see Section 3.1.2 for details).

The following cohorts are planned:

- Cohort 1: Patients will receive 1800 mg atezolizumab SC co-mix for one cycle (21 days), followed by 1200 mg atezolizumab IV Q3W for subsequent cycles.
- Cohort 2: Patients will receive 1200 mg atezolizumab SC co-mix or atezolizumab SC Q2W (14 days) for 3 cycles, followed by 1200 mg atezolizumab IV Q3W for subsequent cycles.

- Cohort 3: Patients will receive 1800 mg atezolizumab SC co-mix or atezolizumab SC Q3W (21 days) for 3 cycles, followed by 1200 mg atezolizumab IV Q3W for subsequent cycles.

In Cohorts 1 and 2, all SC injections will be administered in the thigh. In Cohort 3, the first subcutaneous dose of atezolizumab will be administered in the lower part of the abdomen and the following 2 doses will be administered in the thigh.

The doses specified for Cohorts 2 and 3 are projected doses. The actual doses will depend on the results from Cohort 1. Additional dose-finding cohorts may be opened if the doses from planned cohorts result in atezolizumab exposure outside of the expected exposure obtained with atezolizumab IV or if the variability in C_{trough} is too high to determine a dose for Part 2 of the study.

Dose Selection

Atezolizumab SC will be developed with the aim of selecting a dose that results in a serum C_{trough} that is comparable to that with atezolizumab 1200 mg IV Q3W. As atezolizumab has not been administered using the SC formulation in a clinical trial, the dose ranges for the SC formulation have been selected assuming a bioavailability of 70% based on prior clinical experience with other monoclonal antibodies administered using rHuPH20. Therefore, the 1800 mg atezolizumab SC co-mix is calculated to have serum C_{trough} comparable to 1200 mg atezolizumab IV Q3W. Doses for Cohorts 2 and 3 may be adjusted based on the Cohort 1 results. These cohorts will be enrolled after evaluation and completion of Cohort 1. Based on the ongoing evaluation of bioavailability data, it may be necessary to adjust the dose within the same cohort.

In the event the 1800 mg atezolizumab SC co-mix dose results in atezolizumab exposure consistent with the 1200 mg atezolizumab IV dose, it is expected that 1200 mg atezolizumab SC co-mix or atezolizumab SC Q2W will result in atezolizumab serum C_{trough} comparable to 840 mg atezolizumab IV Q2W. However, if the PK characteristics of atezolizumab SC remain uncertain, dosing regimens for Cohorts 2 and 3 may be modified to achieve comparable exposure to that observed with 1200 mg IV.

Safety Monitoring for the Different Cohorts

All patients must report any symptoms and adverse events immediately to the investigator, particularly during the first 72 hours after the first injection. Enrollment of the first 6 patients in Cohort 1 will be staggered in order to closely monitor the safety and tolerability resulting from the first atezolizumab SC co-mix administration. This will allow for a 72-hour interval during which safety will be assessed by the investigator and communicated to the Sponsor. Safety of the first 72 hours in these patients will be evaluated by the Sponsor before enrollment of the next patient. For Cohorts 2 and 3, enrollment of only the second patient will be dependent on the outcome of the safety assessment of the 72 hours from the first patient. Further enrollment in Cohorts 2 and 3 will be completed without staggering.

Gating Criteria and Treatment in Cohorts 2 and 3

Following assessment of PK and safety data for Cohort 1 provided the investigated dose has shown to be safe and tolerated (if PK properties have shown to be similar to PK properties for atezolizumab IV in Cohort 1), Cohorts 2 and 3 may be opened at the same time. On the basis of Sponsor decision (see Section 3.1.3.1) and cohort enrollment initiation requirements, Cohorts 2 and 3 will enroll independently, which may lead to enrollment overlap of Cohorts 2 and 3.

In Cohorts 2 and 3, patients will receive 3 cycles of atezolizumab SC co-mix or atezolizumab SC before switching to atezolizumab IV. This will allow further assessment of safety, as well as an early assessment of the immunogenicity of atezolizumab following multiple SC doses. For Cohort 2 only and upon consultation with the Medical Monitor, additional atezolizumab SC co-mix or atezolizumab SC cycles may be administered if this is deemed to be in the patients' best interest.

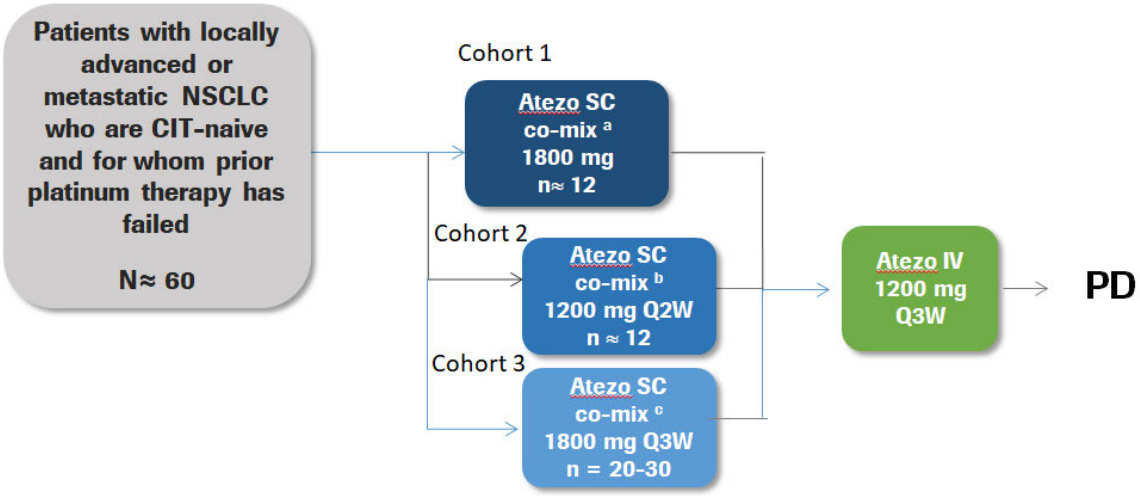
Data from all cohorts will be analyzed to determine the optimal atezolizumab SC dose to be tested in Part 2.

Patients will be followed until 90 days after the final dose of study treatment, initiation of new systemic anti-cancer therapy, withdrawal from the study, or study termination by the Sponsor, whichever occurs first.

Part 1 will be conducted at up to approximately 20 sites globally.

Figure 1 presents an overview of the Part 1 dose finding design. Schedules of activities for Part 1 are provided in Appendix 1 and Appendix 3.

Figure 1 Part 1: Overview of the Dose Finding Study Design



Atezo = atezolizumab; NSCLC = non–small cell lung cancer; PD = progressive disease; Q2W = every 2 weeks; Q3W = every 3 weeks.

[a] Single dose of atezolizumab SC co-mix (in the thigh).

[b] Three cycles of atezolizumab SC co-mix or atezolizumab SC Q2W (in the thigh).

[c] Three cycles of atezolizumab SC co-mix or atezolizumab SC Q3W (first injection in the abdomen and subsequent two injections in the thigh).

3.1.1.2 Part 2: Dose Confirmation

Part 2 will be initiated once a dose has been identified based on the cumulative data collected from Part 1 (see Section 3.3.1). In Part 2, patients will be randomized in a 2:1 ratio to receive monotherapy with either 1875 mg of atezolizumab SC Q3W or 1200 mg of atezolizumab IV Q3W, respectively, starting on Day 1 of each 21-day cycle.

Part 2 of this study will initially randomize approximately 327 patients across approximately 150 sites in a global enrollment phase.

To ensure a patient population representative of standard clinical practice, the Sponsor will periodically evaluate the prevalence of *EGFR* mutation and limit the number of patients with *EGFR*-positive mutation to a maximum of approximately 10% of all randomized patients if required. The Sponsor may also monitor other biomarkers such as PD-L1 expression levels and, if considered appropriate, carry out actions to ensure a balanced distribution in the study population.

A structured evaluation of safety data will be conducted after the first 24 patients (approximately 16 patients in the atezolizumab SC arm and another 8 patients in the atezolizumab IV arm) have completed at least one cycle to ensure that the safety of atezolizumab SC (provided as a ready-to-use mixture of atezolizumab and rHuPH20) is comparable to that of the atezolizumab SC co-mix formulation administered in Part 1.

The totality of available safety data will be used for the assessment. At the time of the structured evaluation of safety data, the available Cycle 1 C_{trough} data will be reviewed for these 24 patients. This data review will be performed in a blinded fashion and will provide a check that the Cycle 1 C_{trough} with the atezolizumab SC formulation is similar to the Cycle 1 C_{trough} measured after administration of the atezolizumab co-mix formulation. Randomization will not be interrupted, and patients will continue being treated.

A blinded sample-size re-estimation will be conducted once approximately 210–250 patients have been randomized. A blinded estimation of the total coefficient of variation percent (CV%) from all available Cycle 1 C_{trough} and AUC data will be compared with the CV% used in the calculation of sample size. Depending on the observed, blinded CV%, the Sponsor may decide to increase or decrease the number of patients to be randomized (see Section 6.3.2).

Atezolizumab SC Cycle 1 observed serum C_{trough} (predose Cycle 2) and model-predicted $AUC_{0–21\ d}$ will be measured and compared with atezolizumab IV Cycle 1 C_{trough} and model-predicted $AUC_{0\text{-}21\ d,}$ respectively, to confirm non-inferiority between atezolizumab SC and atezolizumab IV (co-primary PK endpoints). Model-predicted $C_{trough,Cycle\ 1}$, $C_{trough,ss}$, and AUC_{ss} will be evaluated and compared between atezolizumab SC and atezolizumab IV (for more details, refer to Section 6). Efficacy and safety information will be collected on a regular basis to assess secondary efficacy and safety endpoints.

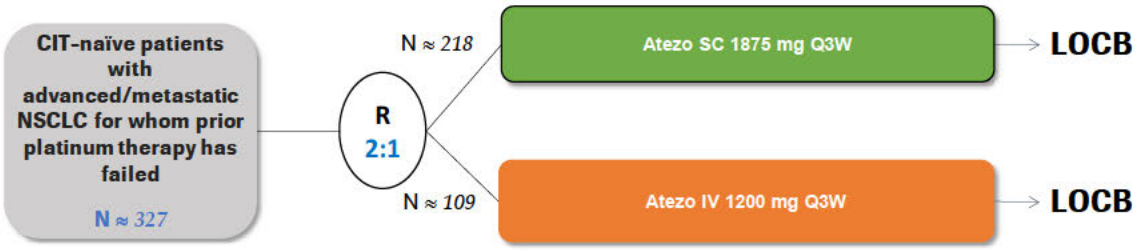
Patients will receive atezolizumab SC or atezolizumab IV, as indicated, until disease progression, loss of clinical benefit, or unacceptable toxicity (see Section 3.1.2 for details). Crossover is not allowed.

For Part 2, patients will undergo tumor assessments at baseline, every 6 weeks for the first 36 weeks following treatment initiation, and every 9 weeks thereafter, regardless of treatment delays, until radiographic disease progression per RECIST v1.1 or (for patients who continue atezolizumab after radiographic disease progression) loss of clinical benefit as determined by the investigator. Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy. Follow-up data capture, including survival status and subsequent anti-cancer therapies, will continue for each patient until death, loss of follow-up, withdrawal of consent, or study termination by Sponsor, whichever occurs first.

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per the NCI CTCAE v5.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab. Patient-reported outcome (PRO) assessments will also be performed at regular intervals as detailed in the schedule of activities (Appendix 2).

Figure 2 presents an overview of the Part 2 design. Schedules of Activities for Part 2 are provided in Appendix 2, Appendix 4, and Appendix 5.

Figure 2 Part 2: Overview of the Dose Confirmation Study Design



LOCB = loss of clinical benefit; NSCLC = non–small cell lung cancer; Q3W = every three weeks; R = randomization.

3.1.2 Treatment with Atezolizumab and Disease Progression according to RECIST v1.1

Irrespective of the administration route (SC or IV), treatment with atezolizumab will be administered, as indicated, until disease progression, loss of clinical benefit, unacceptable toxicity, or withdrawal of consent. Patients may continue treatment with atezolizumab beyond radiographic progression by RECIST v1.1, provided they are experiencing 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). 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 the 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 Eastern Cooperative Oncology Group (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

3.1.3 Monitoring Committees

3.1.3.1 Internal Monitoring Committee

An IMC will be established for Part 1 of the study and will be composed of Sponsor members who are independent from the study team. The IMC will share responsibility with the study team for the monitoring of patient safety.

The IMC will meet on a regular basis over the course of the Part 1 of the study as specified in the IMC charter. The IMC may also meet on an unscheduled basis should any unexpected safety concerns arise. Further details on the composition, roles, and responsibilities of the IMC are documented in the IMC charter.

3.1.3.2 Joint Monitoring Committee

A JMC will be convened to evaluate safety data during Part 2 of the study. The JMC will be composed of internal and external members; further details on the composition, roles and responsibilities, and meeting schedule of the JMC are documented in the JMC charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or when the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 33 months after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

The total duration of the study, from screening of the first patient to the end of the study, is expected to be approximately 5.3 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Dose, Administration Site, and Schedule for Part 2

Refer to Section 3.1.1.1 for a rationale of the dose and schedule selection in Part 1 of the study. PK, ADA, and safety results from Part 1 of the study have provided the rationale for dose, administration site, and schedule selection for atezolizumab SC for Part 2. These results are summarized below.

In Part 1, atezolizumab SC co-mix, given at a dose of 1800 mg Q3W in the thigh, provided similar observed Cycle 1 C_{trough} and $AUC_{0-21\,d}$ values as atezolizumab given at a dose of 1200 mg IV Q3W in Phase III study GO28915 (OAK) (observed Cycle 1 C_{trough} [CV %]: 121.1 μg/mL [42.8%] and 76.0 μg/mL [53.9%], respectively; Cycle 1 $AUC_{0-21\,d}$: 3868 μg*day/mL [38.6%] (observed) and 2978 μg*day/mL [26.1%] [model-predicted], respectively).

Atezolizumab PK data after both SC and IV administrations from Part 1 were modeled using a population PK (popPK) approach. A higher bioavailability was estimated for administration in the thigh (82.9%) compared with in the abdomen (71.1%), with an inter-individual variability of 124%. Using the popPK model, simulations of the proposed Phase III study in Part 2 indicated that an SC dose of 1800 mg Q3W given in the thigh had a high probability of providing comparable PK exposures to atezolizumab IV 1200 mg Q3W, in terms of Cycle 1 and steady state C_{trough} and $AUC_{0-21\,d}$.

The observed treatment-emergent ADA incidence for atezolizumab SC co-mix is within the range of ADA incidence rates observed across multiple Phase II and III studies with atezolizumab IV. Overall, the distributions of Cycle 1 C_{trough} values for ADA-positive and ADA-negative patients largely overlap each other for the three cohorts in Part 1. Thus, no impact of ADA status on PK exposure was observed. All atezolizumab C_{trough} levels, regardless of ADA status, were above the target concentration of 6 μg/mL.

Overall, atezolizumab administered subcutaneously was well tolerated and exhibited a safety profile consistent with the known risks of atezolizumab IV monotherapy. No new or significant safety concerns were identified. No clinically significant difference of safety profile for different dose regimens (1800 mg Q3W vs. 1200 mg Q2W) was observed. Comparison between Cohort 1 and Cohort 3 of Cycle 1 (SC only) adverse events did not show a meaningful difference of safety profile between dosing in the thigh and dosing in the abdomen.

The dose of 1800 mg corresponds to an atezolizumab SC volume of 14.4 mL. To improve dosing precision with the use of a 20 mL syringe, 15 mL of atezolizumab SC, corresponding to a dose of 1875 mg, will be administered in Part 2. The predicted exposures after the administration of an SC dose of 1875 mg are comparable to those observed after the administration of an 1800 mg dose, and as such, the safety profile is expected to be similar.

