Official Title: A Randomized, Multicenter, Open-Label Cross-Over Study to Evaluate Participant and Healthcare Professional Reported Preference for Subcutaneous Atezolizumab Compared with Intravenous Atezolizumab Formulation in Participants with Non-Small Cell Lung Cancer

NCT Number: NCT05171777

Document Date: Protocol Version 4: 27-February-2024

PROTOCOL

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL CROSS-OVER STUDY TO EVALUATE PARTICIPANT AND HEALTHCARE PROFESSIONAL REPORTED PREFERENCE FOR SUBCUTANEOUS ATEZOLIZUMAB COMPARED WITH INTRAVENOUS ATEZOLIZUMAB FORMULATION IN PARTICIPANTS WITH NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	MO43576
STUDY NAME	IMscin002
VERSION NUMBER:	4
TEST PRODUCT:	Atezolizumab (RO5541267)
STUDY PHASE	Phase II
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: IND 140100 EudraCT Number: 2021-004067-28 EU Trial Number: Not applicable *PS* ID: Not applicable NCT Number: *NCT05171777*
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
4	See electronic signature and date stamp on the final page of this document.
3	7 March 2023
2	28 February 2022
1	16 August 2021

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol MO43576 has been amended to include updates following the Atezolizumab Investigator's Brochure, Version 20, release, and to clarify several aspects of the study. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The adverse event management guidelines have been streamlined by removing standard of care information and restructured, for consistency with regulatory guidelines and industry standards (Appendix 9).
- The adverse event management guidelines have been updated to align with the atezolizumab Investigator's Brochure, Version 20 (Appendix 9).
- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma (Section 1.4).
- The safety follow-up duration was clarified to include safety follow-up every 90 days until the end of the trial (Section 3.1.1 and Appendix 1).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- Text in Section 4.3.4 has been modified to align with updates to the Roche Global Policy on Continued Access to Investigational Medicinal Products.
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front matter and Section 5.4.1). Medical Monitor contact information in Section 5.4.1 has been replaced with a sentence indicating that this information will be provided separately to sites.

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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TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL CROSS-OVER STUDY TO EVALUATE PARTICIPANT AND HEALTHCARE PROFESSIONAL REPORTED PREFERENCE FOR SUBCUTANEOUS ATEZOLIZUMAB COMPARED WITH INTRAVENOUS ATEZOLIZUMAB FORMULATION IN PARTICIPANTS WITH NON–SMALL CELL LUNG CANCER**
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SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL CROSS-OVER STUDY TO EVALUATE PARTICIPANT AND HEALTHCARE PROFESSIONAL REPORTED PREFERENCE FOR SUBCUTANEOUS ATEZOLIZUMAB COMPARED WITH INTRAVENOUS ATEZOLIZUMAB FORMULATION IN PARTICIPANTS WITH NON–SMALL CELL LUNG CANCER**
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INDICATION:	Non–small cell lung cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate participant-reported preference for atezolizumab SC or atezolizumab IV in participants with non–small cell lung cancer (NSCLC). The study will also evaluate participant-reported satisfaction with atezolizumab SC and atezolizumab IV; Healthcare Professional (HCP)-reported perception of time/resource use and convenience of atezolizumab SC and atezolizumab IV; participant-reported health-related quality of life (HRQoL); as well as the safety of each study administration modality alone and after the transition from one modality to the other.

PRIMARY OBJECTIVE

The primary objective for this study is to evaluate participant preference for atezolizumab SC compared with atezolizumab IV on the basis of the following endpoint:

- Proportion of participants who preferred atezolizumab SC to atezolizumab IV, with treatment preference assessed using Question 1 of the Patient Preference Questionnaire (PPQ)

SECONDARY OBJECTIVES

Secondary objectives for this study are to:

- Evaluate participant-reported satisfaction with atezolizumab SC and atezolizumab IV assessed using Question 1 of the Therapy Administration Satisfaction Questionnaire – subcutaneous (TASQ-SC) and TASQ – intravenous (TASQ-IV)
- Evaluate participants' choice of atezolizumab SC for the Treatment Continuation Period based on the proportion of participants who select atezolizumab SC for this study period

- Evaluate HCP perception of time/resource use and convenience for administration with atezolizumab SC and IV based on HCP responses to the Healthcare Professional Questionnaires (HCPQs), by individual question
- Evaluate HRQoL with atezolizumab SC and atezolizumab IV based on change in symptoms and function from baseline and over time as assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) scores, and mean and mean changes from baseline score in HRQoL by cycle as assessed by the Global Health Status/Quality of Life (GHS/QoL) scale (items 29 and 30) of the EORTC QLQ-C30
- Monitor the ongoing clinical benefit of atezolizumab as measured by the percentage of participants with continuing clinical benefit after 16 cycles of atezolizumab, as assessed by the investigator according to local standard of care

SAFETY OBJECTIVES

There are two safety objectives for this study. The first is to evaluate the overall safety and tolerability of atezolizumab SC and atezolizumab IV based on the following endpoints:

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

The second safety objective for this study is to evaluate the safety of switching from atezolizumab SC to atezolizumab IV and from atezolizumab IV to atezolizumab SC based on:

- Incidence, severity, and nature of adverse events, with severity determined according to NCI CTCAE v5.0 during the study Treatment Cross-over Period by treatment arm

EXPLORATORY PHARMACOKINETIC AND IMMUNOGENICITY OBJECTIVES

The exploratory pharmacokinetic (PK) objective for this study is to characterize the exposure of atezolizumab when given intravenously or subcutaneously on the basis of the following endpoint:

- Serum atezolizumab concentration at specified timepoints during SC and IV administration

The exploratory immunogenicity objective for this study is to evaluate the immune response to atezolizumab on the basis of the following endpoints:

- Prevalence of anti-drug antibodies (ADAs) to atezolizumab at baseline (baseline prevalence) and incidence of ADAs to atezolizumab after initiation of study treatment (post-baseline incidence)
- Evaluation of safety and PK endpoints by atezolizumab ADA status

HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of participants treated with atezolizumab SC compared with atezolizumab IV on the basis of the following endpoint:

- Change from baseline over time in EuroQol EQ-5D-5L index-based and visual analogue scale (VAS) scores

STUDY DESIGN

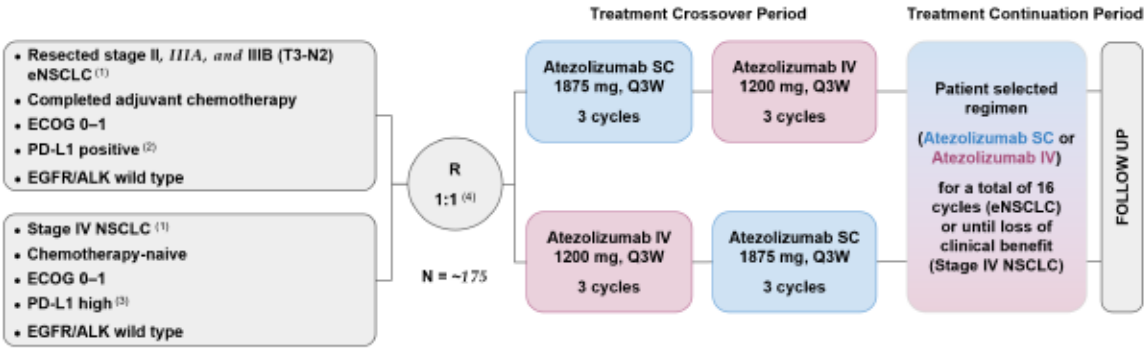
DESCRIPTION OF STUDY

OVERVIEW OF STUDY DESIGN

This is a Phase II, randomized, multi-center, multinational, open-label, cross-over study in adult participants with PD-L1-positive NSCLC. Two populations will be included: participants with resected Stage II, IIIA, and selected IIIB (early-stage) NSCLC who have completed adjuvant platinum-based chemotherapy without evidence of disease relapse/recurrence, and chemotherapy-naive participants with Stage IV NSCLC.

The study will evaluate participant- and HCP-reported preference for atezolizumab SC compared with atezolizumab IV. An overview of the study design is provided in Figure 1. The schedule of activities is provided in Appendix 1.

FIGURE 1 STUDY SCHEMA



eNSCLC = early non–small cell lung cancer; IV = intravenous; PD-L1 = programmed death-ligand 1; Q3W = every 3 weeks; R = randomization; SC = subcutaneous; TC = tumor cells; TPS = tumor proportion score.

(1) Histological or cytological diagnosis per UICC/AJCC staging system, 8th Ed.

(2) PD-L1 positive defined as minimum TC ≥1% by VENTANA PD-L1 (SP263) IHC assay or TPS ≥1% by Dako PD-L1 IHC 22C3 pharmDx assay performed by a local or central laboratory.

(3) PD-L1 high defined as minimum TC ≥50% by VENTANA PD-L1 (SP263) IHC assay, minimum TPS ≥50% by Dako PD-L1 IHC 22C3 pharmDx assay, or TC3 or IC3 by VENTANA PD-L1 (SP142) IHC assay, performed by a local or central laboratory.

(4) Stratification: disease stage and type of surgery.

Participants whose tumors have an EGFR mutation or ALK rearrangement will be excluded from enrolment. Participants with tumors of non-squamous histology with unknown EGFR or ALK mutational status will be required to be tested at prescreening/screening centrally if the local test cannot be done or does not meet the required criteria.

Eligibility will be assessed within a 28-day screening period. A pre-screening period will be available for those participants who need to assess their eligibility in terms of PD-L1 expression, EGFR mutation, or ALK rearrangement. Participants who do not meet the criteria for participation in this study (screen failure) may qualify for two re-screening opportunities (for a total of three screenings per participant) at the investigator's discretion, provided all initial and subsequent screening assessments are performed within 56 days prior to Day 1. Re-screened participants must meet all eligibility criteria and re-sign the Informed Consent Form prior to re-screening. The investigator will maintain a record of reasons for screen failure.

Participants must have PD-L1-positive or high NSCLC to be enrolled in the study. Participants that do not have prior PD-L1 testing will be prospectively tested for PD-L1 expression by central testing at prescreening/screening.

Participants will undergo a tumor assessment at baseline to confirm eligibility criteria. Subsequent tumor assessments will be conducted as per local standard of care.

PARTICIPANTS WITH EARLY-STAGE NSCLC

Eligible participants with early-stage NSCLC will have had a complete resection of NSCLC and must be adequately recovered from surgery and adjuvant chemotherapy. Prior to treatment with adjuvant atezolizumab, all participants should have received up to four cycles of adjuvant platinum-based chemotherapy, with no evidence of disease relapse/recurrence.

CHEMOTHERAPY-NAIVE PARTICIPANTS WITH STAGE IV NSCLC

Participants with Stage IV NSCLC will be eligible to join the study if they have not received prior chemotherapy for advanced NSCLC and satisfy the eligibility criteria.

STUDY TREATMENT PERIOD

During the study treatment period, participants will be randomly allocated in a 1:1 ratio to treatment Arm A (atezolizumab SC followed by atezolizumab IV) or treatment Arm B (atezolizumab IV followed by atezolizumab SC). Participants will be stratified according to disease stage (II, III, or IV) and type of surgery (no surgery, pneumonectomy, and any other lung surgery).

Atezolizumab will be administered on Day 1 of each 21-day cycle. Participants will receive atezolizumab according to their assigned route of administration (i.e., SC or IV) for the first three treatment cycles. At Cycle 4, participants will cross-over and receive atezolizumab administered according to the alternative route of administration for Cycles 4–6. This period of 3+3 cycles in both treatment arms constitutes the study Treatment Cross-over Period.

After Cycle 6, participants will select how they would like atezolizumab to be administered (SC or IV) for the Treatment Continuation Period. The Treatment Continuation Period will continue until Cycle 16 for participants with early-stage NSCLC or until loss of clinical benefit, as determined by the investigator according to local standard of care, for patients with advanced NSCLC.

Participants will undergo an End of Treatment Visit within 30 days after completing study treatment and will enter *the* safety follow-up *period. Safety follow-up should occur approximately 90 days after the last dose of study treatment. Thereafter, participants will be contacted for survival status and to collect details of new anti-cancer therapy, if any.*

Participant preference will be assessed based on the PPQ (administered following treatment administration on Day 1, Cycle 6 of the Treatment Cross-over Period). Treatment satisfaction will be assessed based on the TASQ (administered following treatment administration on Day 1 of Cycles 3 and 6 of the Treatment Cross-over Period). Healthcare professionals will record their perception of time/resource use and convenience of treatment administration completing the HCPQs. Perception of time/resource use will be captured during the Treatment Cross-over Period and perception of convenience will be captured after administration of each participant's treatment Cycle 6. Health-related quality of life will be assessed using the EORTC QLQ-C30 completed during the Treatment Cross-over Period (at Cycle 1, Cycle 3, and Cycle 6), during the Treatment Continuation Period (at Cycle 7, Cycle 10, Cycle 13, and Cycle 16), and at the end of study treatment visit. Health utilities will be collected using the EQ-5D-5L questionnaire at the same time points as the EORTC QLQ-C30.

Participants will be assessed for safety by regular evaluation of adverse events, vital signs, and routine clinical laboratory tests (hematology, blood chemistry), and by physical examinations. Adverse events will be graded according to the NCI CTCAE v5.0.

Up to one-third of the study population will comprise chemotherapy-naïve participants with Stage IV NSCLC; this proportion may be increased if sufficient participants with early-stage NSCLC are not recruited. Participants who withdraw from the study following randomization will not be replaced, with the exception of patients who withdraw consent prior to receiving the first dose.

NUMBER OF PARTICIPANTS

Approximately 175 participants from approximately 40–50 study sites worldwide will be randomized in the study.

TARGET POPULATION

Inclusion Criteria

Participants must meet the following criteria for study entry:

All participants

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- ECOG performance status of 0 or 1

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, 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 postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  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 participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- Adequate hematologic and end-organ function, defined by the following laboratory 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)

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

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

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

    Participants with known Gilbert disease: total bilirubin ≤ 3 × ULN
  - Creatinine clearance ≥ 45 mL/min (calculated through use of the Cockcroft-Gault formula)
  - Albumin ≥ 25 g/L (≥ 2.5 g/dL)
  - For participants not receiving therapeutic anticoagulation: INR and aPTT ≤ 1.5 × ULN
- For participants receiving therapeutic anticoagulation: stable anticoagulant regimen
- Intact normal skin without potentially obscuring tattoos, pigmentation, or lesions in the area for intended injection
- Negative HIV test at screening, with the following exception: participants with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count ≥ 200/µL, and have an undetectable viral load
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Positive hepatitis B surface antibody (HBsAb) test at screening, or negative HBsAb at screening accompanied by either of the following:
  - Negative total hepatitis B core antibody (HBcAb)

- Positive total HBcAb test followed by a negative (per local laboratory definition) hepatitis B virus (HBV) DNA test

  The HBV DNA test must be performed for participants who have a negative HBsAg test, a negative HBsAb test, and 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 must be performed for participants who have a positive HCV antibody test.

- If a port for IV delivery is present, acceptance to receive atezolizumab IV, and any other IV medication which may be required, through a peripheral line

Participants with Early-stage NSCLC

- Participants must have a complete resection of a histologically or cytologically confirmed Stage II, IIIA, and selected IIIB (early-stage) NSCLC (per the UICC/AJCC staging system, 8th edition; Brierley et al. 2017)

  Accepted types of resection include any of the following: lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy.

  Resection by segmentectomy or wedge resection is not allowed.

  If mediastinoscopy was not performed preoperatively, it is expected that, at a minimum, mediastinal lymph node systematic sampling will have occurred. Systematic sampling is defined as removal of at least one representative lymph node at specified levels. For a right thoracotomy, sampling is required at levels 4 and 7 and for a left thoracotomy, levels 5 and/or 6 and 7. Levels 10 and 11 are required irrespective of tumor laterality. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is an accepted sampling method.

- PD-L1 expression TC ≥ 1% (VENTANA PD-L1 [SP263] IHC assay) or TPS ≥ 1% (Dako PD-L1 IHC 22C3 pharmDx assay), as documented through local or central testing of a representative tumor tissue specimen

  Participants may be enrolled based on local documentation of PD-L1 expression, if the criteria outlined below are met. If the participant does not have local documentation of PD-L1 expression or local documentation of PD-L1 expression does not meet the defined criteria, central PD-L1 testing is required as outlined below.

  Local PD-L1 testing: Documentation of known PD-L1 status, as determined by the VENTANA PD-L1 (SP263) IHC assay or the Dako PD-L1 IHC 22C3 pharmDx assay is required. The PD-L1 assay must be a Health Authority approved test (i.e., adhering to local drug/device regulations) and performed per manufacturer's recommendations and requirements.

  Central PD-L1 testing: When central testing is required, a formalin-fixed, paraffin-embedded (FFPE) tumor specimen (archival or fresh) in a paraffin block (preferred) or at least 5 serial slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment.

- Participants must have completed adjuvant chemotherapy at least 4 weeks and up to 12 weeks prior to randomization and must be adequately recovered from chemotherapy. For patients in the adjuvant setting, neoadjuvant chemotherapy or chemoradiotherapy is acceptable provided that patients also received adjuvant chemotherapy as per protocol's requirement.

Participants with Stage IV NSCLC

- Histologically or cytologically confirmed, Stage IV non-squamous or squamous NSCLC (per the UICC/AJCC staging system, 8th edition; Brierley et al. 2017)

  Participants with tumors of mixed histology must be classified as non-squamous or squamous based on the major histological component.

- Life expectancy ≥ 18 weeks in the opinion of the investigator

- PD-L1 expression TC ≥50% (VENTANA PD-L1 (SP263) IHC assay) or TPS ≥50% (Dako PD-L1 IHC 22C3 pharmDx assay), or TC3 or IC3 (VENTANA PD-L1 (SP142) IHC assay), as documented through local or central testing of a representative tumor tissue specimen.

  Participants may be enrolled based on local documentation of PD-L1 expression, if the criteria outlined below are met. If the participant does not have local documentation of PD-L1 expression or local documentation of PD-L1 expression does not meet the defined criteria, central PD-L1 testing is required as outlined below.

  Local PD-L1 testing: Documentation of known PD-L1 status as determined by the VENTANA PD-L1 (SP263) IHC assay, Dako PD-L1 IHC 22C3 pharmDx assay or VENTANA PD-L1 (SP142) IHC assay is required. The PD-L1 assay must be a Health Authority approved test (i.e., adhering to local drug/device regulations) and performed per manufacturer's recommendations and requirements.

  Central PD-L1 testing: When central testing is required, a formalin-fixed, paraffin-embedded (FFPE) tumor specimen (archival or fresh) in a paraffin block (preferred) or at least 5 serial slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment.
- No prior systemic treatment for Stage IV non-squamous or squamous NSCLC
- Participants who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy, radiotherapy, or chemoradiotherapy cycle.

Exclusion Criteria

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

All participants

- History of malignancy within 5 years prior to initiation of study treatment, with the exception of the cancer under investigation in this study and malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Uncontrolled tumor-related pain

  Participants 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. Participants should be recovered from the effects of radiation. There is no required minimum recovery period.

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

  Participants with indwelling catheters (e.g., PleurX®) are allowed.
- Participants known to have a sensitizing mutation in the EGFR gene or an ALK fusion oncogene

  Participants with unknown EGFR or ALK mutational status who may harbor a sensitizing EGFR mutation (i.e., participants with non-squamous histology (including those with a mixed histology that includes any non-squamous component), and without any other known driver mutation) will be required to be tested at prescreening/screening. Participants with tumors of squamous histology who have an unknown EGFR or ALK mutational status will not be required to be tested at prescreening/screening.

EGFR and/or ALK may be assessed locally or at a central laboratory. EGFR status assessed locally must be performed on tissue using a test that detects mutations in exons 18–21. The assays must be a Health Authority approved test (i.e., adhering to local drug/device regulations) and performed per manufacturer's recommendations and requirements. If the assay does not meet the criteria above, EGFR and/or ALK must be assessed centrally. If samples are submitted for central EGFR and/or ALK testing, additional slides must be provided (see laboratory manual) along with an associated pathology report prior to study enrollment.