Based on the PK and safety results of Part 1, and to allow more precise dosing, the dose of 1875 mg Q3W administered in the thigh has been selected for atezolizumab SC for a randomized comparison of PK, efficacy, and safety with atezolizumab IV 1200 mg Q3W in Part 2.

3.3.2 Rationale for Patient Population and Control Arm

This study is to be conducted in patients with locally advanced or metastatic NSCLC who are "CIT- naive" and for whom first-line platinum-based therapy has failed. Atezolizumab IV is currently approved as a monotherapy in this setting based on the results of the Phase III study GO28915 (OAK) (Tecentriq U.S. Package Insert). Study GO28915 demonstrated that atezolizumab IV in monotherapy provides a survival improvement as compared with chemotherapy (docetaxel) in previously treated patients with advanced NSCLC (HR = 0.73; 95% CI: 0.62, 0.87; p = 0.0003; median OS 13 vs. 9.6 months). In addition to being a regimen with which atezolizumab has demonstrated

to be efficacious and its safety well-characterized, this monotherapy regimen also provides the possibility to assess the safety, efficacy, and immunogenicity of atezolizumab without the confounding effects of chemotherapy.

3.3.3 Rationale for Restricting the Number of Patients with a Sensitizing *EGFR* Mutation

Data in the second-line NSCLC setting suggest that PD-1/PDL1 inhibition is less effective, irrespective of PDL-1 expression, in patients with *EGFR* mutations compared with patients without *EGFR* mutations (Cavanna et al. 2019). The preferred course of treatment for patients with a sensitizing *EGFR* mutation is to target the acquired resistance and continue therapy under an alternative inhibitor (Jiang et al, 2018). Consequently, limiting the number of patients with a sensitizing *EGFR* mutation will ensure that the results obtained in this study are representative of current clinical practice.

3.3.4 Rationale for Co-Primary Pharmacokinetic Endpoints (Cycle 1 C_{trough} and $AUC_{0–21\ d}$)

The development program and use of co-primary PK endpoints, Cycle 1 observed serum C_{trough} (predose Cycle 2) and model-predicted $AUC_{0–21\ d}$, are based on a PK-bridging approach according to which the lowest exposure (C_{trough}) and the overall drug exposure in a given dosing interval ($AUC_{0–21\ d}$) in a SC formulation that is at least as high as IV C_{trough} and $AUC_{0–21\ d}$ is expected to result in a comparable degree of target-site saturation and therefore the same degree of efficacy, regardless of the route of administration. Cycle 1 exposure metrics were selected to mitigate response-dependent decreases of clearance over time, as is recommended for checkpoint inhibitors (Liu et al. 2017).

Previous experiments based on the PK bridging approach have already shown anti-tumor activity is not impaired by a change in administration route (Shpilberg and Jackisch 2013; Jackisch et al. 2015). Similarly, in Study BP40657, demonstration of PK non-inferiority between the SC and IV formulations in terms of Cycle 1 C_{trough} and $AUC_{0–21\ d}$ will be obtained if the lower bound of the 90% CI for the geometric mean ratio (GMR) is $\geq$ 0.8, with 0.8 being the lower bound of the range recommended for bioequivalence.

A comprehensive assessment of available atezolizumab IV monotherapy PK and exposure-response (ER) analyses for UCC and NSCLC has been conducted on the basis of eight clinical studies (Roche Report 1087176; Pooled Exposure-Response Analysis of Single-Agent Atezolizumab in Patients with UCC and NSCLC from PCD4989g, IMvigor211, and OAK Studies; available on request). The population PK model based on Phase I data (Study PCD4989g) was externally validated by four Phase II studies (GO28753 [POPLAR], GO28754 [BIRCH], GO28625 [FIR], and GO29293 [IMvigor210]) and three Phase III studies (GO28915 [OAK], GO29294 [IMvigor211], and GO29436 [IMpower150]).

In terms of ER for efficacy for both UCC and NSCLC, no clinically meaningful atezolizumab ER relationship with ORR or OS was concluded for the approved IV 1200-mg Q3W dosing regimen. This suggests that the exposure achieved by the approved IV 1200-mg Q3W dosing regimen is in the flat or plateau part of the ER curve. Therefore, as long as the atezolizumab SC formulation achieves exposure (C_{trough}) and $AUC_{0–21\ d}$ greater than the target concentration and within the range expected for the approved IV 1200-mg Q3W dosing regimen, no detrimental impact on efficacy response is expected.

In terms of atezolizumab ER for safety for both UCC and NSCLC, no clinically meaningful ER for atezolizumab for safety was concluded for doses ranging from 10 mg/kg Q3W to 20 mg/kg Q3W, which includes the 1200-mg IV fixed-dose Q3W dosing regimen. Any new atezolizumab SC formulation that provides C_{max} exposure that is not greater than what was observed for doses ranging up to 20 mg/kg Q3W (the highest dose administered in the first-in-human dose-ranging study PCD4989g) should exhibit similar exposure-safety relationships to that observed previously.

3.3.5 Rationale for Clinical Outcome Assessments

It is important that disease and treatment do not compromise patients' function and health-related quality of life, particularly in non-curative settings. Patient-reported impact of their disease and treatment provide important information to complement safety and efficacy data and are critical to fully characterize the benefit-risk profile of atezolizumab SC. To this end, patient experience assessments will be administered in Part 2 to inform overall treatment burden and treatment satisfaction from the patient's perspective.

HCP perspectives on the convenience, overall satisfaction, potential time savings, and/or ease of administration with atezolizumab SC and/or atezolizumab IV will also be examined in Part 2. Together with the patient experience assessments, HCP experience data will help to provide a more comprehensive characterization of atezolizumab SC and atezolizumab IV.

4. MATERIALS AND METHODS

4.1 PATIENTS

Part 1 of the study will enroll approximately 12 evaluable patients for Cohorts 1 and 2 each and approximately 20–30 evaluable patients for Cohort 3 (i.e., a total of approximately 60 evaluable patients). For a definition of evaluable patients, see Section 6.2.

Part 2 of the study is expected to randomize approximately 327 patients with locally advanced or metastatic NSCLC during the global enrollment phase of this study.

4.1.1 Inclusion Criteria

General inclusion criteria applicable to both Parts 1 and 2 are described. Additional inclusion criteria applicable to either Part 1 or 2 are also described.

4.1.1.1 General Inclusion Criteria Applicable to Both Parts 1 and 2 (All Patients)

All patients must meet all the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Measurable disease as defined by RECIST v1.1

  Previously irradiated lesions can only be considered as measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of disease.
- ECOG Performance Status of 0 or 1
- Life expectancy ≥ 12 weeks
- 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 ALP $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:

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

    Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
  - Total bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Patients with known Gilbert disease: total bilirubin level $\leq 3 \times$ ULN
  - Serum creatinine $\leq 1.5 \times$ ULN
  - Serum albumin ≥ 25 g/L (2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN
- 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 patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, 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.

  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.

- Patients must have recovered (i.e., improvement to Grade 1 or better) from all acute toxicities from previous therapy, excluding alopecia

  For peripheral neuropathy, improvement to Grade ≤ 2 is acceptable.

- Intact normal skin without potentially obscuring tattoos, pigmentation, or lesions in the area for intended injection
- Histologically or cytologically documented NSCLC that is currently locally advanced or metastatic (i.e., Stage IIIB not eligible for definitive chemoradiotherapy, Stage IV, or recurrent) NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 8th edition)

  Pathological characterization may be from tumor specimens collected at a time when the NSCLC was at an earlier stage but must be sufficient to define patients as having either squamous or non-squamous histology.

- Disease progression during or following treatment with a platinum-containing regimen for locally advanced, unresectable/inoperable, or metastatic NSCLC or disease recurrence within 6 months of treatment with a platinum-based adjuvant/neoadjuvant regimen or combined modality (e.g., chemoradiation) regimen with curative intent

  Patients may have received one additional cytotoxic chemotherapy regimen provided no interval disease progression has occurred. Chemotherapy regimens will be counted based on interval disease progression and not the number of agents or switches in agents (e.g., a first-line therapy that consists of several cycles of a platinum doublet and subsequent maintenance therapy that introduces or switches to a new chemotherapy agent without interval disease progression will all be considered one chemotherapy regimen).

  Adjuvant/neoadjuvant chemotherapy or chemoradiation counts as a prior chemotherapy regimen if < 6 months have elapsed between the last dose and the date of recurrence. Combined treatment with chemotherapy and radiation constitutes a single regimen; surgery is not considered a regimen.

  Patients with advanced lung cancer and a sensitizing *EGFR* mutation will additionally be required to have experienced disease progression (during or after treatment) or intolerance with one or more *EGFR* TKIs appropriate for the treatment of *EGFR*-mutant NSCLC as outlined below:

  – 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 (for example: erlotinib, gefitinib, afatinib, dacomitinib) and who have no evidence of the EGFR T790M mutation in the tumor tissue after TKI therapy are eligible. Patients whose T790M mutational status is unknown are also eligible if this is in accordance to local standard practice.

  – Patients who have progressed on or were intolerant to first- or second-generation EGFR TKIs and who have evidence of the EGFR T790M mutation in the tumor tissue after TKI therapy must also have progressed on, were intolerant to, or lack access to third-generation TKIs such as osimertinib or others.

  Patients with a previously detected *ALK* fusion oncogene must additionally have experienced disease progression (during or after treatment) or intolerance to treatment with one or more *ALK* inhibitors (e.g., alectinib, crizotinib, brigatinib, ceritinib, lorlatinib, or others) appropriate for the treatment of NSCLC in patients having an *ALK* fusion oncogene.

  The last dose of prior systemic anti-cancer therapy must have been administered ≥ 21 days prior to enrollment/randomization, with the exception being TKIs approved for treatment of NSCLC have to be discontinued ≥ 7 days prior to Cycle 1, Day 1. The baseline scan must be obtained after discontinuation of prior TKIs (washout not required prior to obtaining the scan).

The last dose of treatment with any investigational agent or participation in another interventional study must have ended ≥28 days prior to enrollment/randomization.

Anti-cancer agents used for pleurodesis are not counted as a line of therapy.

Prior radiation therapy is allowed provided the patient has recovered from any toxic effects thereof.

4.1.1.2 Additional Inclusion Criteria Applicable to Part 1 Only

Patients in Part 1 must also meet the following additional criteria for study entry:

- A body mass index (BMI) between 18 and 32 kg/m^2 inclusive

4.1.1.3 Additional Inclusion Criteria Applicable to Part 2 Only

Patients in Part 2 must also meet the following additional criteria for study entry:

- For patients whose tumor may harbor a sensitizing *EGFR* mutation, known *EGFR* test results at the time of randomization

  Patients who may harbor a sensitizing EGFR mutation are defined as having non-squamous histology (including those with a mixed histology that includes any non-squamous component), and without any other known driver mutation (e.g., KRAS status wild-type/unknown, BRAF status wild-type unknown, or ALK fusion oncogene negative/unknown).

  EGFR tests may be assessed locally or submitted for central laboratory testing. If available, EGFR status assessed locally should be performed on tissue samples using a validated health authority–approved test that detects mutations in exons 18–21. Patients recruited in China are required to be tested centrally, even if local results are available.

  If patients are recruited in China or if no local results are available, tissue is required for central testing as promptly as possible and always prior to randomization (see below and in Section 4.5.7.3).

  Patients with a sensitizing *EGFR* mutation will be excluded once approximately 10% of the total target sample size has been reached.

- Availability of a pre–study treatment representative formalin-fixed paraffin-embedded (FFPE) tumor specimen in paraffin block (preferred) or at least six slides containing unstained, freshly cut, serial sections from an FFPE tumor specimen for exploratory biomarker analysis (e.g., PD-L1) (see Section 4.5.7.3 for further details)

  For patients recruited in China, availability of nine slides (including six for exploratory biomarker testing) containing unstained, freshly cut, serial sections from a pre–study treatment representative formalin-fixed paraffin embedded (FFPE) tumor specimen.

For both patients recruited in China and ex-China, if fewer slides are available at baseline, additional slides may be requested in case of testing failure (see Section 4.5.7.3 and the laboratory manual for further details).

4.1.2 Exclusion Criteria

General exclusion criteria applicable to both Parts 1 and 2 are described. Additional exclusion criteria applicable to either Part 1 or 2 are also described.

4.1.2.1 General Exclusion Criteria Applicable to Both Parts 1 and 2 (All Patients)

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

Cancer-Specific Exclusions

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

- Symptomatic, untreated, or actively progressing CNS metastases

  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.

  Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to enrollment, if all other criteria are met.

- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for $\geq$2 weeks prior to enrollment
- History of leptomeningeal disease
- 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 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 have 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 or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected serum calcium $>$ ULN)
- History of malignancy other than NSCLC within 5 years prior to screening, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated with curative intent, or ductal carcinoma in situ treated surgically with curative intent)

General Medical Exclusions

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

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

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

- History of severe anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or any component of the atezolizumab formulation
- Active or history of autoimmune disease or immune deficiency, including, but not limited to (for a comprehensive list, see Appendix 8), myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, *granulomatosis with polyangiitis*, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, 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.
  - There is 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
- Current treatment with anti-viral therapy for HBV
- 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, or any active infection that, in the opinion of the investigator, could impact patient safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.

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

  Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded.

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

- 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 course of the study
- Prior allogeneic stem cell or solid organ transplantation
- 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
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, or that may affect the interpretation of the results, or may render the patient at high risk from treatment complications

Exclusion Criteria Related to Medications

- Prior treatment with CD137 agonists or immune checkpoint blockade therapies including anti-TIGIT, anti−PD-1, and anti−PD-L1 therapeutic antibodies

  Patients who have had prior anti−CTLA-4 treatment may be enrolled, provided the following requirements are met:

  – Last dose of anti−CTLA-4 at least 6 weeks prior to enrollment

  – No history of severe immune-mediated adverse effects from anti-CTLA-4 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 3 or 4)

- 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

  Prior treatment with cancer vaccines is allowed.

- 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 enrollment

  Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study.

  The use of corticosteroids (≤ 10 mg oral prednisone or equivalent) for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency is allowed.

- Known allergy or hypersensitivity to hyaluronidase, bee or vespid venom, or any other ingredient in the formulation of rHuPH20

4.1.2.2 Additional Exclusion Criteria Applicable to Part 1 Only

Patients in Part 1 who meet the following additional criterion will be excluded from study entry:

- Pathology (e.g., lower extremity edema, cellulitis, lymphatic disorder or prior surgery, preexisting pain syndrome, previous lymph node dissection, etc.) that could interfere with any protocol-specified outcome assessment (e.g., PK)

4.1.2.3 Additional Exclusion Criteria Applicable to Part 2 Only

Patients in Part 2 who meet any of the following additional criteria will be excluded from study entry:

- Tested tumor PD-L1 expression status with an intention to treat the patient if positive. This implies that:

  – Patients who had access to PD-1 or PD-L1 first line therapies and were tested for PD-L1 expression status are not eligible, irrespective of the test result

- Patients who had no access to PD-1 or PD-L1 first line therapies but were tested anyway as part of a testing routine despite lack of access are eligible, irrespective of the test result

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study.

Patients should receive their first dose of study drug on the day of enrollment for Part 1 or on the day of randomization for Part 2, if possible. If this is not possible, the first dose should occur within 5 days after enrollment/randomization.

Patients in Part 2 will be randomly assigned to one of two treatment arms: atezolizumab SC or atezolizumab IV. Randomization will occur in a 2:1 ratio using a permuted-block randomization method to ensure a balanced assignment to each treatment arm.