- History of leptomeningeal disease
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected calcium greater than ULN)
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, anti-phospholipid antibody syndrome, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

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

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

  Participants with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., participants 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 has been no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Active tuberculosis
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- 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 could impact participant safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Participants receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease (COPD) exacerbation) are eligible for the study.
- Prior allogeneic stem cell or solid organ transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the participant at high risk from treatment complications

- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Current treatment with anti-viral therapy for HBV
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–PD-1 and anti–PD-L1 therapeutic antibodies

  Participants 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 randomization
  - No history of severe immune-mediated adverse effects from anti–CTLA-4 (NCI CTCAE Grades 3 and 4)
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5 drug-elimination half-lives (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-tumor necrosis factor-α [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  - Participants who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.
  - Participants who received mineralocorticoids (e.g., fludrocortisone), inhaled or low-dose corticosteroids for COPD or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or 5 months after the final dose of study treatment

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Known allergy or hypersensitivity to hyaluronidase, bee or vespid venom, or any other ingredient in the formulation of rHuPH20
- 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)
- 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 ≥ 2 weeks prior to randomization

Participants with Stage IV NSCLC

- Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases

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

  - The participant has no history of intracranial hemorrhage or spinal cord hemorrhage.

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

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

END OF STUDY

The end of the study is defined the Last Participant, Last Visit (LPLV) which is estimated to occur one year after the last participant is randomized or the date at which the last data point required for the final statistical analysis or safety follow-up is received from the last participant, whichever occurs later.

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

LENGTH OF STUDY

The study is estimated to last approximately 2 years.

INVESTIGATIONAL MEDICINAL PRODUCTS

TEST PRODUCT (INVESTIGATIONAL DRUG)

The investigational medicinal products (IMPs) for this study are atezolizumab SC and atezolizumab IV. IMPs will be supplied by the Sponsor. Atezolizumab (1875 mg) SC and atezolizumab (1200 mg) IV will be administered by a health care professional in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Atezolizumab SC injections will be administered subcutaneously in the anterior thigh region.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary objective of this study is to evaluate participant preference for atezolizumab SC based on the proportion of participants indicating an overall preference for atezolizumab SC compared with atezolizumab IV in Question 1 of the PPQ. Question 1 of the PPQ is as follows: "All things considered, which route of administration did you prefer?".

A point estimate with associated 95% CI for the proportion of participants who preferred atezolizumab SC will be calculated.

The primary study analysis will take place when all study participants have completed their last study treatment administration in the Treatment Cross-over Period. Summaries of secondary study endpoints, including PK and ADA measurements, participant-reported TASQ and EORTC QLQ-C30 responses, selection of treatment administration method for the Treatment Continuation Period, HCP reported HCPQ responses, and safety endpoints, up to Day 1, Cycle 7 will be included in the primary analysis. The final study analysis that includes all secondary endpoints including all questionnaires, PK, ADA, and safety endpoints will be conducted after the end of the study (i.e., when all patients have received 16 cycles of atezolizumab or discontinued study treatment).

DETERMINATION OF SAMPLE SIZE

The primary study objective is to estimate the proportion of participants who express a preference for atezolizumab SC compared with atezolizumab IV.

The planned total sample size of 175 participants is based on an assumed rate of 70% of participants preferring atezolizumab SC compared with atezolizumab IV. To achieve a distance of approximately ± 8% from the estimated proportion to 95% CI limits, a total of 126 participants are needed for the evaluation of preference. The final target sample size was increased to approximately 175 participants to allow for 28% of the participants not providing an evaluable preference assessment.

INTERIM ANALYSES

None.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
1L	first-line
ADA	anti-drug antibody
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
AUC	area under the concentration time curve
BID	twice a day
BSC	best supportive care
BUN	blood urea nitrogen
CCOD	clinical cut-off date
CI	confidence interval
CIV ID	Clinical Investigation Identification Number
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRO	contract research organization
CRS	cytokine-release syndrome
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DFS	disease-free survival
DOR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society of Medical Oncology
FDA	Food and Drug Administration

Abbreviation	Definition
FFPE	formalin-fixed, paraffin-embedded
GFR	glomerular filtration rate
GHS/QoL	Global Health Status/Quality of Life
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV/HCV	hepatitis B/C virus
HCP	healthcare professionals
HCPQ	Healthcare Professional Questionnaires
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	health-related quality of life
HUS	hemolytic-uremic syndrome
IC	tumor-infiltrating immune cell
ICH	International Council for Harmonisation
IL	interleukin
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous
IxRS	interactive voice or web-based response system
LDH	lactate dehydrogenase
LFT	liver function test
LPLV	last participant, last visit
MAS	macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non–small cell lung cancer
ORR	objective response rate

Abbreviation	Definition
OS	overall survival
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic
popPK	population PK
PO	by mouth
PPQ	Patient Preference Questionnaire
PRO	participant-reported outcome
Q3W	every 3 weeks
QLQ-C30	Quality of Life Questionnaire C30
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
rHuPH20	recombinant human hyaluronidase enzyme
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SITC	Society for Immunotherapy for Cancer
TASQ-SC	Therapy Administration Satisfaction Questionnaire – subcutaneous
TASQ-IV	Therapy Administration Satisfaction Questionnaire – intravenous
TC	tumor cell
TNF-α	tumor necrosis factor–α
TPS	tumor proportion score
UICC/AJCC	International Union Against Cancer / American Joint Committee on Cancer
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cell

1. BACKGROUND

1.1 BACKGROUND ON NON–SMALL CELL LUNG CANCER

Lung cancer remains the leading cause of cancer deaths worldwide with an estimated 1.8 million deaths and 2.2 million new cases in 2020 (Sung et al. 2012). Lung cancer is the most commonly diagnosed cancer in men and third most common cancer in women, after breast and colorectal. Overall, lung cancer accounts for approximately one in 10 (11.4%) cancers diagnosed and one in 5 (18.0%) deaths (Sung et al. 2012).

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.

In its early stages, NSCLC is treated surgically with curative intent (Duma et al. 2019; Postmus et al. 2017; NCCN 2021). Lobectomy is generally accepted as the optimal procedure. Nonsurgical patients should be considered for conventional or stereotactic radiotherapy (Duma et al. 2019). However, many patients with resected early-stage NSCLC are at risk of lung cancer recurrence, even after complete resection, suggesting that a proportion of these patients have micrometastatic disease at the time of surgical resection. The 5-year survival rate in resected NSCLC patients is over 70% in Stage I patients but only 25% in Stage IIIA patients (Nagasaka and Gadgeel 2018).

More than half of the patients with NSCLC are diagnosed with distant disease, which directly contributes to poor survival prospects. The overall 5-year survival rate for advanced disease is 2%–4%, depending on geographic location (Cetin et al. 2011). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status, and a history of unintentional weight loss. Treatment of advanced disease involves chemotherapy, targeted therapy, and immunotherapy. Patients with activating mutations in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and other oncogenes can be treated with targeted therapies that can lead to durable responses (Giustini et al. 2020). Patients without such mutations are typically treated with platinum-based chemotherapy or cancer immunotherapy (see Section 1.3).

1.2 ADJUVANT TREATMENT OPTIONS FOR PATIENTS WITH SURGICALLY RESECTED NSCLC

Adjuvant platinum-based chemotherapy is the standard of care for fully resected NSCLC; however, the benefits of adjuvant chemotherapy remain modest. The rationale for adjuvant chemotherapy for patients with early-stage lung cancer is based on the

observations that distant metastases are the most common site of failure after potentially curative surgery (Duma et al. 2019; Postmus et al. 2017; NCCN 2021).

The Lung Adjuvant Cisplatin Evaluation (LACE) reported on the results of a pooled analysis of data from several large studies of cisplatin-based adjuvant chemotherapy in patients with NSCLC. The pooled analysis of these data was used to identify treatment options associated with a higher degree of benefit or groups of patients benefiting more from adjuvant treatment (Pignon et al. 2008). With a median follow-up time of 5.2 years, the overall hazard ratio (HR) of death was 0.89 (95% confidence interval [CI]: 0.82, 0.96; p=0.005), corresponding to a 5-year absolute benefit of 5.4% from adjuvant chemotherapy. Further analysis revealed no heterogeneity of chemotherapy effect among studies. The benefit varied with stage, with the strongest effect seen in Stages II and III and a potential deleterious effect in Stage IA.

Of note, the effect of chemotherapy did not vary significantly (test for interaction, p=0.11) with the associated drugs, including vinorelbine (HR=0.80; 95% CI: 0.70, 0.91), etoposide or vinca alkaloid (HR=0.92; 95% CI: 0.80, 1.07), or other treatment (HR=0.97; 95% CI: 0.84, 1.13). In addition, there was no correlation between chemotherapy effect and sex, age, histology, type of surgery, planned radiotherapy, or planned total dose of cisplatin.

A more recent Cochrane meta-analysis also demonstrated the benefit of adjuvant chemotherapy in early-stage NSCLC (Burdett et al. 2015). Among 8447 participants from 26 trials who were treated surgically without radiation, there was clear evidence of a benefit of adding chemotherapy after surgery with a HR of 0.86 (95% CI: 0.81, 0.92, $p < 0.0001$), with an absolute increase in survival of 4% at 5 years.

Molecularly targeted therapies are effective treatments for a proportion of patients with advanced NSCLC with tumors that express targetable mutations in proteins such as EGFR and ALK.

To date, the anti-EGFR agents have shown improvements over standard care for patients with resected early-stage NSCLC in terms of disease-free survival (DFS) (Pennell et al. 2019; Kelly et al. 2015; Zhong et al. 2018; Wu et al. 2020). Regarding ALK inhibitors, trials are ongoing, with initial results pointing to a clinical benefit (Tamura et al. 2017; Tabbo and Novello. 2019).

More recently, atezolizumab has been demonstrated to be efficacious in the adjuvant setting (Felip et al. 2021), which has led to its approval as adjuvant treatment (see Section 1.4.2 below).

1.3 FIRST-LINE TREATMENT FOR LOCALLY ADVANCED AND METASTATIC NON–SMALL CELL LUNG CANCER

Patients with previously untreated advanced NSCLC that does not harbor an activating EGFR mutation or ALK gene rearrangement have been typically treated with platinum-based chemotherapy. The standard-of-care chemotherapy in the first-line (1L) setting (Saini and Twelves 2021) 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 appears to have reached a plateau in objective response rate (ORR; approximately 15%–22%) and median survival (7–10 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 OS from 10–12 months.

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, several Phase III trials have been conducted to investigate chemotherapy-free regimens involving programmed death-ligand 1 (PD-L1) / programmed cell death protein 1(PD-1) inhibitors versus standard cytotoxic chemotherapy in treatment-naive patients with PD-L1–positive NSCLC without an activating EGFR mutation or ALK gene rearrangement. 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% assessed using the PD-L1 immunohistochemistry [IHC] 22C3 pharmDx assay), with OS HR = 0.63 (95% CI: 0.44, 0.91), p = 0.002, median OS 30.0 versus 14.2 months; and progression-free survival (PFS) HR = 0.50, p < 0.001, median PFS 10.3 versus 6.0 months (Reck et al. 2016, 2019). In the KEYNOTE-042 study in which participants with a TPS ≥ 1% (determined using the PD-L1 IHC 22C3 pharmDx assay) were enrolled, survival outcomes of pembrolizumab compared with chemotherapy doublets in the two primary participant populations with a TPS ≥ 50% and a TPS ≥ 1% were OS HR = 0.69, p = 0.0003, median OS: 20.0 versus 12.2 months, and OS HR=0.81, p = 0.0018, median OS: 16.7 versus 12.1 months, respectively. However, participants in a prespecified exploratory subgroup with TPS 1%–49% appeared to have similar OS in the two arms: HR = 0.92, median OS 13.4 versus 12.1 months; 95% CI: 0.77 to 1.11 months (Mok et al. 2019). Based on results from these studies, pembrolizumab is approved for the 1L treatment of patients with metastatic NSCLC without an activating EGFR mutation or ALK gene rearrangement, whose tumors express PD-L1 (TPS ≥ 1%) in the United States and in patients whose tumors express high PD-L1 (TPS ≥ 50%) in the European Union.

Targeted therapies, such as those targeting EGFR and ALK mutations, are approved and recommended as 1L treatment for patients with metastatic NSCLC (Yuan et al. 2019). Improvements in DFS over standard of care have been demonstrated for both anti-EGFR agents and ALK inhibitors as 1L treatment in patients with mutation-positive advanced NSCLC (Douillard et al. 2014; Soria et al. 2018; Markóczy et al. 2018; Solomon et al. 2014; Mok et al. 2020; Soria et al. 2017).

Recently, atezolizumab monotherapy has also demonstrated a statistically significant and clinically meaningful improvement in OS compared with platinum-based doublet chemotherapy as 1L treatment of metastatic NSCLC that expresses high PD-L1 in Study GO29431 (IMpower110) (see Section 1.4.3).

Overall, chemotherapy-free options with 1L immunotherapy offers patients with advanced NSCLC expressing PD-L1 significant survival benefits as well as a more tolerable toxicity profile. Despite improvements and benefits with PD-L1/PD-1–targeting agents, nearly all patients experience disease progression. Consequently, new molecules and combinations, including novel immunotherapy combinations, are needed to address this unmet medical need.

1.4 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; Schmid et al. 2018). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

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

Atezolizumab IV is approved for the treatment of urothelial carcinoma, NSCLC, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, melanoma*, and alveolar soft part sarcoma*.

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

1.4.1 Nonclinical Studies with Subcutaneously Injected Atezolizumab

The nonclinical safety of subcutaneously (SC) 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.

1.4.2 Study GO29527 (IMpower010)

Study GO29527 (IMpower010) is a Phase III, global, multicenter, open-label, randomized study comparing the efficacy and safety of intravenously (IV) administered atezolizumab versus best supportive care (BSC) in patients with Stage IB–Stage IIIA NSCLC following resection and adjuvant chemotherapy. The primary endpoint is DFS; secondary endpoints include OS and safety.

At the clinical cut-off date (CCOD) of 21 January 2021, 1,269 participants had received up to four 21-day cycles of cisplatin-based chemotherapy (plus pemetrexed, docetaxel, gemcitabine or vinorelbine) (Wakelee et al. 2021). Of these, 1,005 participants were subsequently randomized 1:1 to 16 cycles of atezolizumab 1200 mg IV every 3 weeks (Q3W; n=507) or BSC (n=498). Median follow-up at CCOD was 32.2 months in the intent-to-treat (ITT) population. Baseline characteristics were generally balanced between arms. Atezolizumab treatment significantly improved DFS compared with BSC in overall Stage II-IIIA population (n=882); this effect was even more pronounced in the population (n=476) of participants with Stage II-IIIA cancer who were PD-L1 positive (defined as ≥ 1% of tumor cells [TC] staining positive with the VENTANA PD-L1 [SP263] Assay). Median DFS in participants with PD-L1 TC ≥ 1% Stage II–IIIA NSCLC was not reached with atezolizumab versus 35.3 months with best supportive care (stratified HR 0.66; 95% CI: 0.50, 0.88; two-sided p-value=0.0039). Overall survival data were immature at CCOD and not formally tested. The safety profile of atezolizumab was consistent with prior experience of atezolizumab monotherapy. These data have led to the approval of atezolizumab as adjuvant treatment by the FDA for adult patients with NSCLC whose tumors have PD-L1 expression of ≥1% on tumor cells (TECENTRIQ® U.S. Package Insert) and EMA for those whose tumors have PD-L1 expression of ≥50% on tumor cells (Tecentriq® Summary of Product Characteristics [SmPC]).

1.4.3 Study GO29431 (IMpower110)

Study GO29431 (IMpower110) is a Phase III, randomized, open-label study evaluating the efficacy and safety of atezolizumab monotherapy compared with platinum-based chemotherapy in PD-L1-positive, chemotherapy-naive participants with Stage IV non-squamous or squamous NSCLC. The study enrolled 572 people, of whom 554 were in the ITT wild-type population, which excluded people with EGFR or ALK genomic tumor

aberrations. PD-L1 positivity was defined as ≥ 1% PD-L1 expressing tumor cells or ≥ 1% of tumor area occupied by PD-L1 expressing immune cells.

Participants were randomized 1:1 to receive atezolizumab monotherapy until disease progression/loss of clinical benefit, unacceptable toxicity, or death, or cisplatin or carboplatin plus pemetrexed (non-squamous) or gemcitabine (squamous) followed by maintenance therapy with pemetrexed alone (non-squamous) or best supportive care (squamous) until disease progression, unacceptable toxicity, or death. The primary endpoint was OS according to PD-L1 expression level; key secondary endpoints included investigator-assessed PFS, ORR, and duration of response (DoR).

At the CCOD of 10 September 2018, median OS was 7.1 months longer with atezolizumab (20.2 months vs. 13.1 months with chemotherapy; HR for death, 0.59; p=0.01) in the subset of participants (n=205) with wild-type tumors who had the highest expression of PD-L1 (TC3/IC3; i.e., PD-L1 stained ≥ 50% of tumor cells or PD-L1 infiltrate covering ≥ 10% of tumor area; VENTANA PD-L1 (SP142) Assay; Herbst et al. 2020). This improvement in OS with atezolizumab was observed in the majority of clinically relevant subgroups, including non-squamous and squamous histology.

Of note, participant subgroups defined as PD-L1–high by all three IHC assays (SP142, 22C3, SP263) had similar survival benefit with atezolizumab (Herbst et al. 2020). Of the 554 participants with wild-type tumors who had any PD-L1 expression, 534 could be evaluated by the 22C3 PD-L1 assay and 546 by the SP263 PD-L1 assay. Participants with a TPS of ≥ 50% with the 22C3 assay had an OS of 20.2 months in the atezolizumab group and 11.0 months in the chemotherapy group (unstratified HR for death, 0.60; 95% CI: 0.42, 0.86), and participants with PD-L1 expression on ≥ 50% of tumor cells with the SP263 assay had values of 19.5 months and 16.1 months, respectively (unstratified HR for death, 0.71; 95% CI: 0.50, 1.00).

Adverse events were reported in 90.2% of the participants in the atezolizumab group (30.1% had Grade 3/4 events) and in 94.7% of those in the chemotherapy group (52.5% had Grade 3/4 events). These data led to the approval in the U.S., Europe, and elsewhere for atezolizumab as 1L treatment for adults with metastatic NSCLC whose tumors have high PD-L1 expression, with no EGFR or ALK genomic tumor aberrations.

1.4.4 Study BP40657 (IMscin001)

Study BP40657 (IMscin001) is an ongoing Phase Ib/III multicenter study to investigate the pharmacokinetics, efficacy, and safety of SC administered atezolizumab compared with IV atezolizumab in participants with previously treated locally advanced or metastatic NSCLC. All participants will be cancer immunotherapy–naive. Part 1 (dose-finding, Phase Ib) of the study aimed to determine an SC atezolizumab dose that yielded a serum trough concentration (C_{trough}) comparable with IV dosing (Felip et al. 2021). Participants were treated in three cohorts to evaluate two doses (1200 mg and 1800 mg), three administration frequencies (once, every 2 weeks, or every 3 weeks),

and two injection sites (thigh or abdomen). Participants in cohort 1 received SC atezolizumab 1800 mg injected in the thigh for one cycle. In cohort 2, participants received SC atezolizumab 1200 mg injected in the thigh every 2 weeks for three cycles, and in cohort 3, SC atezolizumab 1800 mg was administered every 3 weeks for three cycles in the abdomen for the first dose and then in the thigh for the remaining two doses. Following the SC regimen, participants in all cohorts received IV atezolizumab 1200 mg every 3 weeks for each subsequent cycle until disease progression, loss of clinical benefit, unacceptable toxicity, or withdrawal of consent.