Although Part 2 is open-label, Sponsor's standard operating procedures for blinding and unblinding will be followed (see Section 3.1.1.1 regarding blinded analyses).

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are atezolizumab SC for co-mix, atezolizumab SC, atezolizumab IV, and rHuPH20. IMPs will be supplied by the Sponsor.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Atezolizumab SC for Co-Mix

Atezolizumab SC for co-mix will be provided as a sterile liquid at a concentration of 125 mg/mL. The vial is designed to deliver 20.0 mL (2500 mg) of atezolizumab solution (i.e., a nominal fill of 20.0 mL atezolizumab in 20-mL vials).

For information on the formulation of atezolizumab SC for co-mix, see the Atezolizumab Investigator's Brochure.

4.3.1.2 rHuPH20

rHuPH20 to be manually mixed with atezolizumab SC for co-mix will be provided as a sterile liquid at a concentration of 110 K U/mL. The vial contains 0.5 mL (55,000 U) of rHuPH20 solution.

For information on the formulation of rHuPH20, see the rHuPH20 Investigator's Brochure.

4.3.1.3 Atezolizumab SC

Atezolizumab SC will be provided as a sterile liquid at a concentration of 125 mg/mL. rHuPH20 will be co-formulated with atezolizumab in the atezolizumab SC formulation at a concentration of 2000 U/mL.

For information on the formulation of atezolizumab SC, see the pharmacy manual.

4.3.1.4 Atezolizumab IV

The atezolizumab IV drug product will be provided as a sterile liquid in a single-use, 20-mL glass vial that contains approximately 20.0 mL (1200 mg) of atezolizumab solution (i.e., a nominal fill of 20.0 mL atezolizumab in 20-mL vials).

For more detailed information on the formulation of atezolizumab, see the Atezolizumab Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

No dose modification for atezolizumab is allowed.

Any dose modification 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 5.3.5.12.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 10.

4.3.2.1 Atezolizumab SC for Co-Mix with rHuPH20 or Atezolizumab SC

In order to generate atezolizumab SC co-mix, atezolizumab SC for co-mix will be mixed with rHuPH20 at a concentration of 2000 U/mL. For more details regarding this procedure, refer to the version of the pharmacy manual corresponding to the protocol version to which the patient was last consented.

The drug product will be administered subcutaneously by a health care professional in the anterior thigh region or, for the first dose in Cohort 3 of Part 1 only, in the lower part of the abdomen. Depending on the Part 1 cohort, patients will receive one or several doses of atezolizumab SC co-mix or atezolizumab SC via the SC route. Atezolizumab SC co-mix and atezolizumab SC injections will be administered per the instructions outlined in Table 2. In Part 2 of the study, atezolizumab SC will be provided as a ready-to-use mixture of atezolizumab and rHuPH20 at a concentration of 2000 U/mL.

When applicable the injection site should be alternated between the left and right thigh. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. If administered in the abdomen, injection should be given in either of the two lower quadrants around the umbilicus; it should not be administered above the umbilicus. In all cases (abdomen or thigh), start and stop times of the SC injection should be captured.

No premedication will be allowed for the first dose of atezolizumab SC co-mix or atezolizumab SC. Premedication may be administered for Cycles ≥2 at the discretion of the treating physician. Injection sites will be digitally photographed after a SC injection if a severe adverse reaction at the injection site is observed.

In case a patient develops unacceptable toxicity to the SC injection of atezolizumab, treatment with IV infusion may continue. In case a patient develops toxicity that is linked to the treatment with atezolizumab irrespective of the form of administration (SC or IV), further continuation of treatment is not recommended. Refer to Appendix 10 for further guidance on atezolizumab toxicity management.

Administration of atezolizumab SC co-mix or atezolizumab SC 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 9. Atezolizumab SC co-mix and atezolizumab SC injections will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Atezolizumab SC Co-Mix and Atezolizumab SC Injections

First and Subsequent SC Injections
• No premedication is permitted prior to the **first** SC injection. • For subsequent SC injections, if the patient experienced an injection-related reaction with any previous injection, premedication with antihistamines, antipyretics, and/or analgesics may be administered at the discretion of the investigator. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the injection. • Vital signs should be measured at 30 (±10) minutes after the injection (and before any PK sample scheduled to be drawn at the same time) and as clinically indicated. • Patients should be informed about the possibility of delayed post-injection symptoms and instructed to contact their study physician if they develop such symptoms

PK = pharmacokinetic.

4.3.2.2 Atezolizumab IV

Administration of atezolizumab IV 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 9. Atezolizumab IV infusions will be administered per the instructions outlined in Table 3.

Table 3 Administration of First and Subsequent Atezolizumab IV 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 • Vital signs should be measured at 30 (±10) minutes after the infusion and before any PK sample scheduled to be drawn at the same time. • 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. • Vital signs should be measured at 30 (±10) minutes after the infusion and before any PK sample scheduled to be drawn at the same time.

PK = pharmacokinetic.

Guidelines for medical management of infusion-related reactions and injection-related reactions are provided in Appendix 10.

No dose modification for atezolizumab is allowed.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab SC for co-mix, rHuPH20, atezolizumab IV, and atezolizumab SC) will be provided by the Sponsor where required by local health authority regulations. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

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 accountability log.

Refer to the pharmacy manual and/or the Atezolizumab Investigator's Brochure or rHuPH20 Investigator’s Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Investigational Medicinal Products

Currently, the Sponsor does not have any plans to provide Roche IMPs (atezolizumab SC, atezolizumab SC for co-mix, rHuPH20, and atezolizumab IV) or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing IMPs 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)
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section 4.4.3)
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids (≤10 mg oral prednisone or equivalent) administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Palliative radiotherapy (e.g., treatment of known bony metastases) provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion being irradiated is not the only site of disease, as that would render the patient not evaluable for response by tumor assessments according to RECIST v1.1)

  It is not a requirement to withhold atezolizumab during palliative radiotherapy.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab administration 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 Section 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 9).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.2.1 Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

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

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 10 for details).

4.4.2.2 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.

4.5 STUDY ASSESSMENTS

The schedules of activities to be performed during the study are provided in Appendix 1 and Appendix 3 (Part 1) and Appendix 2, Appendix 4, and Appendix 5 (Part 2). 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.

Patients who are willing to participate in the study and have given written informed consent will undergo a thorough screening medical examination (including a physical examination, baseline tumor scan, vital signs, and laboratory tests) within 28 days prior to drug administration. Laboratory tests will be performed within 14 days prior to drug administration.

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, smoking history, will be recorded at screening. 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. 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.

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

4.5.3 Physical Examinations

A complete physical examination 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 post-baseline 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.

Height and weight will be recorded at screening and weight only at Day 1 of each cycle, or whenever the investigator considers there is a substantial change from baseline. Results will be recorded on the eCRF.

4.5.4 Vital Signs

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

Vital signs should be measured within 60 minutes prior to and 30 (±10) minutes after each atezolizumab infusion/injection and as clinically indicated. In addition, vital signs should be measured at other specified timepoints as outlined in the schedules of activities (see Appendix 1 and Appendix 2) and Section 4.3.2.

4.5.5 Tumor and Response Evaluations

4.5.5.1 Screening Assessments

The screening assessment must include CT scans (with oral and/or IV contrast) or magnetic resonance imaging (MRI) scans of the chest, abdomen, pelvis, and head. 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 non-contrast CT scan of the chest may be performed, and MRI scans of the abdomen, pelvis, and head should be performed. A CT scan with contrast or MRI scan of the head must be performed 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. 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.

4.5.5.2 Assessments during Treatment

For Part 1, patients will be monitored as per local practice and no protocol-specific scans will be mandated during treatment. **Note that the following tumor assessments apply only to Part 2.**

For Part 2, tumor assessments should occur every 6 weeks (±3 business days) for the first 36 weeks following treatment initiation, and every 9 weeks (±7 days) thereafter, regardless of treatment delays, until radiographic disease progression per RECIST v1.1 or (for patients who continue atezolizumab after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1.2). Thus, tumor assessments are to continue according to schedule in patients who discontinue

treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

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 identified at baseline 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). Tumor assessments must be continued after disease progression per RECIST v1.1 for patients who receive treatment beyond progression (or further if patient is thought to be deriving benefit from the investigator; see Section 3.1.2). This includes continued measurement of target lesions, evaluation of non-target lesions (including monitoring for further worsening of any non-target lesions that have shown unequivocal progression), and evaluation of any newly identified lesions (including measurements, if lesions are measurable; see Appendix 7) at all subsequent assessments).

Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 7) prior to treatment administration at each cycle. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

Patients who discontinue study drug for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments at the same frequency as would have been followed if the patient had remained on study drug until death, disease progression, loss of clinical benefit, withdrawal of consent, or until the study closes, whichever occurs first. Patients who start a new anti-cancer therapy in the absence of disease progression should be followed according to the protocol schedule until disease progression, death, withdrawal of consent, or study termination by Sponsor, whichever occurs first.

4.5.6 Digital Photography Images

In case of severe injection-site reactions, unscheduled photographs will be taken. Photographs should include a label showing the subject’s identification number and initials, date and time of calendar date, and a centimeter ruler to provide scale. Efforts will be made to standardize the photography with regard to parameters such as angle, light, distance from body and settings.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

4.5.7.1 Local Laboratories

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 lactate dehydrogenase (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 (or serum, if urine is not feasible) pregnancy tests will be performed at specified timepoints as detailed in the schedules of activities (Appendix 1 and Appendix 2). 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

4.5.7.2 Central Laboratories

The following samples will be sent to one or more central laboratories or to the Sponsor or a designee for analysis (see Appendix 6 for instructions on PK and ADA sampling procedures):

- Serum samples will be assayed for atezolizumab concentrations with use of a validated assay
- Plasma samples will be assayed for hyaluronidase (rHuPH20) concentration with use of a validated assay (during Part 1 only).
- Serum samples will be assayed for the presence of ADAs to atezolizumab with use of validated immunoassays.
- Plasma samples will be assayed for the presence of ADAs to hyaluronidase (rHuPH20) with use of validated immunoassays.
- C-reactive protein

4.5.7.3 Central Laboratories, Applicable to Part 2 Only

The following samples for Part 2 will be sent to one or more central laboratories or to the Sponsor or designee for analysis:

- Archival or newly collected tumor tissue sample obtained at baseline for exploratory research on biomarkers (e.g., PD-L1, as well as *ALK* and/or *EGFR* status if required.

  A representative FFPE tumor specimen in a paraffin block (preferred) or at least six slides containing unstained, freshly cut, serial sections from an FFPE tumor specimen must be submitted along with an associated pathology report. For patients recruited in China, see additional details below.

  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 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 pre–study treatment tumor biopsy is required. A pre–study treatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria. Note that in all cases, if tissue does not meet the required quality, additional material may be requested.

  If a patient is recruited in China or if no local EGFR results are available, all tissue must be submitted prior to randomization and as early as possible during screening to avoid compromising the duration of the screening period. When local EGFR results are already available in a patient recruited ex-China, the pre–study treatment

tumor tissue (archival or freshly obtained) sample may be submitted within 4 weeks after randomization. All material should be sent in a single shipment.

In all cases, it is preferred that additional slides for EGFR and ALK are serial sections with those used for PD-L1 testing. Note that samples that are not serial sections with PD-L1 slides (e.g., from different blocks) will have different sample requirements. See the laboratory manual for details on tumor sample requirements. The numbers of required samples are outlined in Table 4 below.

Table 4 Tumor Tissue Sample Requirements

Testing Performed	Ex-China	China [a]
PD-L1	1 block or ≥6 slides	NA
PD-L1 + EGFR [b]	1 block or ≥7 slides	7 slides
PD-L1 + ALK [c]	1 block or ≥8 slides	NA
PD-L1 + EGFR [b] + ALK [c]	1 block or ≥9 slides	9 slides
EGFR [a]	NA	3 slides

NA = not applicable.

[a] Patients recruited in China require slides for central EGFR testing and exploratory biomarker testing, if permitted by local regulation. Exploratory biomarker testing includes PD-L1 and ALK (the latter requires slides only if not locally available). Central testing of EGFR is required for enrollment.

[b] For patients recruited ex-China, EGFR testing is required if no local assessment is available and the patient could have an EGFR mutation (i.e., non-squamous histology or lack of other driver mutation, please refer to section 4.1.1.3 for more details).

[c] ALK testing is required if no local assessment is available and the patient could have an ALK mutation (i.e., non-squamous histology or lack of other driver mutation).

With the exception of patients recruited in China, exploratory biomarker research may include, but will not be limited to, analysis of genes or gene signatures associated with tumor immunobiology, PD-L1, EGFR, ALK, lymphocyte subpopulations, T-cell receptor repertoire, or cytokines associated with T-cell activation. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants.

For patients recruited in China, exploratory biomarker research may include PD-L1, EGFR, and ALK (the latter only if central testing is required).

4.5.7.4 Applicable to All Laboratory, Biomarker, and Other Biological Samples

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma and serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For enrolled patients for whom a block has been sent, remaining archival tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

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.

4.5.8 Cardiac Assessments

Triplicate electrocardiogram (ECG) recordings will be obtained at specified timepoints, as outlined in the schedules of activities (see Appendix 1 and Appendix 2). ECGs acquired on different days should be as closely time-matched as feasible. Three interpretable ECG recordings (e.g., without artifacts) must be obtained at each timepoint. The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS, QT). Single ECG recordings may be obtained at unscheduled timepoints as indicated. All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. 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. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). 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. Digital recordings will be stored at site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

In Part 2, patients with a known history of pericardial effusions or with evidence of pericardial effusion on screening chest CT must have an LVEF assessment prior to the administration of study drugs as specified in the schedule of activities (Appendix 2). LVEF can be assessed using echocardiogram (ECHO) as the preferred method. The same method must be used for baseline and subsequent LVEF measurements in each patient. New York Heart Association Class II Congestive Heart Failure or greater must be confirmed by a cardiologist.

4.5.8.1 Assessments of Patient- and Health Care Professional–Reported Experience

PRO instruments will be completed to assess the treatment benefit and more fully characterize the safety profile of atezolizumab SC versus atezolizumab IV in Part 2. In addition, PRO instruments will enable the capture of each patient's direct experience with atezolizumab. The HCP-reported experience instruments will be completed to assess the convenience, potential time savings, ease of administration, and overall satisfaction regarding administration of atezolizumab SC and atezolizumab IV.

PRO data will be collected using ten selected items from the EORTC Item Library (EORTC IL57) and the modified satisfaction with therapy (SWT) scale from the CTSQ. HCP-reported experience data will be collected using the HCP SC versus IV Perspective Questionnaire and the HCP Subcutaneous Perspective Questionnaire.

4.5.8.2 Data Collection Methods for Assessments of Patient- and Health Care Professional-Reported Experience

PRO instruments will be self-administered at the clinic at specified timepoints during the study (see Appendix 2). At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments or any study assessments that may bias patient responses, and prior to the administration of study treatment, unless otherwise specified.

Paper-based PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor to enable the instruments to be administered at each specified timepoint. Patients may be exempted from completing PRO instruments that are not available in their native language.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 5 minutes at most specified visits and 10 minutes at the Cycle 3 visit (or at the treatment discontinuation visit if study treatment is discontinued prior to the Cycle 3 visit).

- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.
- Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.
- Site staff must enter the responses from the instruments into the eCRF

The HCP Perspective Questionnaires will be completed at the clinic by the HCP(s) who administer study treatment (e.g., nurse, physician). The HCP Subcutaneous Perspective Questionnaire will be completed after administration of at least three doses of atezolizumab SC across all patients in Part 2 (see Appendix 2). The HCP SC versus IV Perspective Questionnaire will be completed after administration of at least three doses of atezolizumab SC and at least three doses of atezolizumab IV across all patients in Part 2 (see Appendix 2). The instruments will be provided by the Sponsor. HCPs must complete the official version of the instruments, as provided by the Sponsor. The instruments must not be copied from the protocol.

The data from the HCP Perspective Questionnaires will be entered in a Vendor database and the data transferred to the Sponsor.

4.5.8.3 Description of Instruments for Assessments of Patient- and Health Care Professional–Reported Experience

EORTC IL57

The EORTC IL57 consists of three scales and a single item from the EORTC Item Library, for a total of 10 items (Aaronson et al. 1993; Kulis et al. 2018). The EORTC IL57 physical functioning scale includes five items evaluating the extent to which patients have trouble doing strenuous activities; taking long walks; taking short walks; needing to stay in bed or a chair; and needing help with eating, dressing, bathing, or using the toilet. The EORTC IL57 role functioning scale includes two items evaluating the extent to which patients are limited in doing their work and pursuing their leisure activities in the previous week. The EORTC IL57 global health status/quality of life (GHS/QoL) scale includes two items evaluating patients' overall health and quality of life in the previous week. The EORTC global impression of cancer treatment side effects burden item asks patients to rate how much they are bothered by treatment side effects. A similarly worded item has been shown to be a valid and useful summary measure of overall adverse event burden from the patient's perspective to complement clinician-rated

adverse event reporting (Pearman et al. 2018). The item is rated on a 4-point Likert scale that ranges from “not at all” to “very much” and has a recall period of one week. The ten items in the EORTC IL57 (see Appendix 11) take approximately 5 minutes to complete.

Cancer Therapy Satisfaction Questionnaire

The CTSQ is a validated 16-item questionnaire measuring three domains related to patients’ satisfaction with cancer therapy: expectations of therapy, feelings about side effects, and satisfaction with therapy (Abetz et al. 2005; Trask et al. 2008; Cheung et al. 2016). This study will utilize the modified SWT scale, which consists of seven items that are rated on a 5-point scale, with 1 representing the worst response and 5 representing the best response, except in the case of one reverse-scored item (see Appendix 12). The SWT scale takes approximately 5 minutes to complete.

Health Care Professional Perspective Questionnaires

The HCP Subcutaneous Perspective Questionnaire consists of five items evaluating the convenience, ease of administration and overall satisfaction with atezolizumab SC, as well as reasons for HCP-reported satisfaction or dissatisfaction (see Appendix 13). The HCP SC versus IV Perspective Questionnaire consists of five items evaluating the convenience, potential time savings, and overall satisfaction with atezolizumab SC and atezolizumab IV, as well as reasons for HCP-reported satisfaction (see Appendix 14).

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

At any point in time and without reason, patients can withdraw their consent to discontinue treatment from the study.

Patients must permanently discontinue study treatment (atezolizumab SC co-mix, atezolizumab IV, or atezolizumab SC) 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 3.1.2 for details)

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. In Part 1 of the study, patients who discontinue study treatment prematurely may be replaced if they are not considered evaluable (see Section 6.2.1). In Part 2 of the study, patients who discontinue study treatment prematurely will not be replaced, with the exception of patients who withdraw prior to receiving the first dose.

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. After treatment discontinuation, adverse events will continue to be recorded as outlined in the schedules of activities (see Appendix 1 and Appendix 2).

In Part 2, patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit are required to continue undergoing tumor response assessments as outlined in the schedule of activities (see Appendix 2). 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 2–3 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
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor
- Changes that result in failure to meet eligibility criteria (i.e., pregnancy)
- Investigator or Sponsor determines it is in the best interest of the patient

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 Part 1 of the study may be replaced if they are not considered evaluable (see Section 6.2.1). In Part 2, patients who withdraw may be replaced if withdrawal occurs before the first dose. The decision to replace a withdrawn subject will be made at the discretion of the Sponsor depending on the overall number of

premature withdrawals. In Part 2, no patient prematurely discontinued from the study, for any reason, after receiving at least a single dose of treatment, will 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
- Development of atezolizumab SC formulation is discontinued
- Following advice from the JMC or Health Authorities

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 rHuPH20 in completed and ongoing studies. The anticipated important safety risks are outlined below in Sections 5.1.1 and 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 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 treatment interruption or discontinuation, are provided in Appendix 10. Refer to Sections 5.2–5.7 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

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, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *pericardial disorders,* myositis, nephritis, and severe cutaneous adverse reactions. *In addition, i*mmune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH)*, including macrophage activation syndrome (MAS)*. Refer to Appendix 10 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 rHuPH20

rHuPH20 is administered with atezolizumab. For more details regarding the safety profile of rHuPH20, refer to the rHuPH20 Investigator's Brochure. Refer to Appendix 10 for adverse management guidelines for rHuPH20 administered with atezolizumab.

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 in patients treated with atezolizumab 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.
- 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, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- *Myelitis*
- *Facial paresis*

5.2.4 Selected Adverse Events

Injection-Site Reactions

With SC administration, local reactions at site of injection (erythema, pruritus, edema, rash, and pain) may occur. In case of severe injection-site reactions, unscheduled photographs will be taken. Photographs should include a label showing the subject's identification number and initials, date and time of calendar date, and a centimeter ruler to provide scale. Efforts will be made to standardize the photography with regard to parameters such as angle, light, distance from body, and settings.

See Section 5.3.5.1 instructions on reporting injection-related reactions and infusion related reactions.

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 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 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 (v5.0), 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 5):

- 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 6 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, Injection-Related Reactions, and Cytokine-Release Syndrome

There may be significant overlap in signs and symptoms of infusion-related reactions/injection-related reactions and CRS. While infusion-related reactions/injection-related reactions 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 or injection should be captured on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction", “injection-related reaction”, or "cytokine-release syndrome"). 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 of an infusion-related reaction/injection-related reaction should be recorded on the dedicated Infusion-Related Reaction and Injection-Related Reaction eCRF.

If a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with associated signs and symptoms of an of an infusion-related reaction/injection-related reaction also recorded separately on the dedicated Infusion-Related Reaction or Injection-Related Reaction eCRF.

In recognition of the challenges in clinically distinguishing between these two events, consolidated guidelines for medical management of infusion-related reactions/injection-related reactions and CRS are provided in Appendix 10.

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

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

In Part 2 of the study, duration of survival is a secondary 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). In Part 1, an IMC will monitor the frequency of deaths from all causes. In Part 2, a JMC will monitor the frequency of deaths from all causes.

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 criteria. 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 Reporting Requirements for 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 or qualifies as an adverse event of special interest, 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). For atezolizumab SC co-mix, atezolizumab SC, atezolizumab IV, and rHuPH20, 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 SC co-mix, atezolizumab SC, atezolizumab IV, and rHuPH20, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor 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.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

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: [redacted], *M.D.*
(Primary)

Telephone No.: [redacted]
Mobile Telephone No.: [redacted]

Medical Monitor: [redacted], *M.D.* (Secondary)

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 Adverse Event/Special Situations 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 and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations 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 and submitted via 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 through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab. 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. 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 Abortions

A 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).

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.

5.4.3.3 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).

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

In both Part 1 and Part 2, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. 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 Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

In Part 2, 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.

If a non-serious-related adverse event becomes serious after the reporting period, this should be reported as per the serious adverse event reporting process.

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
- rHuPH20 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

The global population will include all patients randomized during the global enrollment phase of Part 2 (including patients randomized at qualified sites in China during that phase), whereas the China subpopulation will include all patients randomized at qualified sites. Separate analyses may be performed for the China subpopulation (see Section 6.15 for information on the China subpopulation analyses).

6.1 ANALYSIS TIMING

The data in Part 1 of the study will be analyzed on an ongoing basis in order to inform the dose selection for subsequent cohorts, and for Part 2.

In Part 2, the analysis of the co-primary endpoints, Cycle 1 observed serum C_{trough} (predose Cycle 2) and model-predicted $AUC_{0–21\ d}$, will be performed when the planned number of patients has been randomized and the last required data point has been reported. The cutoff for the primary analysis will therefore be approximately one month after randomizing the last patient in Part 2. Analyses of available data on secondary and exploratory endpoints up to this time point will also be presented.

After that, patients will continue to be followed until the end of the study, approximately 33 months after randomizing the last patient, or when all patients have discontinued from the study, whichever occurs first. An additional analysis will be performed afterwards to evaluate the longer-term efficacy and safety data for atezolizumab SC.

6.2 ANALYSIS POPULATIONS

6.2.1 Part 1: Dose Finding

PK analyses of Part 1 will be performed on data from all PK-evaluable patients enrolled in Part 1. A PK-evaluable patient is defined as one who has received at least one dose of atezolizumab (atezolizumab SC co-mix, atezolizumab SC, or atezolizumab IV) and has at least one evaluable postdose PK sample and who does not have protocol deviations that could affect PK results.

Specific criteria for exclusion from the primary analysis will be defined prior to the analysis and documented in the Statistical Analysis Plan.

The Part 1 safety analysis population is defined as all patients who received at least one dose of atezolizumab (atezolizumab SC co-mix, atezolizumab SC, or atezolizumab IV).

6.2.2 Part 2: Dose Confirmation

The primary analysis will be performed in the Per Protocol PK analysis population. This population will include patients in the atezolizumab SC and atezolizumab IV treatment arms who do not have protocol deviations that could affect PK results.

Patients will be excluded from the Per Protocol PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete, where the PK analysis might be influenced.

Reasons for exclusion from the analysis may include, but are not limited to, lack of the Cycle 1 C_{trough} (predose Cycle 2) PK sample, a C_{trough} sample collected outside the pre-specified window, administration of a dose amount that significantly deviates from the planned dose, a dose delay of more than 7 days, use of an injection site other than the thigh, use of expired or quarantined study treatment, or duplicate times of collection for the Cycle 1 C_{trough} sample. Excluded cases will be documented, including the reason for exclusion. Specific criteria for exclusion from the primary analysis will be defined prior to database closure and documented in the Statistical Analysis Plan.

Efficacy analyses of OS and PFS will be performed in the Full Analysis Set (FAS), defined as all patients who were randomized in Part 2, with patients grouped according to their assigned treatment. ORR and DOR will be assessed in patients in the subpopulation of FAS with measurable disease at baseline. Patients who do not receive the intended treatment (i.e., treatment assigned per randomization) will be grouped according to their assigned treatment.

The safety analysis population in Part 2 is defined as all patients who received at least one dose of any amount of any component of protocol treatment, with patients grouped according to treatment received.

6.2.3 Immunogenicity Analyses

Immunogenicity analyses will be performed on the post-treatment ADA-evaluable analysis population, defined as patients who have received at least one dose of protocol treatment and have at least one post-treatment ADA result.

6.3 STATISTICAL HYPOTHESIS AND PLANNED SAMPLE SIZE

6.3.1 Part 1: Dose Finding

The primary objective for Part 1 is to determine the dose of atezolizumab that, when given subcutaneously, would result in a comparable exposure, in terms of serum C_{trough}, to atezolizumab IV.

The sample size for Part 1 was determined by using simulation methods. Cohorts 1 and 2 are planned to enroll approximately 12 eligible patients each and Cohort 3 is planned to enroll approximately 20–30 eligible patients for a total of approximately

60 patients in Part 1. Based on the known PK profile of atezolizumab IV, such a sample size should allow estimation of the PK parameters with sufficient precision.

6.3.2 Part 2: Dose Confirmation

The primary objective of Part 2 is to demonstrate non-inferiority of the PK of atezolizumab SC compared with atezolizumab IV on the basis of two co-primary endpoints, Cycle 1 observed serum C_{trough} (predose Cycle 2) and model-predicted $AUC_{0\text{-}21\ d}$.

A statistical hypothesis test will be performed on the GMR of C_{trough} following SC administration ($C_{trough,SC}$) to C_{trough} following IV administration ($C_{trough,IV}$), both values taken from data observed in Cycle 1: $C_{trough,SC}/C_{trough,IV}$.

The null and alternative hypotheses will be as follows:

- H_0: The SC dose is inferior to the IV dose with a non-inferiority margin of 0.8 (i.e., the GMR $C_{trough,SC}/C_{trough,IV}$ is less than 0.8), versus
- H_1: The SC dose is non-inferior to the IV dose (i.e., the GMR $C_{trough,SC}/C_{trough,IV}$ is equal or greater than 0.8).

Model-predicted $AUC_{0–21\ d}$ in Cycle 1 is the other co-primary endpoint used for the primary objective of Part 2. The model-predicted AUC in Cycle 1 after atezolizumab SC administration will be compared with the model-predicted $AUC_{0–21\ d}$ in Cycle 1 after IV administration.

A statistical hypothesis test will be performed on the GMR of $AUC_{0–21\ d}$ following SC administration ($AUC_{0–21\ d,SC}$) to $AUC_{0–21\ d}$ following IV administration ($AUC_{0–21\ d,IV}$), both values taken from data predicted in Cycle 1: $AUC_{0–21\ d,\ SC}$ /$AUC_{0–21\ d,\ IV}$.

The null and alternative hypotheses will be as follows:

- H_0: The SC dose is inferior to the IV dose with a non-inferiority margin of 0.8 (i.e., the GMR $AUC_{0–21\ d,\ SC}$ /$AUC_{0–21\ d,\ IV}$ is less than 0.8), versus
- H_1: The SC dose is non-inferior to the IV dose (i.e., the GMR $AUC_{0–21\ d,\ SC}/AUC_{0–21\ d,\ IV}$ is equal to or greater than 0.8).

Cycle 1 observed serum C_{trough} (predose Cycle 2) and model-predicted $AUC_{0–21\ d}$ will be tested using the Hochberg procedure (Hochberg and Tamhane 1987; FDA 2017). In Step 1 of this procedure, if the lower bound of the 90% CI for the GMR $C_{trough,SC}/C_{trough,IV}$ and the GMR $AUC_{0–21\ d,\ SC}/AUC_{0–21\ d,\ IV}$ are $\geq$0.8, both null hypotheses will be rejected. In this case it will be concluded that SC administration is non-inferior to IV administration in terms of C_{trough} and AUC in Cycle 1.

If in Step 1 the null hypotheses are not rejected, the procedure continues to Step 2. In Step 2, if the 95% CI for one GMR (i.e., either $C_{trough,SC}/C_{trough,IV}$ or $AUC_{0–21\ d,\ SC}/AUC_{0–21\ d,\ IV}$) is $\geq$0.8, the corresponding null hypothesis will be rejected. In

this case, it will be concluded that SC administration is non-inferior to IV administration in terms of C_{trough} or AUC in Cycle 1.

A total of 327 patients are planned to be randomized in Part 2 of the study. This sample size will provide sufficient power for the statistical hypothesis test for the primary endpoint, based on the following assumptions:

- 2:1 randomization ratio
- True GMR $\geq$ 0.95 for Cycle 1 C_{trough}
- True GMR $\geq$ 0.95 for Cycle 1 $AUC_{0–21\ d}$
- One-sided significance level 0.05
- Coefficient of variation (CV%) of geometric mean C_{trough} in Cycle 1 is $<$55%; this value is based on the results observed after atezolizumab SC co-mix administration in Part 1 of the study (CCOD 10 March 2020)
- CV% of geometric mean Cycle 1 $AUC_{0–21\ d}$ is $<$45%; this value is based on the results observed after atezolizumab SC co-mix administration in Part 1 of the study (CCOD 10 March 2020)
- Positive correlation between Cycle 1 $AUC_{0–21\ d}$ and Cycle 1 C_{trough} $>$0.8; this value is based on the results observed after atezolizumab SC co-mix administration in Part 1 of the study (CCOD 10 March 2020)

Under these assumptions, a sample size of $\geq$261 PK-evaluable patients in the atezolizumab SC and atezolizumab IV arms would provide at least 80% power to conclude non-inferiority of Cycle 1 $C_{trough,SC}$ and $AUC_{0–21\ d,\ SC}$ with a non-inferiority margin of 0.8 for the GMR, or more concisely: $C_{trough,SC} > 0.8\ C_{trough,IV}$ and $AUC_{0\text{-}21\ d,\ SC} > 0.8\ AUC_{0–21\ d,\ IV}$ (see Table 7). It is expected that up to 20% of randomized patients will need to be excluded from the Per Protocol PK population. The total number of 327 patients was chosen in order to ensure the Per Protocol PK population will be large enough to meet the primary study objective and to assess comparable safety and efficacy data.