Sixty-seven participants were enrolled in Part 1: 13 participants in cohort 1, 15 in cohort 2, and 39 in cohort 3 (Felip et al. 2021). SC atezolizumab 1800 mg every 3 weeks and 1200 mg every 2 weeks provided similar C_{trough} and area under the curve (AUC) values in Cycle 1 to the corresponding IV atezolizumab reference. C_{trough} values were 121 µg/mL in cohort 1 (1800 mg SC every 3 weeks, thigh), 83.2 µg/mL in cohort 2 (1200 mg SC every 2 weeks, thigh), and 97.3 µg/mL in cohort 3 (1800 mg SC every 3 weeks, abdomen). Exposure following SC injection in the abdomen was lower (20%, 28%, and 27% for C_{trough}, maximum concentration, and area under the concentration-time curve from time 0 to day 21, respectively) than in the thigh.

Atezolizumab SC was well tolerated, and the safety profile was consistent with the known risks of atezolizumab IV. Injection-site reactions were low grade and well tolerated. Seven of 11 participants experienced an injection site reaction in Cycle 1; six were Grade 1 and one was Grade 2 which resolved without sequelae.

Based on these results, a SC dose/regimen of 1875 mg q3w was selected for evaluation in Part 2 of the study (Dose confirming, Phase III, randomized). Part 2 will aim to confirm that this SC dose yields drug exposure that is comparable to that of IV atezolizumab.

In IMscin001 Part 2 (randomized Phase III of the study), adults with previously treated locally advanced/metastatic NSCLC (no prior cancer immunotherapy) and ECOG PS 0 or 1 were randomized 2:1 to receive 2L atezolizumab SC (1875 mg) or IV (1200 mg) every 3 weeks. Primary endpoints were non-inferiority for Cycle 1 observed serum C_{trough} and model-predicted $AUC_{0–21}$ days; secondary endpoints were steady-state pharmacokinetics, safety, efficacy (PFS, ORR), patient-reported outcomes and immunogenicity.

There were 247 and 124 patients in the atezolizumab SC and IV arms, respectively (median follow-up: 4.6 months; data cut-off: 26 April 2022). Median age was 64.0 years (range: 27–85), 69% were male and 74% had ECOG PS 1. The lower bounds of the 90% CI of the geometric mean ratios (GMRs) for C_{trough} (GMR 1.05 [90% CI: 0.88, 1.24]) and AUC (GMR 0.87 [90% CI: 0.83, 0.92]) were above the predefined non-inferiority margin of 0.8. Efficacy, immunogenicity, and safety were similar between arms (Burotto et al. 2022).

Atezolizumab SC demonstrated non-inferior exposure versus IV for both co-primary pharmacokinetic (PK) endpoints. Efficacy and safety were similar between arms and consistent with the known atezolizumab IV profile. Atezolizumab immunogenicity was comparable between arms and within the historical range for atezolizumab IV across indications. These results were submitted to the FDA and EMA for approval in all current or future indications of atezolizumab IV.

1.5 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® recombinant) 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 depolymerizes 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. The hyaluronan in the SC space is restored within 24–48 hours. rHuPH20, a recombinant human molecule, has a higher purity and is associated with improved tolerability compared with the animal-derived enzyme (Hylenex recombinant 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. This is not a safety concern for the human recombinant rHuPH20. 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. 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 (PHESGO™ U.S. Package Insert; DARZALEX® U.S. Package Insert; HERCEPTIN HYLECTA™ U.S. Package Insert; RITUXAN HYCELA™ U.S. Package Insert) and four in the European Union (Darzalex® SmPC; Herceptin® SmPC; MabThera® SmPC; HyQvia® SmPC).

1.6 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 SC 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 in under 10 minutes.

Results as of the CCOD of 10 March 2020 from Part 1 of Study BP40657 (IMscin001), with safety of Cycle 1 where all 67 participants received atezolizumab SC administration, demonstrated that although the percentage of participants with adverse events were 69.2% (9 of 13 participants) in Cohort 1, 53.3% (8 of15 participants) in Cohort 2, and 61.5% (24 of 39 participants) 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. All injection site reactions

were mild in nature (Grade 1 except for an AE with Grade 2 in Cohort 3 [PT: injection site reaction]), and none of the events led to treatment interruptions or discontinuations. The Phase III results (247 patients in the atezolizumab SC arm) confirmed the mild and transient nature of the injection site reactions and yielded a safety profile similar to that of atezolizumab IV (Burotto et al. 2022).

The development of an SC formulation of atezolizumab provides an opportunity to reduce the burden associated with treatment for NSCLC. By formally assessing, from the participants' perspective, whether SC administration of atezolizumab is preferable to IV administration, this study will provide participant experience data to supplement the results of Study BP40657 (IMscin001) that is comparing the pharmacokinetics, efficacy, and safety of these regimens. This study will also document healthcare professionals (HCP) reported perceptions of resource use with atezolizumab SC administration to evaluate the impact of SC delivery on clinical resources. Study safety analyses will further characterize the safety profiles of SC administration of atezolizumab as well as the safety of switching from atezolizumab IV to atezolizumab SC and vice versa.

The risks for participants entering this study is expected to be low. Atezolizumab is an approved treatment for patients with advanced NSCLC whose tumors have high PD-L1 expression. The efficacy and safety data from Study GO29527 (IMpower010) indicate that atezolizumab is also an effective treatment in patients with resected early-stage NSCLC who have received prior adjuvant chemotherapy (see Section 1.4.2).

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-γ (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 COVID-19 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 COVID-19 vaccination (Society for Immunotherapy for Cancer [SITC] 2020).

Per recommendations of the National Cancer Comprehensive Network® (NCCN®) COVID-19 Vaccination Advisory Committee, COVID-19 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 COVID-19 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 COVID-19 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.

Society for Immunotherapy for Cancer and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 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 participant-reported preference for atezolizumab SC or atezolizumab IV in participants with NSCLC. The study will also evaluate participant-reported satisfaction with atezolizumab SC and atezolizumab IV; HCP-reported perception of time/resource use and convenience of atezolizumab SC and atezolizumab IV; participant-reported health-related quality of life (HRQoL); as well as the safety of each study administration modality alone and after the transition from one modality to the other.

2.1 PRIMARY OBJECTIVE

The primary objective for this study is to evaluate participant preference for atezolizumab SC compared with atezolizumab IV on the basis of the following endpoint:

- Proportion of participants who preferred atezolizumab SC to atezolizumab IV, with treatment preference assessed using Question 1 of the Patient Preference Questionnaire (PPQ)

2.2 SECONDARY OBJECTIVES

Secondary objectives for this study are to:

- Evaluate participant-reported satisfaction with atezolizumab SC and atezolizumab IV assessed using Question 1 of the Therapy Administration Satisfaction Questionnaire – subcutaneous (TASQ-SC) and TASQ – intravenous (TASQ-IV)
- Evaluate participants' choice of atezolizumab SC for the Treatment Continuation Period based on the proportion of participants who select atezolizumab SC for this study period
- Evaluate HCP perception of time/resource use and convenience for administration with atezolizumab SC and IV based on HCP responses to the Healthcare Professional Questionnaires (HCPQs), by individual question
- Evaluate HRQoL with atezolizumab SC and atezolizumab IV based on change in symptoms and function from baseline and over time as assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) scores, and mean and mean changes from baseline score in HRQoL by cycle as assessed by the Global Health Status/Quality of Life (GHS/QoL) scale (items 29 and 30) of the EORTC QLQ-C30
- Monitor the ongoing clinical benefit of atezolizumab as measured by the percentage of participants with continuing clinical benefit after 16 cycles of atezolizumab, as assessed by the investigator according to local standard of care

2.3 SAFETY OBJECTIVES

There are two safety objectives for this study. The first is to evaluate the overall safety and tolerability of atezolizumab SC and atezolizumab IV based on the following endpoints:

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

The second safety objective for this study is to evaluate the safety of switching from atezolizumab SC to atezolizumab IV and from atezolizumab IV to atezolizumab SC based on:

- Incidence, severity, and nature of adverse events, with severity determined according to NCI CTCAE v5.0 during the study Treatment Cross-over Period by treatment arm

2.4 EXPLORATORY PHARMACOKINETIC AND IMMUNOGENICITY OBJECTIVES

The exploratory PK objective for this study is to characterize the exposure of atezolizumab when given intravenously or subcutaneously on the basis of the following endpoint:

- Serum atezolizumab concentration at specified timepoints during SC and IV administration

The exploratory immunogenicity objective for this study is to evaluate the immune response to atezolizumab on the basis of the following endpoints:

- Prevalence of anti-drug antibodies (ADAs) to atezolizumab at baseline (baseline prevalence) and incidence of ADAs to atezolizumab after initiation of study treatment (post-baseline incidence)
- Evaluation of safety and PK endpoints by atezolizumab ADA status

2.5 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of participants treated with atezolizumab SC compared with atezolizumab IV on the basis of the following endpoint:

- Change from baseline over time in EuroQol EQ-5D-5L index-based and visual analogue scale (VAS) scores

3. STUDY DESIGN

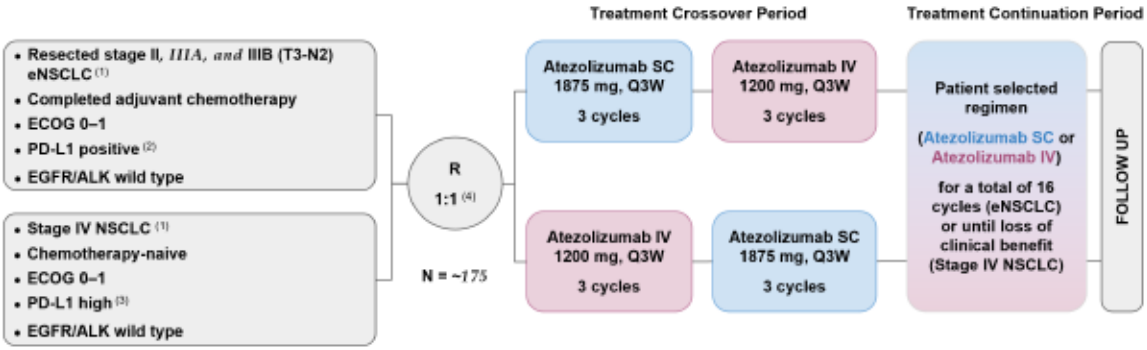
3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase II, randomized, multi-center, multinational, open-label, cross-over study in adult participants with PD-L1-positive NSCLC. Two populations will be included: participants with resected Stage II, IIIA, and selected IIIB (early-stage) NSCLC who have completed adjuvant platinum-based chemotherapy without evidence of disease relapse/recurrence, and chemotherapy-naive participants with Stage IV NSCLC.