The total number of patients to be enrolled in Part 2 of the study may be increased or decreased, after taking into account the actually observed PK variability during the blinded sample-size re-estimation (once approximately 210–250 patients have been randomized). For example, for a coefficient of variation of 70% for Cycle 1 C_{trough}, the number of patients enrolled in Part 2 would be increased to 477 in order to ensure sufficient power for the non-inferiority test (see Table 7).

Table 7 Statistical Power of Test of Non-Inferiority of C_{trough} and $AUC_{0–21\ d}$

Coefficient of Variation for Cycle 1 C_{trough}	PK-Evaluable Patients	Probability to reject the null hypothesis for both co-primary endpoints	Estimated Required Randomized Patients [a]
50%	234	80%	293
55%	261	80%	327
60%	297	80%	372
65%	336	80%	420
70%	381	80%	477

[a] Assuming up to 20% not PK-evaluable.

6.4 SUMMARIES OF CONDUCT OF STUDY

For both parts of the study, the numbers of patients who enroll or are randomized in the study, discontinue from the study, or complete the study will be summarized separately for each part. Reasons for patient discontinuations from the study treatment and from the study will be presented in listings and summary tables. Protocol deviations will be evaluated for their potential effects on the interpretation of study results, and reasons for exclusion of patients from the analyses will be presented.

6.5 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Baseline will be defined as the last available assessment prior to study entry. Study entry is defined as either the day of the first dose of study treatment, or, for patients who were not dosed, the date they were enrolled into the study according to the IxRS.

6.5.1 Part 1: Dose Finding

Demographic and baseline disease characteristics will be summarized by treatment cohort using descriptive statistics (e.g., means, standard deviations, medians, and ranges for continuous variables, and proportions for categorical variables, as appropriate). A demographic listing will also be provided.

The analyses will be performed in all enrolled patients in Part 1 and for the PK-evaluable population.

6.5.2 Part 2: Dose Confirmation

Demographic and baseline disease characteristics will be summarized using descriptive statistics (e.g., means, standard deviations, medians, and ranges for continuous variables, and proportions for categorical variables, as appropriate) by treatment arm. A demographic listing will also be provided. These analyses will be performed in the FAS and the Per Protocol PK analysis population.

The safety analyses will be performed in the safety population.

6.6 ANALYSES OF PRIMARY ENDPOINT

6.6.1 Part 1: Dose Finding

Pharmacokinetics of atezolizumab will be characterized following administration of atezolizumab SC co-mix or atezolizumab SC. Modeling of the PK data will be performed using a population approach with combined SC and IV data from Part 1 of the study to characterize the absorption phase of the SC route of administration. The existing population PK model developed on data from study PCD4989g will be used as a basis.

Individual exposure metrics (i.e., C_{trough} and AUC at Cycle 1) will be derived from the final PK model.

Model-based simulations may be performed to predict Cycle 1 C_{trough} (predose Cycle 2) in Part 2 of the study to select the atezolizumab SC dose that will yield a mean SC C_{trough} non-inferior to that following atezolizumab IV administration.

6.6.2 Part 2: Dose Confirmation

One of the co-primary endpoints is the observed serum C_{trough} in Cycle 1.

The primary analysis of C_{trough} will be based on logarithmic values of observed C_{trough} in Cycle 1 to compensate the known skewness of its distribution. For natural logarithm (Ln) (C_{trough}), the statistical hypothesis will be tested using an analysis of covariance model

$$Ln(C_{trough})_{ij} = \mu + \tau_i + \varepsilon_{ij} \quad (i=SC, IV; j=1, 2, \ldots, n_i)$$

where μ denotes the overall mean, τ_i the effect of atezolizumab route of administration i (SC or IV), n_i the number of patients in arm i (SC or IV), and ε_{ij} a random error variable assumed to be independently and identically normally distributed with mean zero and variance σ_ε^2.

The contrast $\tau_{SC} - \tau_{IV}$, its 90% confidence limits, and the variance σ_ε^2 will be estimated from the model. An estimate of the treatment effects ratio and the corresponding 90% confidence limits for the untransformed variables will be calculated by exponentiation of the estimate of contrast $\tau_{SC} - \tau_{IV}$ and the 90% confidence limits. The CV for the untransformed primary variable will be estimated using the relationship $CV_\varepsilon = sqrt(exp(\sigma_\varepsilon^2)-1)$.

If the lower confidence interval bound of $exp(Ln[C_{trough,SC}]-Ln[C_{trough,IV}])=C_{trough,SC}/C_{trough,IV}$ is equal or greater than 0.8, then the null hypothesis can be rejected (see Section 6.3.2).

The estimand for the primary analysis follows a principal stratum strategy based on the following attributes:

- Treatment: atezolizumab IV versus atezolizumab SC, at the determined dose at baseline. All randomized patients are expected to receive the baseline infusion or injection.

- Population: Patients with locally advanced or metastatic patients NSCLC who are CIT-naive and for whom prior platinum therapy has failed. The analysis population will consist of the Per Protocol PK analysis population, with patients grouped according to their received treatment (see Section 6.2.2).
- Variable: The Cycle 1 observed serum C_{trough} (predose Cycle 2), using the measured concentration from the PK sample.
- Intercurrent events, handled as follows:

  Premature discontinuation from treatment: every effort will be made to ensure all randomized patients will receive the treatment at baseline and will have the PK sample collected appropriately. Treatment will start within 5 days of randomization. Withdrawal after randomization, prior to baseline treatment is not expected. In case of such an event, those patients are excluded from the analysis population and those patients will not be replaced, as outlined in Section 4.6.2.

  Premature discontinuation from study: Some patients could discontinue the study prior to the time point of predose Cycle 2 due to death or other reasons. Considering the short interval between randomization and Cycle 2, this situation is expected to be exceptional. Those patients are excluded from the population.

  Missing or outside of window PK samples: Some patients could have a Cycle 1 C_{trough} PK sample missing or outside of the accepted window, due to early withdrawal or other reasons. Every effort will be made to collect PK samples on schedule. Those patients are excluded from the analysis population.
- Summary measure: GMR and 90% CI of atezolizumab SC versus atezolizumab IV of Cycle 1 C_{trough}. The non-interiority would be established if the lower bound of the 90% CI is ≥ 0.8.

Supplementary analyses may be conducted to assess any potential impact of imbalances in baseline characteristics between treatment arms. In addition to the analysis of observed serum C_{trough} values, the same statistical hypothesis test for non-inferiority will be performed descriptively using Cycle 1 C_{trough} values derived from the population PK model. For each patient, individual empirical Bayesian estimates of PK parameters will be used to compute the model-predicted C_{trough} at Cycle 1. The aim of using predicted C_{trough} is to take into account possible deviations from the protocol (i.e., sampling schedule or dosing interval) and to reduce noise (i.e., precision of analytical measurement). The Cycle 1 C_{trough} values derived from the PK model is a different estimand with respect to the observed serum C_{trough}; the treatment, population and summary measure have the same definition as the primary endpoint. The intercurrent events will be handled using the same strategies as the model-predicted Cycle 1 AUC.

The model-predicted Cycle 1 $AUC_{0–21\ d}$ is a co-primary endpoint and will be analyzed using the same method as for the other co-primary endpoint, Cycle 1 observed serum C_{trough}.

The estimand for this co-primary analysis follows a principal stratum and treatment policy strategy based on the following attributes:

- Treatment: same as for co-primary endpoint Cycle 1 observed serum C_{trough}
- Population: Patients with locally advanced or metastatic NSCLC who are CIT-naïve and for whom prior platinum therapy has failed. The analysis population for the pharmacokinetic analysis set will consist of the population pharmacokinetic analysis set, with patients grouped according to their received treatments.
- Variable: model-predicted Cycle 1 $AUC_{0–21\ d}$, derived from the popPK model.
- Intercurrent events, handled as follows:

  Premature discontinuation from treatment: same as for the other co-primary endpoint

  Premature discontinuation from study: Some patients could discontinue the study following their Cycle 1 dose prior to providing a post-baseline PK blood sample or PK blood samples could not be collected. Considering the short interval between the first study drug treatment (Cycle 1) and the first PK blood sample (8 ± 2 hours) as well as the numerous PK blood samples collected on study, these situations are expected to be exceptional. Those patients are excluded from the analysis population.

  Missing or inaccurate time and date reported for treatment administration or PK blood samples: Some patients could be missing some scheduled PK samples, or have PK samples collected outside of the schedule, due to early withdrawal or other reasons. Every effort will be made to ensure that all randomized patients will receive the treatment and will have the time and date of dosing and PK blood samples reported accurately. Missing or inaccurate dosing time and date can occur during any cycle however, it is very rare. In case of such an event, only such affected samples are excluded and patients are retained as long as they have a single reportable dose and corresponding PK sample, regardless of the cycle.
- Summary measure: GMR and 90% CI of atezolizumab SC versus atezolizumab IV of Cycle 1 AUC. The non-interiority would be established if the lower end of the 90% CI is ≥ 0.8.

The co-primary endpoints will be statistically tested at the same α level (one-sided significance level of 0.05) using the Hochberg procedure as described in Section 6.3.2.

6.7 SECONDARY AND EXPLORATORY PHARMACOKINETIC ANALYSES

6.7.1 Part 1: Dose Finding

Concentration versus time data will be tabulated and plotted by cohort. PK parameters (e.g., C_{trough}, AUC, C_{max}, T_{max}) will be presented in summary tables with descriptive summary statistics by cohort. Patient listings will be provided.

Additional PK analyses may be conducted as appropriate.

6.7.2 Part 2: Dose Confirmation

Model-predicted Cycle 1 (C_{trough} only) and steady state C_{trough} and AUC will be descriptively compared between atezolizumab SC and IV.

Other PK data will be analyzed using statistical summary measures, listings, and graphs as appropriate.

Exploratory exposure–response analyses may be performed to link atezolizumab exposure (e.g., C_{trough}, $C_{max,}$ and AUC Cycle 1) to safety (Grade 3–5 adverse events, adverse events of special interest) and efficacy (ORR and OS) endpoints. These analyses may be reported separately from the CSR.

6.8 EFFICACY ANALYSES

Efficacy analyses will be performed for Part 2 of the study only.

6.8.1 Objective Response Rate

ORR is a secondary endpoint and is defined as the proportion of patients with a PR or CR as determined by the investigator according to RECIST v1.1.

The ORR and 95% confidence intervals according to Pearson-Clopper will be calculated and presented by treatment arm. For the difference in response rates, 95% two-sided CIs (Hauck-Andersen) will be calculated.

The estimand corresponding to this secondary endpoint will be defined in the Statistical Analysis Plan.

The planned sample size in Part 2 is 218 patients in the atezolizumab SC group. The table below summarizes the resulting 95% CI for the ORR, assuming it will be in the range of 10%–15%.

Analyses of ORR will be performed both at the time of the primary analysis of C_{trough} and at the end of the study. The latter time point is expected to provide a better estimate because of the longer follow-up.

Table 8 95% Confidence Interval for ORR in Atezolizumab SC Group

Number of Responders	ORR	95% Confidence Interval
22	10.1%	[6.43 to 14.88]
29	13.3%	[9.09 to 18.54]
33	15.1%	[10.65 to 20.60]

Table shows the Pearson-Clopper 95% CI for a given observed ORR in 218 patients dosed with atezolizumab SC.

6.8.2 Progression-Free Survival

The duration of PFS is defined as the time from the date of study entry to the date of documented disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever is earlier.

Patients who have not progressed at the time of the analysis will be censored at the last available tumor assessment. Patients without post-baseline tumor assessment will be censored on the date of study entry + one day.

The estimand corresponding to this secondary endpoint will be defined in the Statistical Analysis Plan.

PFS will be analyzed using Kaplan-Meier methodology, including survival plots, median duration and corresponding 95% confidence intervals according to the Brookmeyer-Crowley method. The proportion of patients who are PFS event-free at 6 and 12 months after study entry will be estimated at the final analysis of the study when sufficient follow-up data are available. The corresponding 95% CI will be calculated using the standard error derived from Greenwood's formula.

Additional sensitivity analyses of PFS may be conducted as appropriate in order to investigate the effect of baseline characteristics on the result.

6.8.3 Overall Survival

The duration of OS is defined as the time from the date of study randomization to the date of death from any cause.

Patients without a death record will be censored at the last date they were known to be alive. Patients with no post-baseline information will be censored on the day of study entry +1 day.

The estimand corresponding to this secondary endpoint will be defined in the Statistical Analysis Plan.

OS will be analyzed using Kaplan-Meier methodology, including survival plots, median duration and corresponding 95% confidence intervals according to the Brookmeyer-Crowley method. The proportion of patients alive at one and two years will be estimated at the final analysis of the study when sufficient follow-up data are available. The corresponding 95% CI will be calculated using the standard error derived from Greenwood's formula.

Additional sensitivity analyses of OS may be conducted as appropriate in order to investigate the effect of baseline characteristics on the result.

6.8.4 Duration of Response

DOR will be assessed in the subpopulation of FAS patients who had measurable disease at baseline and who achieved an objective response as determined by the investigator according to RECIST v1.1. DOR is defined as the time interval from the date of the first occurrence of a complete or partial response (whichever status is recorded first) until the first date that progressive disease or death is documented, whichever occurs first. 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 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 estimand corresponding to this secondary endpoint will be defined in the Statistical Analysis Plan.

DOR is based on a non-randomized subset of patients (specifically, patients who achieved an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes. The methodologies detailed for the PFS analysis will be used for the DOR analysis.

6.9 SAFETY ANALYSES

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. Laboratory toxicities will be defined based on local laboratory normal ranges and NCI CTCAE, v5.0.

6.9.1 Part 1: Dose Finding

For safety-evaluable patients, data on study drug administration and dose modifications will be presented as descriptive summary statistics or listings by cohort and by route of administration as appropriate. All adverse events occurring on or after the first dose of study medication will be summarized by treatment cohorts. Analyses will also be performed by NCI CTCAE grade. In addition, serious adverse events, Grade 5 adverse events, Grade 3-4 adverse events, adverse events of special interest, and adverse events leading to study drug discontinuation will be presented in summary tables and listings.

Deaths reported during study treatment and during the follow-up period (see Section 5.4.2) will be reported by treatment cohort.

Data on safety laboratory test values and vital signs will be presented by treatment cohort and grade, including shift tables and analyses of change from baseline as appropriate.

6.9.2 Part 2: Dose Confirmation

The safety analysis population in Part 2 is defined as all patients who received at least one dose of any amount of any component of protocol treatment, with patients grouped according to treatment received. All adverse events, deaths due to adverse events, serious adverse events, Grade 3–4 adverse events, adverse events of special interest, and adverse events leading to study drug 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.

A summary and listing of deaths reported during Part 2 of the study (see Sections 5.4.2 and 5.6) will be provided.

Data on safety laboratory test values and vital signs will be presented by treatment received and grade, including shift tables and analyses of change from baseline as appropriate.

6.10 SUBGROUP ANALYSES

In Part 1, there will be no prespecified subgroup analyses. In Part 2, data on secondary endpoints may be analyzed in patient subgroups by, e.g., demographic or baseline prognostic characteristics. These analyses will be performed in an exploratory manner.

6.11 IMMUNOGENICITY ANALYSES

The atezolizumab and rHuPH20 immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received.

The number and proportion of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized for ADA-evaluable patients. When determining post-baseline incidence, patients are considered to be ADA-positive if they are ADA-negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment–induced ADA response), or if they are ADA-positive at baseline and the titer of one or more post-baseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be post-treatment ADA-negative if they are ADA-negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA-positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

Demographic and baseline characteristics in ADA-evaluable patients will be summarized by treatment arm (as appropriate). The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized for both atezolizumab and rHuPH20.

In Part 2, additional analyses may investigate the relationship between atezolizumab and rHuPH20 ADA status and safety, efficacy, and PK endpoints via descriptive statistics if appropriate.

6.12 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.

6.13 PATIENT- AND HEALTH CARE PROFESSIONAL–REPORTED EXPERIENCE ANALYSES

Patient- and HCP-reported experience analyses will be performed for Part 2 of the study only.

Descriptive analyses, including summary statistics, will be performed and presented by treatment arm for each patient-reported experience measure (item- and scale-level, as appropriate). Item-level analyses will include frequencies and proportions and change from baseline at each visit by treatment arm. Summary statistics (e.g., mean, median, minimum, maximum, interquartile range) of scale scores and score changes from baseline at each visit will be evaluated by treatment arm.

For each of the EORTC scales, a prorated scale score will be calculated if 50% or more of the constituent items in the scale are completed. The scale score will be considered missing if $<$50% of the constituent items were not completed. A SWT scale score will be calculated if five or more items have been completed (out of seven). The scale score will be considered missing if fewer than five items have been completed.

For the HCP-reported experience data, descriptive summaries for each item will be presented by country or region and by other categories as appropriate for all HCPs who completed at least one question in a questionnaire.

6.14 INTERIM ANALYSIS

No formal interim statistical analysis is planned in the study.

During Part 1, PK data will be analyzed on an ongoing basis. In addition, data will be reviewed by an IMC at regular intervals as outlined in Section 3.1.3.1 and the IMC charter. All required analyses will be performed by the study team and provided to the IMC. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRBs/ECs.

During Part 2, a JMC will be set up to evaluate PK and safety data on an ongoing basis as outlined in Section 3.1.3.2 and the JMC charter. All analyses for this review will be prepared by the study team, who will maintain the blind of treatment allocation.

A review of PK and safety data from the first 24 patients (approximately 16 patients in the atezolizumab SC arm and approximately 8 patients in the atezolizumab IV arm) who have completed at least one cycle of treatment will also be conducted (see Section 3.1.1.2). These analyses will be blinded while recruitment into Part 2 continues.

Any outcomes of these PK and safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRBs/ECs.

A blinded sample-size re-estimation will be conducted after approximately 210–250 patients have been randomized. A blinded estimation of the total CV% from all available Cycle 1 C_{trough} and Cycle 1 AUC data will be compared with the CV% used in the calculation of sample size. Depending on the total observed CV%, the Sponsor may decide to increase or decrease the number of patients randomized.

6.15 CHINA SUBPOPULATION ANALYSES

The China subpopulation will include all patients randomized at qualified sites.

The analyses for the China subpopulation will be performed in a similar way as done for the global population or summarized descriptively as appropriate. Results from these analyses will be summarized in a separate Report. Further details will be provided in the Statistical Analysis Plan.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory, IxRS data, and any other externally generated electronic study data will be sent directly to the Sponsor, using the Sponsor's standard procedures 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 by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Data from the PROs will be entered directly in the eCRF and data from the HCPs will be entered into a Vendor database and the data transferred to the Sponsor.

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, 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.

The Sponsor will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

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 applicable 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) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form 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.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

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 9.7).

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

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 9.6).

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 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The

Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 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.

9.5 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.

Up to approximately 150 sites globally will participate to enroll approximately 327 patients. Screening and enrollment will occur through an IxRS.

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 4.5.7. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC and a JMC will be employed to monitor and evaluate patient safety throughout the study (see Section 3.1.3).

9.6 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 health care professionals and to the public, at scientific congresses, in clinical trial registries, 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 (see Section 8.4 for details), and redacted clinical study reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

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.

9.7 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).

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Appendix 1
Schedule of Activities: Part 1

Assessment	Screening [a]	All Cycles	Treatment Discontinuation [b]	Safety Follow-Up [c]
	Days –28 to –1	Day 1 (±3 Days for Cycles >2)	≤30 Days after Last Dose	Up to 90 Days after Last Dose
Signed Informed Consent Form [d]	x			
Review of eligibility criteria	x			
Medical, surgical, and cancer histories, including demographic information, EGFR, and ALK mutational status [e]	x			
HIV, HBV, HCV serology [f]	x			
Concomitant medications [g]	x	x	x	
Complete physical examination [h]	x			
Limited physical examination [i]		x	x	
ECOG performance status [j]	x	x	x	
Vital signs [k]	x	x	x	
12-lead electrocardiogram [l]	x	(x)	(x)	
Echocardiogram [m]	x	(x)		
Weight	x	x	x	

Appendix 1: Schedule of Activities for Part 1 (cont.)

Assessment	Screening [a]	All Cycles	Treatment Discontinuation [b]	Safety Follow-Up [c]
	Days –28 to –1 [a]	Day 1 (±3 Days for Cycles >2)	≤30 Days after Last Dose	Up to 90 Days after Last Dose
Height	x			
Hematology [n]	x	x	x	
Serum chemistry [o]	x	x	x	
Coagulation panel (aPTT, INR) [p]	x		x	
C-reactive protein sample (central laboratory) [q]	x	x		
Urinalysis [r]	x	x	x	
Pregnancy test [s]	x	x		
TSH, free T3, free T4	x		x	
Serum and plasma samples for PK and ADA assessment (central laboratory) [t]		x	x	
Adverse events [c, u]	◄———	———	———	———►
Atezolizumab SC co-mix, atezolizumab SC injection, or atezolizumab IV infusion [v]		x		
Tumor assessment [w]	x			

ADA = anti-drug antibody; *ALK* = anaplastic lymphoma kinase; anti-HBc= antibody against hepatitis B core antigen; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; *EGFR* = epidermal growth factor receptor; HBsAG = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IV = intravenous; PD-L1 = programmed death–ligand 1; PK = pharmacokinetic; SC = subcutaneous; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Notes: Assessments in parentheses are optional or as clinically indicated. Assessments scheduled on the days of study treatment injection/infusions should be performed before the injection/infusion unless otherwise noted.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry (except where otherwise specified) may be used for screening assessments rather than repeating such tests.

[b] Patients will be asked to return to the clinic not more than 30 days after the last dose of treatment for a treatment discontinuation visit.

[c] 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. In addition, the Sponsor should be notified if the investigator becomes aware of any study treatment–related serious adverse event (see Section 5.6).

[d] Written informed consent is required prior to performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur before the 28-day screening period.

[e] Cancer history includes stage, date of diagnosis, results of *EGFR* mutation and *ALK* rearrangement testing (if available), and prior anti-tumor treatment. *EGFR* and/or *ALK* may be provided only if already available. Demographic information includes sex, age, and self-reported race/ethnicity.

[f] All patients will be tested for HIV prior to inclusion into the study; HIV-positive patients will be excluded from the study. HBV DNA must be collected on or before Cycle 1, Day 1 in patients who have negative serology for hepatitis B surface antigen and positive serology for anti-HBc. Patients with active hepatitis B (chronic or acute; defined as having a positive HBsAg test result at screening) will be excluded from the study. Patients with past or resolved HBV infection (defined as the presence of HBcAb and absence of HBsAg) are eligible only if their HBV DNA test is negative. Patients with HCV will be excluded from the study; patients who test positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

[g] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

[h] Complete physical examinations are defined in Section 4.5.3.

[i] Limited physical examinations are defined in Section 4.5.3. Limited physical examinations may be obtained $\leq$4 days before Day 1 of each cycle.

[j] ECOG performance status may be obtained $\leq$4 days before Day 1 of each cycle.

[k] Vital signs include pulse rate, respiratory rate, blood pressure, and temperature. At all administrations, vital signs should be determined within 60 minutes before and 30 ($\pm$10) minutes after the administration (before any PK sample scheduled to be drawn at the same time) and as clinically indicated. Refer to Section 4.3.2.

[l] ECG recordings will be obtained during screening and when clinically indicated. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[m] Required in patients with a known history of pericardial effusions or with evidence of pericardial effusion on screening chest CT. Echocardiogram is the preferred modality for this assessment. The same method must be used throughout the study. Echocardiograms will be performed at screening, as clinically indicated or per standard of care thereafter during treatment, and at the treatment discontinuation visit if pericardial effusions are not resolved during the study. Patients who develop new pericardial effusions while in the study must be followed by echocardiography.

[n] Local laboratory assessments may be obtained ≤4 days before Day 1 of each cycle. Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated.

[o] Local laboratory assessments may be obtained ≤4 days before Day 1 of each cycle. Serum chemistry includes BUN/urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.

[p] To be completed ≤14 days prior to start of study treatment.

[q] C-reactive protein assessment may be obtained ≤4 days before Day 1 of each cycle.

[r] Urinalysis includes specific gravity, pH, glucose, protein, ketones, and blood. To be performed ≤4 days before dosing.

[s] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1. A urine (or serum, if urine is not feasible) pregnancy test must be carried out every 2 cycles for Cohort 2 and before each cycle for Cohort 3. If the urine test result is positive, a confirmatory serum test must be done.

[t] See Appendix 3 for further details on the sampling schedule and Appendix 6 for further details on the sampling procedure.

[u] After informed consent has been obtained but prior to initiation of study drug (screening), only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of another non-protocol systemic anti-cancer therapy, whichever occurs first. 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 non-protocol systemic anti-cancer therapy, whichever occurs first. After this period, investigators should report any other serious adverse events that are considered to be related to study drug. 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 drug or study-related procedures until a final outcome can be reported.

[v] Patients in Cohort 1 will only receive one cycle of atezolizumab SC co-mix. Patients in Cohorts 2 and 3 will receive 3 cycles. Patients should receive their first dose of study drug on the day of enrollment, if possible. If this is not possible, the first dose should occur no later than 5 days after enrollment. Atezolizumab treatment may be continued in the absence of meeting discontinuation criteria if the patient is experiencing clinical benefit.

[w] Tumor assessments performed as standard-of-care prior to obtaining informed consent and within 28 days prior to randomization may be used rather than repeating tests as long as they comply with RECIST 1.1 requirements and cover all required body areas (see Section 4.5.5).

Appendix 2
Schedule of Activities: Part 2

Assessment Window (Days)	Screening [a]	All Cycles	Treatment Discontinuation [b]	Follow-Up [x, bb]
	Days –28 to –1	Day 1 (±3 Days for Cycles >2)	≤30 Days after Last Dose	
Signed Informed Consent Form [c]	x			
Review of eligibility criteria	x			
Medical, surgical, and cancer histories, including demographic information, EGFR (and ALK, if available) mutational status [d]	x			
HIV, HBV, HCV serology [e]	x			
Concomitant medications [f]	x	x	x	
Tumor assessment [g, h]	x	x		
Complete physical examination [i]	x			
Limited physical examination [j]		x	x	
ECOG performance status [k]	x	x	x	
Vital signs [l]	x	x	x	
Electrocardiogram [m]	x	(x)	(x)	
Echocardiogram [n]	(x)	(x)		
Weight	x	x	x	

Appendix 2: Schedule of Activities for Part 2 (cont.)

Assessment Window (Days)	Screening [a]	All Cycles	Treatment Discontinuation [b]	Follow-Up [x,bb]
	Days –28 to –1	Day 1 (±3 Days for Cycles >2)	≤30 Days after Last Dose	
Height	x			
Hematology [o]	x	x	x	
Serum chemistry [p]	x	x	x	
Coagulation panel (aPTT, INR) [q]	x			
C-reactive protein sample (central laboratory) [r]	x	x		
Urinalysis [s]	x	x	x	
Pregnancy test [t]	x	x	x	(x)
TSH, free T3, free T4 [u]	x	x	x	
Baseline tumor tissue for PD-L1, ALK (if applicable), and EGFR (if needed) testing [v]	x			
Serum and plasma samples for PK and ADA assessment (central laboratory) [w]		x	x	
Adverse events [x]	◄———	———	———	———►
Atezolizumab SC injection or IV infusion [y]		x		
Patient-reported experience [z]		x		
HCP-reported experience [aa]		x		
Survival follow-up and anti-cancer treatment [x, bb]				x

ADA = anti-drug antibody; *ALK* = anaplastic lymphoma kinase; anti-HBc = antibody against hepatitis B core antigen; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; *EGFR* = epidermal growth factor receptor; HBsAG = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PD-L1 = programmed death–ligand 1; PK = pharmacokinetic; SC = subcutaneous; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Notes: Assessments in parentheses are optional or as clinically indicated. Assessments scheduled on the days of study treatment infusions/ injections should be performed before the infusion/injection unless otherwise noted.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to start of treatment (except where otherwise specified) may be used for screening assessments rather than repeating such tests.

[b] Patients will be asked to return to the clinic not more than 30 days after the last dose of treatment for a treatment discontinuation visit.

[c] Written informed consent is required prior to performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur before the 28-day screening period.

[d] Cancer history includes stage, date of diagnosis, results of EGFR mutation and ALK rearrangement testing (if available), and prior anti-tumor treatment. Local EGFR results must be tested centrally for those patients who may harbor sensitizing EGFR mutations and do not have local results and for patients enrolled in China. Additional tissue will be required for EGFR central testing (see Section 4.5.7.3). ALK may be assessed locally or at a central laboratory. Additional tissue will be required for central testing for patients who may be carriers of an ALK fusion oncogene, if no local results are available (see Section 4.5.7.3). Demographic information includes sex, age, and self-reported race/ethnicity.

[e] All patients will be tested for HIV prior to the inclusion into the study; HIV-positive patients will be excluded from the study. HBV DNA must be collected on or before Cycle 1, Day 1 in patients who have negative serology for hepatitis B surface antigen and positive serology for anti-HBc. Patients with active hepatitis B (chronic or acute; defined as having a positive HBsAg test result at screening) will be excluded from the study. Patients with past or resolved HBV infection (defined as the presence of HBcAb and absence of HBsAg) are eligible only if their HBV DNA test is negative. Patients with HCV will be excluded from the study; patients who test positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

[f] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

[g] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to start of treatment may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. The same radiographic procedure must be used throughout the study for each patient. Results must be reviewed by the investigator before dosing at the next cycle. Tumor assessments should continue regardless of whether patients start new anti-cancer therapy in the absence of disease progression unless they withdraw consent. If an optional biopsy is to be performed at approximately the same timepoint of a tumor assessment or as a result of the radiographic determination (e.g., response or progression), samples should be acquired after all imaging scans have been performed, if at all possible. Patients who continue treatment beyond radiographic disease progression will be monitored with a follow-up scan

at the next scheduled tumor assessment when the scan frequency is every 6 weeks. If the scan frequency is every 9 weeks, the follow-up scan must be performed at 6 weeks (±2 weeks) as an unscheduled tumor assessment, or earlier if clinically indicated. Investigators may perform additional scans or more frequent assessments if clinically indicated.

[h] Patients will undergo tumor assessments at baseline, every 6 weeks (approximately every two cycles)±3 business days for the first 36 weeks following treatment initiation, and every 9 weeks (± 1 week) thereafter, regardless of dose delays, until disease progression per RECIST v1.1 or (for patients who continue atezolizumab after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy.