The study will evaluate participant- and HCP-reported preference for atezolizumab SC compared with atezolizumab IV. An overview of the study design is provided in Figure 1. The schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



eNSCLC = early non–small cell lung cancer; IV = intravenous; PD-L1 = programmed death-ligand 1; Q3W = every 3 weeks; R = randomization; SC = subcutaneous; TC = tumor cells; TPS = tumor proportion score.

(1) Histological or cytological diagnosis per UICC/AJCC staging system, 8th Ed.

(2) PD-L1 positive defined as minimum TC ≥ 1% by VENTANA PD-L1 (SP263) IHC assay or TPS ≥ 1% by Dako PD-L1 IHC 22C3 pharmDx assay performed by a local or central laboratory.

(3) PD-L1 high defined as minimum TC ≥ 50% by VENTANA PD-L1 (SP263) IHC assay, minimum TPS ≥ 50% by Dako PD-L1 IHC 22C3 pharmDx assay, or TC3 or IC3 by VENTANA PD-L1 (SP142) IHC assay, performed by a local or central laboratory.

(4) Stratification: disease stage and type of surgery.

Participants whose tumors have an EGFR mutation or ALK rearrangement will be excluded from enrolment. Participants with tumors of non-squamous histology with unknown EGFR or ALK mutational status will be required to be tested at prescreening/screening centrally if the local test cannot be done or does not meet the required criteria (see the specific exclusion criteria in Section 4.1.2 and Section 4.5.6).

Eligibility will be assessed within a 28-day screening period. A pre-screening period will be available for those participants who need to assess their eligibility in terms of PD-L1 expression, EGFR mutation, or ALK rearrangement (see Section 4.1 for further details).

Participants who do not meet the criteria for participation in this study (screen failure) may qualify for two re-screening opportunities (for a total of three screenings per participant) at the investigator's discretion, provided all initial and subsequent screening assessments are performed within 56 days prior to Day 1. Re-screened participants must meet all eligibility criteria and re-sign the Informed Consent Form prior to re-screening. The investigator will maintain a record of reasons for screen failure (see Section 4.5.1).

Participants must have PD-L1-positive or high NSCLC to be enrolled in the study. Participants that do not have prior PD-L1 testing will be prospectively tested for PD-L1 expression by central testing at prescreening/screening (see Section 4.1.1 and 4.5.6 for more details).

Participants will undergo a tumor assessment at baseline to confirm eligibility criteria. Subsequent tumor assessments will be conducted as per local standard of care (see Section 4.5.5).

Participants with Early-stage NSCLC

Eligible participants with early-stage NSCLC will have had a complete resection of NSCLC and must be adequately recovered from surgery and adjuvant chemotherapy. Prior to treatment with adjuvant atezolizumab, all participants should have received up to four cycles of adjuvant platinum-based chemotherapy, with no evidence of disease relapse/recurrence.

Chemotherapy-naive Participants with Stage IV NSCLC

Participants with Stage IV NSCLC will be eligible to join the study if they have not received prior chemotherapy for advanced NSCLC and satisfy the eligibility criteria described in Section 4.1.

Study Treatment Period

During the study treatment period, participants will be randomly allocated in a 1:1 ratio to treatment Arm A (atezolizumab SC followed by atezolizumab IV) or treatment Arm B (atezolizumab IV followed by atezolizumab SC). Participants will be stratified according to disease stage (II, III, or IV) and type of surgery (no surgery, pneumonectomy, and any other lung surgery).

Atezolizumab will be administered on Day 1 of each 21-day cycle. Participants will receive atezolizumab according to their assigned route of administration (i.e., SC or IV) for the first three treatment cycles. At Cycle 4, participants will cross-over and receive atezolizumab administered according to the alternative route of administration for Cycles 4–6. This period of 3+3 cycles in both treatment arms constitutes the study Treatment Cross-over Period.

After Cycle 6, participants will select how they would like atezolizumab to be administered (SC or IV) for the Treatment Continuation Period. The Treatment Continuation Period will continue until Cycle 16 for participants with early-stage NSCLC or until loss of clinical benefit, as determined by the investigator according to local standard of care, for patients with advanced NSCLC.

Participants will undergo an End of Treatment Visit within 30 days after completing study treatment and will enter *the* safety follow-up *period. Safety follow-up should occur approximately 90 days after the last dose of study treatment. Thereafter, participants will be contacted for survival status and to collect details of new anti-cancer therapy, if any.*

Participant preference will be assessed based on the PPQ (administered following treatment administration on Day 1, Cycle 6 of the Treatment Cross-over Period). Treatment satisfaction will be assessed based on the TASQ (administered following treatment administration on Day 1 of Cycles 3 and 6 of the Treatment Cross-over Period). Healthcare professionals will record their perception of time/resource use and convenience of treatment administration completing the HCPQs. Perception of time/resource use will be captured during the Treatment Cross-over Period and perception of convenience will be captured after administration of each participant's treatment Cycle 6. Health-related quality of life will be assessed using the EORTC QLQ-C30 completed during the Treatment Cross-over Period (at Cycle 1, Cycle 3, and Cycle 6), during the Treatment Continuation Period (at Cycle 7, Cycle 10, Cycle 13, and Cycle 16), and at the end of study treatment visit. Health utilities will be collected using the EQ-5D-5L questionnaire at the same time points as the EORTC QLQ-C30.
The study questionnaires are provided in Appendix 4, Appendix 5, and Appendix 6.

Participants will be assessed for safety by regular evaluation of adverse events, vital signs, and routine clinical laboratory tests (hematology, blood chemistry), and by physical examinations. Adverse events will be graded according to the NCI CTCAE v5.0.

Approximately 175 participants from approximately 40–50 study sites worldwide will be randomized in the study. Up to one-third of the study population will comprise chemotherapy-naive participants with Stage IV NSCLC; this proportion may be increased if sufficient participants with early-stage NSCLC are not recruited. Participants who withdraw from the study following randomization will not be replaced, with the exception of patients who withdraw consent prior to receiving the first dose.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined the Last Participant, Last Visit (LPLV), which is estimated to occur one year after the last participant is randomized or the date at which the last data point required for the final statistical analysis or safety follow-up is received from the last participant, whichever occurs later.

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

The study is estimated to last approximately 2 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Dose and Schedule

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

Subcutaneous atezolizumab will be administered at a fixed dose of 1875 mg Q3W (1875 mg on Day 1 of each 21-day cycle) into the thigh. This dose and administration site was chosen based on the results of Study BP40657 (see Section 1.4.4). In Part 1 of Study BP40657, atezolizumab SC co-mix (an SC formulation of atezolizumab for co-mix with rHuPH20, manually mixed at the local pharmacy), 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 of Study BP40657 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 a SC dose of 1875 mg Q3W given in the thigh had a >99% 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 IMscin001 Phase III study results have demonstrated the non-inferiority of this dose of atezolizumab SC versus IV (Burotto et al. 2022).

Overall, atezolizumab administered subcutaneously in Study BP40657 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.

3.3.2 Rationale for Participant Population

This study is to be conducted in participants with early-stage, or metastatic NSCLC who are PD-L1 positive or PD-L1 high, respectively (Section 4.1.1). Atezolizumab IV is currently approved as a monotherapy for patients with high PD-L1 expression (TC ≥ 50% or IC ≥ 10% [i.e., TC3/IC3]) in the metastatic setting based on the results of the Phase III study GO29431 (IMpower110) (TECENTRIQ® U.S. Package Insert) and for patients with PD-L1 expression of ≥ 1% on tumor cells in the adjuvant setting following the results of GO29527 (IMpower010) (TECENTRIQ® U.S. Package Insert) and PD-L1 expression of ≥ 1% on tumor cells in the EU (Tecentriq® SmPC). These monotherapy regimens provide the possibility to assess the participant's preference and participant-reported outcomes (PROs) of atezolizumab without the confounding effects of chemotherapy. The relatively long mean disease and progression-free intervals of these settings allow the participants to experience both administration routes without the confounding effects of a rapid recurrence or progression of the underlying disease.

3.3.3 Rationale for Randomization Stratification Factors

To include as wide a population as possible while limiting imbalances that may affect study outcomes, randomization will be stratified. Since participants' perceptions and preferences can be influenced by factors affecting their health-related quality of life, the following stratification factors are proposed:

1. Disease stage (II, III, IV)
2. Type of surgery (Pneumonectomy, no surgery, any other surgery)

3.3.4 Rationale for Randomized Cross-Over Design

The primary objective of this study is to assess participant-reported preference for atezolizumab SC compared with atezolizumab IV. Participants will be randomized to receive either atezolizumab SC for three treatment cycles followed by atezolizumab IV for three treatment cycles versus receiving atezolizumab IV first, followed by atezolizumab SC. Participants in both treatment groups will then choose either IV or SC administered atezolizumab for their remaining treatment cycles.

Randomization accommodates potential treatment sequencing-related differences such as in the nature and/or frequency of infusion-related reactions (IRRs) with either administration route (e.g., if IRRs to IV formulation occur more frequently in the early cycles of dosing) or in adverse events attributable to switching administration routes. At the same time, the cross-over design provides exposure to both study regimens allowing each participant to act as their own control for PROs measured after atezolizumab Cycle 3 and atezolizumab Cycle 6.

3.3.5 Rationale for Clinical Outcome Assessments

The PPQ used to assess the primary study endpoint has been developed in clinical trials assessing patient preference for SC administered monoclonal antibodies. An interview-based assessment was first developed to assess patient preference for Herceptin SC in a clinical trial of adjuvant Herceptin SC and IV in human epidermal growth factor receptor 2-positive (HER2+) early breast cancer (Study MO22982; Pivot et al. 2013). Interview questions were based on input from experienced clinicians, chemotherapy nurses and psychologists and were tested with patient volunteers prior to use in the study. The three interview questions identified as most informative in the Herceptin MO22982 study were then administered as the patient-completed PPQ in a subsequent lymphoma study evaluating preference for SC or IV administered rituximab (PrefMab study; Rummel et al. 2017). Notably, PPQ endpoints collected in this study were considered adequate evidence for preference claims included in rituximab SC product labelling (RITUXAN HYCELA™ U.S. Package Insert). The PPQ was also used to evaluate the participant preference for the SC administration of Phesgo compared to the IV administration of Perjeta (pertuzumab) and Herceptin (trastuzumab) in the PHrancheSCa study (Study MO40628; O'Shaughnessy et al. 2021).

The TASQ questionnaires used in this study have been adapted from administration satisfaction questionnaires used in the aforementioned PrefMab study.

Health-related quality of life evaluations in this study will contextualize a participant's experience on trial, elucidating symptom- and treatment-burden between atezolizumab IV and atezolizumab SC. Because treatment-related side effects have the potential to affect participant functioning and HRQoL, it is crucial to characterize not only the incidence of these side effects but also the associated trends and burden from the participant's perspective, which would contribute to a more comprehensive understanding of treatment impact and tolerability. The EORTC QLQ-C30, is a well-known and commonly used questionnaire with strong demonstrated psychometric properties of both reliability and validity.

The HCPQs will be used to investigate whether the shorter administration times anticipated for SC versus IV atezolizumab dosing, combined with the fact that SC dosing does not require IV access, translate into positive HCP-reported perceptions of resource use for atezolizumab SC administration. A similar approach has already been followed in previous studies (Jackisch et al. 2015; Burcombe et al. 2013).

4. MATERIALS AND METHODS

4.1 PARTICIPANTS

Approximately 175 participants with early-stage or metastatic NSCLC will be enrolled in this study.

4.1.1 Inclusion Criteria

Participants must meet the following criteria for study entry:

4.1.1.1 All Participants

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- ECOG performance status of 0 or 1
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, 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 postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  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 participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- Adequate hematologic and end-organ function, defined by the following laboratory 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)

    Participants may be transfused to meet this criterion.

- AST, ALT, and ALP ≤ 2.5 × upper limit of normal (ULN), with the following exceptions:

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

  Participants with documented liver or bone metastases: ALP ≤ 5 × ULN

- Total bilirubin ≤ 1.5 × ULN with the following exception:

  Participants with known Gilbert disease: total bilirubin ≤ 3 × ULN

- Creatinine clearance ≥ 45 mL/min (calculated through use of the Cockcroft-Gault formula)
- Albumin ≥ 25 g/L (≥ 2.5 g/dL)
- For participants not receiving therapeutic anticoagulation: INR and aPTT ≤ 1.5 × ULN

- For participants receiving therapeutic anticoagulation: stable anticoagulant regimen
- Intact normal skin without potentially obscuring tattoos, pigmentation, or lesions in the area for intended injection
- Negative HIV test at screening, with the following exception: participants with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count ≥ 200/µL, and have an undetectable viral load
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Positive hepatitis B surface antibody (HBsAb) test at screening, or negative HBsAb at screening accompanied by either of the following:
  - Negative total hepatitis B core antibody (HBcAb)
  - Positive total HBcAb test followed by a negative (per local laboratory definition) hepatitis B virus (HBV) DNA test

    The HBV DNA test must be performed for participants who have a negative HBsAg test, a negative HBsAb test, and 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 must be performed for participants who have a positive HCV antibody test.

- If a port for IV delivery is present, acceptance to receive atezolizumab IV, and any other IV medication which may be required, through a peripheral line

4.1.1.2 Participants with Early-stage NSCLC

- Participants must have a complete resection of a histologically or cytologically confirmed Stage II, IIIA, and selected IIIB (early-stage) NSCLC (per the UICC/AJCC staging system, 8th edition; Brierley et al. 2017)

  Accepted types of resection include any of the following: lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy.

  Resection by segmentectomy or wedge resection is not allowed.

If mediastinoscopy was not performed preoperatively, it is expected that, at a minimum, mediastinal lymph node systematic sampling will have occurred. Systematic sampling is defined as removal of at least one representative lymph node at specified levels. For a right thoracotomy, sampling is required at levels 4 and 7 and for a left thoracotomy, levels 5 and/or 6 and 7. Levels 10 and 11 are required irrespective of tumor laterality. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is an accepted sampling method.

- PD-L1 expression TC ≥ 1% (VENTANA PD-L1 [SP263] IHC assay) or TPS ≥ 1% (Dako PD-L1 IHC 22C3 pharmDx assay), as documented through local or central testing of a representative tumor tissue specimen

  Participants may be enrolled based on local documentation of PD-L1 expression, if the criteria outlined below are met. If the participant does not have local documentation of PD-L1 expression or local documentation of PD-L1 expression does not meet the defined criteria, central PD-L1 testing is required as outlined below and in Section 4.5.6.

  Local PD-L1 testing: Documentation of known PD-L1 status, as determined by the VENTANA PD-L1 (SP263) IHC assay or the Dako PD-L1 IHC 22C3 pharmDx assay is required. The PD-L1 assay must be a Health Authority approved test (i.e., adhering to local drug/device regulations) and performed per manufacturer's recommendations and requirements.

  Central PD-L1 testing: When central testing is required, a formalin-fixed, paraffin-embedded (FFPE) tumor specimen (archival or fresh) in a paraffin block (preferred) or at least 5 serial slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. Refer to Section 4.5.6 for additional information on tumor specimens collected at prescreening/screening.

- Participants must have completed adjuvant chemotherapy at least 4 weeks and up to 12 weeks prior to randomization and must be adequately recovered from chemotherapy. For patients in the adjuvant setting, neoadjuvant chemotherapy or chemoradiotherapy is acceptable provided that patients also received adjuvant chemotherapy as per protocol's requirement.

4.1.1.3 Participants with Stage IV NSCLC

- Histologically or cytologically confirmed, Stage IV non-squamous or squamous NSCLC (per the UICC/AJCC staging system, 8th edition; Brierley et al. 2017)

  Participants with tumors of mixed histology must be classified as non-squamous or squamous based on the major histological component.

- Life expectancy ≥ 18 weeks in the opinion of the investigator

- PD-L1 expression TC ≥50% (VENTANA PD-L1 (SP263) IHC assay) or TPS ≥50% (Dako PD-L1 IHC 22C3 pharmDx assay), or TC3 or IC3 (VENTANA PD-L1 (SP142) IHC assay), as documented through local or central testing of a representative tumor tissue specimen.

  Participants may be enrolled based on local documentation of PD-L1 expression, if the criteria outlined below are met. If the participant does not have local documentation of PD-L1 expression or local documentation of PD-L1 expression does not meet the defined criteria, central PD-L1 testing is required as outlined below and in Section 4.5.6.

  Local PD-L1 testing: Documentation of known PD-L1 status as determined by the VENTANA PD-L1 (SP263) IHC assay, Dako PD-L1 IHC 22C3 pharmDx assay or VENTANA PD-L1 (SP142) IHC assay is required. The PD-L1 assay must be a Health Authority approved test (i.e., adhering to local drug/device regulations) and performed per manufacturer's recommendations and requirements.

  Central PD-L1 testing: When central testing is required, a formalin-fixed, paraffin-embedded (FFPE) tumor specimen (archival or fresh) in a paraffin block (preferred) or at least 5 serial slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. Refer to Section 4.5.6 for additional information on tumor specimens collected at screening.
- No prior systemic treatment for Stage IV non-squamous or squamous NSCLC
- Participants who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy, radiotherapy, or chemoradiotherapy cycle.

4.1.2 Exclusion Criteria

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

4.1.2.1 All Participants

- History of malignancy within 5 years prior to initiation of study treatment, with the exception of the cancer under investigation in this study and malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer

- Uncontrolled tumor-related pain

  Participants 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. Participants should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to enrollment.

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Participants with indwelling catheters (e.g., PleurX®) are allowed.

- Participants known to have a sensitizing mutation in the EGFR gene or an ALK fusion oncogene

  Participants with unknown EGFR or ALK mutational status who may harbor a sensitizing EGFR mutation (i.e., participants with non-squamous histology (including those with a mixed histology that includes any non-squamous component), and without any other known driver mutation) will be required to be tested at prescreening/screening. Participants with tumors of squamous histology who have an unknown EGFR or ALK mutational status will not be required to be tested at prescreening/screening.

  EGFR and/or ALK may be assessed locally or at a central laboratory. EGFR status assessed locally must be performed on tissue using a test that detects mutations in exons 18–21. The assays must be a Health Authority approved test (i.e., adhering to local drug/device regulations) and performed per manufacturer's recommendations and requirements. If the assay does not meet the criteria above, EGFR and/or ALK must be assessed centrally. If samples are submitted for central EGFR and/or ALK testing, additional slides must be provided (see laboratory manual) along with an associated pathology report prior to study enrollment.

- History of leptomeningeal disease
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected calcium greater than ULN)

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, anti-phospholipid antibody syndrome, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 7 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

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

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

  Participants with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., participants 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 has been no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

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

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

- Active tuberculosis
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- 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 could impact participant safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Participants receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease (COPD) exacerbation) are eligible for the study.

- Prior allogeneic stem cell or solid organ transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the participant at high risk from treatment complications
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Current treatment with anti-viral therapy for HBV
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–PD-1 and anti–PD-L1 therapeutic antibodies

  Participants 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 randomization
  – No history of severe immune-mediated adverse effects from anti–CTLA-4 (NCI CTCAE Grades 3 and 4)
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5 drug-elimination half-lives (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-tumor necrosis factor-α [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

  – Participants who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.
  – Participants who received mineralocorticoids (e.g., fludrocortisone), inhaled or low-dose corticosteroids for COPD or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

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

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

- Known allergy or hypersensitivity to hyaluronidase, bee or vespid venom, or any other ingredient in the formulation of rHuPH20
- 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)
- 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 ≥ 2 weeks prior to randomization

4.1.2.2 Participants with Stage IV NSCLC

- Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases

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

  – The participant has no history of intracranial hemorrhage or spinal cord hemorrhage.