[i] Complete physical examinations are defined in Section 4.5.3.

[j] Limited physical examinations are defined in Section 4.5.3. Assessment may be obtained ≤4 days before Day 1 of each cycle.

[k] ECOG performance status may be obtained ≤4 days before Day 1 of each cycle.

[l] Vital signs include heart rate, respiratory rate, blood pressure, and temperature. For all administrations, vital signs should be determined within 60 minutes before and 30 (±10) minutes after the administration (before any PK sample scheduled to be drawn at the same time) and as clinically indicated. For IV only and if clinically indicated, vital signs will also be collected during the first administration (every 15 [±5] minutes). During SC administrations or during subsequent IV administrations, vital signs will be collected if clinically indicated. Refer to Section 4.3.2 for more details.

[m] Triplicate ECG recordings will be performed during screening and when clinically indicated. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[n] Required in patients with a known history of pericardial effusions or with evidence of pericardial effusion on screening chest CT. Echocardiogram is the preferred modality for this assessment. The same method must be used throughout the study. Echocardiograms will be performed at screening, as clinically indicated or per standard of care thereafter during treatment, and at the treatment discontinuation visit if pericardial effusions are not resolved during the study. Patients who develop new pericardial effusions while in the study must be followed by echocardiography.

[o] Local laboratory assessments may be obtained ≤4 days before Day 1 of each cycle. Hematology consists of WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). A manual differential can be done if clinically indicated.

[p] Local laboratory assessments may be obtained ≤4 days before Day 1 of each cycle. Serum chemistry includes 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 lactate dehydrogenase (LDH).

[q] To be completed ≤14 days prior to start of study treatment.

[r] C-reactive protein may be obtained ≤4 days before Day 1 of each cycle.

[s] Urinalysis should be performed ≤4 days before dosing and consists of specific gravity, pH, glucose, protein, ketones, and blood. Dipstick permitted.

[t] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1 of Cycle 1. A urine (or serum, if urine is not feasible) pregnancy test is required on Day 1 of each cycle. If the urine test result is positive, it needs to be confirmed with a serum test. In accordance to country-specific health authority mandates, pregnancy tests may be required beyond treatment discontinuation, monthly for 5 months after the final dose of atezolizumab. Pregnancy tests after study treatment discontinuation can be performed at home. If a home urine pregnancy test is positive, it must be confirmed by a serum pregnancy test and if confirmed, immediately communicated to the treating physician.

[u] 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 (i.e., Cycles 5, 9, 13, etc.). Assessment may be performed ≤4 days before Day 1 of each cycle.

[v] Tumor samples requiring EGFR testing must be submitted prior to randomization and as early as possible to avoid compromising duration of the screening period. Patients not requiring EGFR testing for randomization may have their samples submitted within 4 weeks after randomization. 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. All material should be sent in a single shipment. See Section 4.5.7.3 and the laboratory manual for additional details and tissue sample requirements for central PD-L1, EGFR, and ALK testing.

[w] See Appendix 4 and Appendix 5 for further details on the sampling schedule and Appendix 6 for further details on the sampling procedure.

[x] After informed consent has been obtained but prior to initiation of study drug (screening), only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. 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. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment. 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 drug or study-related procedures until a final outcome can be reported.

[y] Patients should receive their first dose of study drug on the day of randomization, if possible. If this is not possible, the first dose should occur no later than 5 days after enrollment. Atezolizumab treatment may be continued in the absence of meeting discontinuation criteria if the patient is experiencing clinical benefit (see Section 3.1.2).

[z] Patient experience data will be collected through use of the European Organisation for Research and Treatment of Cancer (EORTC) IL57 Questionnaire (see Appendix 11) and the modified Satisfaction with Cancer Therapy (SWT) scale from the Cancer Therapy Satisfaction (CTSQ) Questionnaire (see Appendix 12). The EORTC IL57 questionnaire should be completed at the site by patients on Day 1 of Cycles 1–6, every

even -numbered cycle thereafter (i.e., Cycles 8, 10, etc.) during study treatment, and at the treatment discontinuation visit. The SWT scale should be completed at the site by patients at the Cycle 3 visit, or at the treatment discontinuation visit if study treatment is discontinued prior to the Cycle 3 visit. See additional instructions in Section 4.5.8.2.

[aa] Health Care Professional (HCP) experience data will be collected through use of the HCP Subcutaneous Perspective Questionnaire (see Appendix 13) and the HCP SC versus IV Perspective Questionnaire (see Appendix 14). The HCP Subcutaneous Perspective Questionnaire should be completed after an HCP has administered at least three doses of atezolizumab SC across all patients in Part 2. The HCP SC versus IV Perspective Questionnaire should be completed after an HCP has administered at least three doses of atezolizumab SC and at least three doses of atezolizumab IV across all patients in Part 2.

[bb] 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 2–3 months until death (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 3
Schedule of Pharmacokinetic and Immunogenicity Samples: Part 1, Cohort 1

Cycle	Day	Time/Maximum Window	PK Sample	ADA Sample
Cycle 1	Day 1	Predose [a]	Atezolizumab rHuPH20	Atezolizumab rHuPH20
		8 ± 2 hours	Atezolizumab rHuPH20	—
	Day 2	Between 24 and 48 hours postdose	Atezolizumab rHuPH20	—
	Day 4	Between 72 and 96 hours postdose	Atezolizumab rHuPH20	—
	Day 8	Between Day 8 and Day 11	Atezolizumab rHuPH20	—
Cycle 2	Day 1 [b]	Predose [a]	Atezolizumab rHuPH20	Atezolizumab rHuPH20
Cycles 3, 4, 8, 12, and 16	Day 1	Predose [a]	Atezolizumab rHuPH20	Atezolizumab rHuPH20
Cycles 2, 3, 4, 8, 12, and 16	Day 1	Post-infusion of atezolizumab IV [c]	Atezolizumab	—
Treatment discontinuation visit	At visit	At visit	Atezolizumab rHuPH20	Atezolizumab rHuPH20

ADA = anti-drug antibody, also called anti-therapeutic antibody; PK = pharmacokinetic; rHuPH20 = human hyaluronidase.

Actual sampling dates and times must be recorded precisely for all samples. For detailed sampling instructions, refer to Appendix 6.

[a] Predose sample must be taken on the same day of treatment administration and before administration starts. Exact actual sampling and dosing dates and times will be recorded.

[b] This sample is critical and needs to be **taken precisely 21 days after the first dose.** Please schedule the first dose accordingly.

[c] Post-infusion sample must be taken at 30 (± 10) minutes after the infusion has ended.

Appendix 3 (cont.)
Schedule of Pharmacokinetic and Immunogenicity Samples: Part 1, Cohort 2

Cycle	Day	Time/Maximum Window	PK Sample	ADA Sample
Cycle 1	Day 1	Predose [a]	Atezolizumab rHuPH20	Atezolizumab rHuPH20
		8 ± 2 hours	Atezolizumab rHuPH20	—
	Day 2	Between 24 and 48 hours postdose	Atezolizumab rHuPH20	—
	Day 4	Between 72 and 96 hours postdose	Atezolizumab rHuPH20	—
	Day 8	Between Day 8 and Day 11	Atezolizumab rHuPH20	—
Cycle 2	Day 1 [b]	Predose [a]	Atezolizumab rHuPH20	Atezolizumab rHuPH20
Cycle 3	Day 1	Predose [a]	Atezolizumab rHuPH20	Atezolizumab rHuPH20
Cycle 4	Day 1	Predose [a, c]	Atezolizumab rHuPH20	Atezolizumab rHuPH20
		Post-infusion of atezolizumab IV [c, d]	Atezolizumab	—
Cycle 5	Day 1	Predose [a, c]	Atezolizumab rHuPH20	Atezolizumab rHuPH20
		Post-infusion of atezolizumab IV [c, d]	Atezolizumab	—
Cycles 8, 12, and 16	Day 1	Predose [a]	Atezolizumab rHuPH20	Atezolizumab rHuPH20
Treatment discontinuation visit	At visit	At visit	Atezolizumab rHuPH20	Atezolizumab rHuPH20

ADA = anti-drug antibody, also called anti-therapeutic antibody; PK = pharmacokinetic; rHuPH20 = human hyaluronidase.

Actual sampling dates and times must be recorded precisely for all samples. For detailed sampling instructions, refer to Appendix 6.

[a] Predose sample must be taken on the same day of treatment administration and before administration starts. Exact actual sampling and dosing dates and times must be recorded.

[b] This sample is critical and needs to be **taken precisely 14 days after the first dose, without any time window**. Please schedule the first dose accordingly.

[c] Samples should be collected as scheduled; however, if collection of this sample is impossible, the missing sample must be collected at the Day 1 of the next applicable cycle visit.

[d] Post-infusion sample must be taken at 30 (± 10) minutes after the infusion has ended. Collection of this sample is not required if the patient continues to be treated with atezolizumab SC.

Appendix 3 (cont.)
Schedule of Pharmacokinetic and Immunogenicity Samples: Part 1, Cohort 3

Cycle	Day	Time/Maximum Window	PK Sample	ADA Sample
Cycles 1 and 2 [b]	Day 1	Predose [a]	Atezolizumab rHuPH20	Atezolizumab rHuPH20
		8 ± 2 hours	Atezolizumab rHuPH20	—
	Day 2	Between 24 and 48 hours postdose	Atezolizumab rHuPH20	—
	Day 4	Between 72 and 96 hours postdose	Atezolizumab rHuPH20	—
	Day 8	Between Day 8 and Day 11	Atezolizumab rHuPH20	—
Cycle 3 [b]	Day 1	Predose [a]	Atezolizumab rHuPH20	Atezolizumab rHuPH20
Cycle 4	Day 1	Predose [a, c]	Atezolizumab rHuPH20	Atezolizumab rHuPH20
		Post-infusion of atezolizumab IV [c, d]	Atezolizumab	—
Cycle 5	Day 1	Predose [a, c]	Atezolizumab rHuPH20	Atezolizumab rHuPH20
		Post-infusion of atezolizumab IV [c, d]	Atezolizumab	—
Cycles 8, 12, and 16	Day 1	Predose [a]	Atezolizumab rHuPH20	Atezolizumab rHuPH20
Treatment discontinuation visit	At visit	At visit	Atezolizumab rHuPH20	Atezolizumab rHuPH20

ADA= anti-drug antibody, also called anti-therapeutic antibody; PK= pharmacokinetic; rHuPH20 = human hyaluronidase.

Actual sampling dates and times must be recorded precisely for all samples. For detailed sampling instructions, refer to Appendix 6.

[a] Predose sample must be taken on the same day of treatment administration and before administration starts. Exact actual sampling and dosing dates and times will be recorded.

[b] These samples are critical and needs to be **taken precisely 21 days after the first dose, without any time window**. Please schedule the first dose accordingly.

[c] Samples should be collected as scheduled; however, if collection of this sample is impossible, the missing sample must be collected at the Day 1 of the next applicable cycle visit.

[d] Post-infusion sample must be taken at 30 (±10) minutes after the infusion has ended. Collection of this sample is not required if the patient continues to be treated with atezolizumab SC.

Appendix 4 Schedule of Pharmacokinetic and Immunogenicity Samples: Part 2, SC Arm

Cycle	Day	Time/Maximum Window	PK Sample	ADA Sample
Cycle 1	Day 1	Predose [a]	Atezolizumab	• Atezolizumab • rHuPH20
		8 (±2) hours after start of SC injection	Atezolizumab	—
	Day 2	Between 24 and 48 hours postdose	Atezolizumab	—
	Day 4	Between 72 and 96 hours postdose	Atezolizumab	—
	Day 8	Between Day 8 and Day 11 postdose	Atezolizumab	—
Cycle 2	Day 1	Predose [a, b]	Atezolizumab	• Atezolizumab • rHuPH20
Cycles 3, 4, 8, 12, and 16	Day 1	Predose [a]	Atezolizumab	• Atezolizumab • rHuPH20
Treatment discontinuation visit	At visit	At visit	Atezolizumab	• Atezolizumab • rHuPH20

ADA = anti-drug antibody, also called anti-therapeutic antibody; PK = pharmacokinetic; rHuPH20 = human hyaluronidase.

Actual dosing and sampling dates and times must be recorded precisely for all samples. For detailed sampling instructions, refer to Appendix 6.

[a] Predose sample must be taken on the same day of treatment administration and before administration starts.

[b] This sample is critical and needs to be **taken precisely 21 days after the first dose without any time window**. Please schedule the first dose accordingly.

Appendix 5 Schedule of Pharmacokinetic and Immunogenicity Samples: Part 2, IV Arm

Cycle	Day	Time/Maximum Window	PK Sample	ADA Sample
Cycle 1	Day 1	Predose [a]	Atezolizumab	Atezolizumab
		30 (±10) minutes after end of infusion	Atezolizumab	—
Cycle 1	Day 4	Between 72 and 96 hours postdose	Atezolizumab	—
Cycle 1	Day 8	Between Day 8 and Day 11	Atezolizumab	—
Cycle 2	Day 1	Predose [a, b]	Atezolizumab	Atezolizumab
		30 (±10) minutes after end of infusion	Atezolizumab	—
Cycles 3, 4, 8, 12, and 16	Day 1	Predose [a]	Atezolizumab	Atezolizumab
Treatment discontinuation visit	At visit	At visit	Atezolizumab	Atezolizumab

ADA = anti-drug antibody, also called anti-therapeutic antibody; PK = pharmacokinetic.

Actual dosing and sampling dates and times must be recorded precisely for all samples. For detailed sampling instructions, refer to Appendix 6.

[a] Predose sample must be taken on the same day of treatment administration and before administration starts.

[b] This sample is critical and needs to be **taken precisely 21 days after the first dose without any time window**. Please schedule the first dose accordingly.

Appendix 6
PK and ADA Sampling Instructions for Investigators

Site for PK and ADA for both Atezolizumab and rHuPH20 Sampling

In any case, precise blood drawing site must be recorded for all samples.

On days of SC dosing, PK/ADA blood samples should be drawn preferably from the arm. If a patient is unable to provide venous access from the arm, the hand or leg may be used as alternative back-up sites for PK blood sampling. If the leg is used to collect a PK blood sample, and atezolizumab SC was administered in the thigh, the opposite side from where atezolizumab has been most recently administered should be used. If atezolizumab was administered in the leg and the same leg where atezolizumab has been most recently administered must be used, the area of the injection should be avoided.

For IV dosing, PK/ADA blood samples need to be drawn from the arm not receiving atezolizumab infusion. If a patient is unable to provide venous access of the opposite arm from the infusion arm, the hand or leg may be used as alternative back-up sites for PK blood sampling.

Collecting blood for PK samples from central line and/or port should be avoided. If there is no possible way to avoid the central line and/or port, it is better to collect the PK sample than to avoid this altogether, but site of collection must be documented.

PK and ADA Sampling Time Variability Allowed

Every effort should be made to take PK and ADA samples on the exact day when they are scheduled (see Appendix 3, Appendix 4, and Appendix 5) and prior to any infusion or injection is given (for predose samples). Note that predose Cycle 2 sample has no time window. Our recommendation is to plan the first dose accordingly so that these key days fall into a day when the patient can attend the clinic.

In any case, exact actual sampling and dosing dates and times must be recorded for all samples.

Appendix 7
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 $\leq$ 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 $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 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").

[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.

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.

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.

  Previously irradiated lesions can only be considered as measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of disease.

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 ≤ 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.

ASSESSMENT OF TUMOR BURDEN

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 ≥ 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 ≥ 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.

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.

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.

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 1.

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 8
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 *or pericardial disorder* while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on 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 *myelitis*
- *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
- *Granulomatosis with polyangiitis*
- 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 cholangitis
- Psoriasis
- Reiter syndrome
- Rheumatoid arthritis
- Sarcoidosis
- Scleroderma
- Sjögren syndrome
- Stiff-Person syndrome
- Takayasu arteritis
- Ulcerative colitis
- Vitiligo
- Vogt-Koyanagi-Harada disease

Appendix 9
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

EQUIPMENT NEEDED

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment injection or infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, and/or endotracheal use 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 injection or infusion, the following procedures should be performed:

1. Stop the study treatment injection or infusion (if still ongoing).
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 10
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, when clinically indicated.

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

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections.

- *Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.*
- *In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.*
- *Consider holding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5–1 mg/kg/day of prednisone or equivalent) may be administered.*
- *For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.*
- *Hold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.*
- *In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.*

- The investigator should consider the benefit–risk balance for a given patient prior to further administration of atezolizumab. *R*esumption of atezolizumab may be considered *in patients who are* deriving benefit and *have* fully recovered from the

immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's assessment of *the benefits and risks* and documented by the investigator. The Medical Monitor is available to advise as needed.

DOSE MODIFICATIONS

There will be no dose modifications for atezolizumab in this study.

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 the equivalent of ≤ 10 mg/day oral prednisone 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 patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, *chest pain, fever, dyspnea,* fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. 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. *COVID-19 evaluation should be performed per institutional guidelines where relevant.* Management guidelines for pulmonary events are provided in Table 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. • For Grade 1 pneumonitis, consider withholding atezolizumab.
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 *with or without transbronchial biopsy*. • 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 *the* Medical Monitor. [c, d] • For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.

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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

[d] *In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.*

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c, d] • *Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment.* • Bronchoscopy or BAL *with or without transbronchial biopsy* is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone. • 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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

[d] *In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.*

HEPATIC EVENTS

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 Table 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 the Medical Monitor. [c]

LFT = liver function test.

[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 based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* 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 test.

[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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table 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. • *If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • 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 the 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 *the* 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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

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 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 *the* 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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • 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 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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

ENDOCRINE EVENTS

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. Patients 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
Grade 1 hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• *Consider withholding atezolizumab.* • *Initiate treatment with thyroid replacement hormone.* • *Monitor TSH closely.* • *Consider patient referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled and thyroid function is improving.*
Grade 3 and 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • *Refer* to *an* endocrinologist. • *Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status).* • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • *Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism.*

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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 4 Management Guidelines for Endocrine Events (cont.)

Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for *Grade 2* hyperthyroidism. • Consider patient referral to endocrinologist.
Grade 2 hyperthyroidism	• *Consider withholding 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.*
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid *drugs* such as methimazole or carbimazole as needed. • *Refer* to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact *the* Medical Monitor for life-threatening immune-mediated 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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grades 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 *the* 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. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • 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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

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 *the* Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact *the* 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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 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 *the* 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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table 6 .

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis *or associated with pericarditis (see section on pericardial disorders below)* and should be managed accordingly. Immune-mediated 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 Table 6 .

IMMUNE-MEDIATED PERICARDIAL DISORDERS

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 6 Management Guidelines for Immune-Mediated *Cardiac Events*

Event	Management
Immune-mediated myocarditis, *Grades* 2-4 *Immune-mediated pericardial disorders, Grades 2–4*	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider *antiarrhythmic* drugs, temporary pacemaker, ECMO, VAD *or pericardiocentesis* 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.

INFUSION-RELATED REACTIONS/INJECTION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab co-mix or atezolizumab SC. However, patients who experience an IRR (infusion-related reaction for IV formulation/injection-related reaction for SC formulation) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, *antipyretic medications*, and/or analgesics (e.g., acetaminophen) for subsequent infusions or injections. 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 *the* medical management of IRRs and CRS are provided in Table 7 .

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per *investigator's* judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

Table 7 Management Guidelines for Infusion-Related Reactions, Injection-Related Reactions, and Cytokine-Release Syndrome

Event	Management
Grade 1[a] Fever[b] with or without constitutional symptoms	• Immediately interrupt infusion/injection.[c] • Upon symptom resolution, wait for 30 minutes and then restart infusion/injection[c] at half the rate being given at the time of event onset. • If the infusion[c] is tolerated at the reduced rate for 30 minutes, the infusion[c] rate may be increased to the original rate. If the injection is tolerated at the reduced rate, continue until completion. • If symptoms recur, discontinue infusion/injection[c] of this dose. • Administer symptomatic treatment,[d] 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/injections[c], consider administration of oral premedication with antihistamines, *antipyretic medications*, 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[e] by nasal cannula or blow-by	• Immediately interrupt atezolizumab infusion/injection[c]. • Upon symptom resolution, wait for 30 minutes and then restart infusion/injection[c] at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion/injection[c] 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 as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[f] • 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 *the* Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered.

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

Grade 2[a] (cont.) Fever[b] with hypotension not requiring vasopressors and/or Hypoxia requiring low-flow oxygen[e] by nasal cannula or blow-by	• For subsequent injections/infusions[c], consider administration of oral premedication with antihistamines, *antipyretic medications*, 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 *the* Medical Monitor.
Grade 3[a] Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen[e] by nasal cannula, face mask, non-rebreather mask, or Venturi-mask	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Administer symptomatic treatment. [d] • 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 as described in this appendix. • 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 *the* Medical Monitor. [f] • Administer symptomatic treatment. [d] • 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.

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

Grade 4[a] (cont.) 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)	• 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 as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[f] For patients who are refractory to anti-cytokine therapy, experimental treatments[g] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

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 or injection-related reaction; MAS =macrophage activation syndrome; NCCN =National Cancer Comprehensive Network; NCI =National Cancer Institute.

Note: The management guidelines have been adapted from *the* NCCN guidelines for *the* 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 v5.0 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] For the purposes of this management guideline, “infusion” refers to the IV formulation and “injection” refers to the SC formulation.

[d] Symptomatic treatment may include oral or IV antihistamines, *antipyretic medications*, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[e] Low flow is defined as oxygen delivered at ≤6 L/min, and high flow is defined as oxygen delivered at >6 L/min.

[f] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator’s benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions/injections, administer oral premedication with antihistamines, *antipyretic medications*, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion/injection time may also be considered after assessing the benefit–risk ratio.

[g] Refer to Riegler et al. (2019).

PANCREATIC EVENTS

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 *the* Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact *the* 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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated 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 *the* Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact *the* 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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

DERMATOLOGIC EVENTS

The majority of cases of rash *reported with the use of atezolizumab* were mild in severity and self-limiting, 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. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
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 *the* Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]

Table 9 Management Guidelines for Dermatologic Events (cont.)

Event	Management
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) for evaluation, 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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

NEUROLOGIC DISORDERS

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 *, with specific guidelines for myelitis provided in* Table 11 .

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • *Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.*
Immune-mediated neuropathy, *including facial paresis,* Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patients to neurologist. • Initiate treatment as per institutional guidelines. • *For general immune-mediated neuropathy:* – 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 the Medical Monitor. [c] • *For facial paresis:* – *If event resolves fully, resume atezolizumab.* [b] – *If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated neuropathy, *including facial paresis,* Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • 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 ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 11 *Management Guidelines for Immune-Mediate Myelitis*

Event	*Management*
Immune-mediated myelitis, Grade 1	• *Continue atezolizumab unless symptoms worsen or do not improve.* • *Investigate etiology and refer patient to a neurologist.*
Immune-mediated myelitis, Grade 2	• *Permanently discontinue atezolizumab and contact the Medical Monitor.* • *Investigate etiology and refer patient to a neurologist.* • *Rule out infection.* • *Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.*
Immune-mediated myelitis, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact the Medical Monitor.* • *Refer patient to a neurologist.* • *Initiate treatment as per institutional guidelines.*

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated 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 *Table 12* .

Table 12 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • 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.

RENAL EVENTS

Eligible patients must have adequate renal function. 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 13* .

Table 13 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine and urine protein, 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 *the* Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • 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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED MYOSITIS

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 possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in *Table 14* .

Table 14 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 *the* 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 *the* Medical Monitor. [c]

Table 14 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset[a] and contact *the* 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 *the* Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. *Permanently discontinue atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact *the* 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 based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

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).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

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 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 $\leq 181 \times 10^9$/L (181,000/μL)
  - AST $\geq$ 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 15* .

Table 15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact *the* 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.

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Appendix 11
European Organisation for Research and Treatment of Cancer (EORTC) IL57 Questionnaire

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.

	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. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

9. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

10. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 12
Cancer Therapy Satisfaction Questionnaire (CTSQ)

SATISFACTION WITH CANCER THERAPY (SWT) SCALE
US English

Instructions:

- Your atezolizumab (Tecentriq) treatment was given either:
  - Through a thin plastic tube and a needle that was put directly into a vein in your arm, called an intravenous or IV infusion; or
  - Through a needle injected into your skin, called a subcutaneous or SC injection.

- Please complete the following questions based on your most recent Tecentriq treatment. Please only consider your experience with the treatment. Do not consider study procedures that were performed after you received your Tecentriq treatment at the clinic. For example, please do not consider blood samples or time spent at the clinic to obtain those samples
- Within this questionnaire, "Cancer therapy (IV/pills)" refers to your current or most recent Tecentriq therapy (IV infusion or SC injection).
- Please read each question and answer as honestly as you can without the help of anyone.
- There are no right or wrong answers; the answers should be based on your own personal experiences.
- This questionnaire will take about 5 minutes to complete.

Appendix 12: Cancer Therapy Satisfaction Questionnaire (CTSQ) Satisfaction with Cancer Therapy Scale

The following statements are about your satisfaction with your **most recent cancer therapy (IV/pills)**. Please answer each question below by *checking the box* that best describes your level of satisfaction (check only one box per question).

1. **Overall**, how worthwhile was your cancer therapy (IV/pills)?

5 ☐	4 ☐	3 ☐	2 ☐	1 ☐
Very worthwhile	Quite worthwhile	Moderately worthwhile	A little worthwhile	Not worthwhile at all

2. **Overall**, was taking cancer therapy (IV/pills) as difficult as you expected?

5 ☐	4 ☐	3 ☐	2 ☐	1 ☐
Much more difficult than I thought it would be	Somewhat more difficult than I thought it would be	As difficult than I thought it would be	Somewhat easier than I thought it would be	Much easier than I thought it would be

3. **Overall**, how well did the **benefits** of cancer therapy (IV/pills) meet your expectations?

5 ☐	4 ☐	3 ☐	2 ☐	1 ☐
Much better than my expectations	Somewhat better than my expectations	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations

4. **Overall**, were the **side effects** of cancer therapy (IV/pills) as you expected?

5 ☐	4 ☐	3 ☐	2 ☐	1 ☐
Much better than I expected	Somewhat better than I expected	Exactly as I expected	Somewhat worse than I expected	Much worse than I expected

5. How satisfied were you with the **form** of your cancer therapy (IV/pills)?

5 ☐	4 ☐	3 ☐	2 ☐	1 ☐
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

6. **Overall**, how satisfied were you with your most recent cancer therapy (IV/pills)?

5 ☐	4 ☐	3 ☐	2 ☐	1 ☐
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

7. Taking everything into consideration, if given the choice again, would you decide to take this cancer therapy treatment?

5 ☐	4 ☐	3 ☐	2 ☐	1 ☐
Yes, definitely	Probably Yes	I don't know	Probably not	Definitely not

Thank You for Your Help.

Appendix 13
Health Care Professional Subcutaneous Perspective Questionnaire

Protocol Number: BP40657
Site Number:

HCP Dummy Identifier *: HCP 00
Date of Assessment: __/__/__
DD/MMM/YYYY

Instructions:

**Please register your full name on the "HCP IDENTIFICATION LOG" at the site and assign yourself the lowest HCP number available (range is from HCP001 to HCP009). Write this HCP dummy identifier in the header above, and use the same number on any other HCP perspective questionnaire you might complete.*

Please complete the following questions after you have administered at least three doses of atezolizumab (Tecentriq®) as a subcutaneous (SC) injection across all patients in Part 2 of this study.

1. How many atezolizumab SC injections have you administered at the time of completion of this questionnaire?

   _____

2. Do you think atezolizumab SC is convenient?
   a. Yes
   b. Unsure
   c. No

3. Overall, how easy did you find atezolizumab SC administration?
   a. Very easy
   b. Fairly easy
   c. Not at all easy

4. *Overall*, how satisfied were you with atezolizumab SC?
   a. Very satisfied → Go to Question 5a
   b. Satisfied → Go to Question 5a
   c. Dissatisfied→ Go to Question 5b
   d. Very dissatisfied→ Go to Question 5b

5a. Select the top three reasons for your response in Question 4 ("very satisfied" or "satisfied")

- ☐ Convenience
- ☐ Ease of preparation
- ☐ Ease of administration
- ☐ No or minimal stress or anxiety for patient
- ☐ Positive perception or comfort of patient
- ☐ No or minimal pain or side effects for patient
- ☐ No problems with subcutaneous access
- ☐ None of the above

5b. Select the top three reasons for your response in Question 4 ("dissatisfied" or "very dissatisfied")

- ☐ Inconvenience
- ☐ Preparation was not easy
- ☐ Administration was not easy
- ☐ Stress or anxiety for patient
- ☐ Negative perception or comfort of patient
- ☐ Pain or side effects for patient
- ☐ Problems with subcutaneous access
- ☐ None of the above

Thank you for your help.

Appendix 14
Health Care Professional SC versus IV Perspective Questionnaire

Protocol Number: BP40657
Site Number:

HCP Dummy Identifier *: HCP 00
Date of Assessment: __/__/__
DD/MMM/YYYY

Instructions:

**Please register your full name on the "HCP IDENTIFICATION LOG" at the site and assign yourself the lowest HCP number available (range is from HCP001 to HCP009). Write this HCP dummy identifier in the header above, and use the same number on any other HCP perspective questionnaire you might complete.*

Please complete the following questions after you have administered at least three doses of atezolizumab (Tecentriq®) as an intravenous (IV) infusion and at least three doses of atezolizumab as a subcutaneous (SC) injection across all patients in Part 2 of this study.

1. How many atezolizumab administrations have you administered at the time of completion of the questionnaire?
    a. Number of atezolizumab IV infusions: _____
    b. Number of atezolizumab SC injections: _____

2. Which formulation of atezolizumab (SC or IV) do you think is more convenient for you?
    a. Atezolizumab SC is much more convenient.
    b. Atezolizumab SC is a little more convenient.
    c. Both formulations are equally convenient.
    d. Atezolizumab IV is a little more convenient.
    e. Atezolizumab IV is much more convenient.

3. If used in routine practice, do you think administering atezolizumab SC could save staff time compared to atezolizumab IV?
    a. Yes
    b. Unsure
    c. No

4. Overall, were you more satisfied with atezolizumab SC or atezolizumab IV?
    a. More satisfied with atezolizumab SC → Go to Question 5a
    b. Equally satisfied with both formulations
    c. More satisfied with atezolizumab IV → Go to Question 5b

5a. Select the top three reasons for your response in Question 4 ("more satisfied with atezolizumab SC")

- ☐ Time saving
- ☐ Ease of preparation
- ☐ Ease of administration
- ☐ Less stress or anxiety for patient
- ☐ Positive perception or comfort of patient
- ☐ Pain or side effects for patient (with IV)
- ☐ Problems with venous access (with IV)
- ☐ None of the above

5b. Select the top three reasons for your response in Question 4 ("more satisfied with atezolizumab IV")

- ☐ Time saving
- ☐ Ease of preparation
- ☐ Ease of administration
- ☐ Less stress or anxiety for patient
- ☐ Positive perception or comfort of patient
- ☐ Pain or side effects for patient (with SC)
- ☐ Problems with subcutaneous access (with SC)
- ☐ None of the above

Thank you for your help.

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