  – The participant 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 participant has no ongoing requirement for corticosteroids as therapy for CNS disease.

  – If the participant is receiving anti-convulsant therapy, the dose is considered stable.

  – Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).

  – There is no evidence of interim progression between completion of CNS-directed therapy and initiation of study treatment.

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

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, open-label study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from the interactive voice or web-based response system (IxRS).

Participants will be randomly assigned to one of two treatment arms: Arm A (atezolizumab SC followed by atezolizumab IV) or Arm B (atezolizumab IV followed by atezolizumab SC). Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified by disease stage and type of surgery (see Section 3.1.1 for details).

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are atezolizumab SC and atezolizumab IV.

IMPs will be supplied by the Sponsor.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 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.

4.3.1.2 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.

For Atezolizumab SC or IV, refer to the pharmacy manual for detailed instructions on drug preparation and administration.

No dose modification for atezolizumab is allowed.

Any atezolizumab dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental atezolizumab overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for atezolizumab treatment interruption or atezolizumab discontinuation for participants who experience adverse events are provided in Appendix 9.

4.3.2.1 Atezolizumab SC

Atezolizumab (1875 mg) SC injections will be administered subcutaneously by a health care professional in the anterior thigh region per the instructions outlined in Table 1.

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. In all cases, start and stop times of the SC injection should be captured.

No premedication will be allowed for the first dose of 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. Digital recordings will be stored at the site.

In case a participant develops unacceptable toxicity to the SC injection of atezolizumab, treatment with IV infusion may continue. In case a participant 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 9 for further guidance on atezolizumab toxicity management.

Administration of 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 8. Atezolizumab SC injections will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Atezolizumab SC Injections

First and Subsequent SC Injections
• No premedication is permitted prior to the **first** SC injection. • For subsequent SC injections, if the participant 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 should be measured as described in Section 4.5.4. • Participants 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 (1200 mg) 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 8. Atezolizumab IV infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Atezolizumab IV Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs should be measured as described in Section 4.5.4. • Atezolizumab should be infused over 60 (±15) minutes. • Participants 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 participant experienced an IRR with any previous infusion, premedication with antihistamines, anti-pyretic medications, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured as described in Section 4.5.4. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an IRR, or 60 (±15) minutes if the participant experienced an IRR with the previous infusion.

IRR=infusion-related reaction.

Guidelines for medical management of infusion-related reactions are provided in Appendix 9.

No dose modification for atezolizumab is allowed.

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study (atezolizumab SC, atezolizumab IV) will be provided by the Sponsor. 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 participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants 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 participants 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 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 for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Investigational Medicinal Products

The Sponsor will offer continued access to Roche IMPs (atezolizumab IV and atezolizumab SC) free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Roche IMPs (atezolizumab IV and atezolizumab SC) after completing the study if all of the following conditions are met:

- The participant has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being.
- There are no appropriate alternative treatments available to the participant.
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

Eligible participants will be provided access to Roche IMP(s) until the loss of clinical benefit (as judged by the investigator) after completing the study, unless mandated otherwise by local regulations.

A participant will not be eligible to receive Roche IMPs (atezolizumab IV and atezolizumab SC) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant).
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for NSCLC.
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for NSCLC.
- Provision of the Roche IMP is not permitted under the laws and regulations of the participant's country.
- *The Roche IMP is no longer manufactured.*

In *these situations, the investigator and primary care physician will transition the study participant to an alternative therapy in accordance with institutional or local guidelines.* The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

https://assets.cwp.roche.com/f/176343/x/92d6b13ee6/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 participant in addition to protocol-mandated treatment from 7 days prior to initiation of study drug 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

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

- Oral contraceptives with a failure rate of < 1% per year (see Section 4.1.1)

- 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)
- Inhaled or low-dose corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- For participants with metastatic disease: Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Treatment with atezolizumab may be continued during palliative radiotherapy.
- For participants with metastatic disease: Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Participants experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.

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

In general, investigators should manage a participant's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.1 and 4.4.2) as clinically indicated, per local standard practice. Participants 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 8.

4.4.2 Cautionary Therapy

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 9 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 4.4.2) 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, 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 participant 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 within 28 days prior to initiation of study treatment and during study treatment.
- Live attenuated vaccines (e.g., FluMist®) 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) within 4 weeks or 5 drug-elimination half-lives (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 schedule of activities to be performed during the study are provided in Appendix 1. All activities should be performed and documented for each participant.

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

4.5.1 Informed Consent Forms and Prescreening/Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Results of standard-of-care tests or examinations performed prior to obtaining informed consent but within 28 days of randomization (see schedule of assessments) may be used; such tests do not need to be repeated for screening. Informed Consent Forms for enrolled participants and for individuals who are not subsequently enrolled will be maintained at the study site.

Prior to signing the main Informed Consent Form for the study, participants may consent to the collection of tumor tissue (archival or newly obtained via biopsy) for determination of PD-L1 expression by signing a Prescreening Informed Consent Form. Participants who may harbor a sensitizing EGFR mutation (i.e., those having non-squamous histology (including those with a mixed histology that includes any non-squamous component), and without any other known driver mutation) may also allow for central evaluation of EGFR and/or ALK status.

All screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before enrollment. The investigator will maintain a detailed record of all individuals prescreened/screened, to document eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the participant 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.

Documentation from the initial lung cancer diagnosis and from lung cancer surgery (if applicable) will be collected prior to randomization.

Results of any prior PD-L1 and EGFR/ALK testing conducted by a local laboratory, if available, will be collected retrospectively to assure study eligibility. If prior test results are available, submission of local test results document is required.

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

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the

cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

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

4.5.4 Vital Signs

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

Vital signs are to be measured before, during, and after infusions as outlined in, and at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

Table 3 Timing for Vital Sign Measurements for First and Subsequent Infusions

Drug	Timing for Vital Sign Measurements
Atezolizumab IV	• Within 60 minutes prior to the atezolizumab infusion • Record participant's vital signs during or after the infusion (and before any PK sample scheduled to be drawn at the same time) if clinically indicated
Atezolizumab SC	• Within 60 minutes prior to the atezolizumab injection • Measure at 30 (±10) minutes after the injection (and before any PK sample scheduled to be drawn at the same time) and as clinically indicated

4.5.5 Tumor and Response Evaluations

Participants will undergo tumor assessments at screening to confirm eligibility criteria.

All measurable and/or evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening, so long as they meet criteria outlined below.

During study treatment, patients will undergo regular tumor assessments as per local standard of care. Disease progression or loss of clinical benefit as determined by the investigator should be recorded on the eCRF.

4.5.5.1 Radiographic Assessments

Screening assessments must include CT scans with contrast or MRI scans of the chest, abdomen, pelvis, and brain. 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 participants with impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and brain should be performed. A CT scan with contrast or MRI scan of the brain must be done at screening to evaluate CNS metastasis in all participants (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the brain 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.

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.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH
- Coagulation: INR, and aPTT
- Thyroid function testing: thyroid-stimulating hormone, free T3 (or total T3 for sites where free T3 is not performed), and free T4
- HIV serology
- HBV serology: HBsAg, HBsAb, and total HBcAb for all participants; HBV DNA for participants with negative HBsAg and HBsAb tests and a positive total HBcAb test
- HCV serology: HCV antibody for all participants; HCV RNA for participants with a positive HCV antibody test
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test performed at screening. Urine (or serum, if urine is not feasible) pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes,

and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

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

- Serum samples for atezolizumab PK analysis through use of a validated assay
- Serum samples for assessment of ADAs to atezolizumab through use of a validated assay
- Archival or newly collected tumor tissue sample obtained at baseline for determination of PD-L1 expression and EGFR and/or ALK, if central testing is required

  For PD-L1 expression, a representative FFPE tumor specimen in a paraffin block (preferred) or at least 5 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment.

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

  If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, tumor tissue must be obtained from a biopsy performed at prescreening/screening. A biopsy may also be performed at prescreening/screening if a participant's archival tissue test results do not meet eligibility criteria (see Section 4.1) or does not meet the required quality criteria explained above.

  For participants who may harbor EGFR and/or ALK mutations and their status is unknown or not assessed with a Health Authority approved test (i.e., adhering to local drug/device regulations) and performed per manufacturer's recommendations and requirements, these must be assessed at a central laboratory (see Section 4.1.2.1 for exclusion criteria). If samples are submitted for central testing, additional unstained slides must be provided (see additional details in the laboratory manual) along with an associated pathology report prior to study enrollment.

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

Biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- 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 screening will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For enrolled participants, remaining archival tissue blocks will be returned to the site upon request or no later than the time of completion of the Clinical Study Report, whichever occurs first. For individuals who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

When a participant withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the participant 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.

4.5.7 Electrocardiograms

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

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

4.5.8 Clinical Outcome Assessments

Participant-reported outcome (PRO) instruments and HCP questionnaires (HCPQ) will be completed to characterize the clinical profile of atezolizumab infusions and injections. In addition, these instruments will enable the capture of the participant's and HCP's direct experience with atezolizumab infusions and injections.

PRO data will be collected through use of the following instruments: Patient Preference Questionnaire (PPQ), Therapy Administration Satisfaction Questionnaires (SC and IV versions; TASQ-SC and TASQ-IV), EORTC QLQ-C30, and EQ-5D-5L. HCP data will be collected through the use of the HCPQs (treatment room and drug preparation area versions). PRO and HCPQ data will be collected on paper questionnaires.

4.5.8.1 Data Collection Methods for Clinical Outcome Assessments

PRO and HCP instruments will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1). At the clinic, the EORTC QLQ-C30 and EQ-5D-5L will be administered before the participant receives any information on disease status, and prior to the performance of non-PRO assessments. The PPQ and TASQ will be administered following treatment administration per the schedule of activities.

PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor.

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

- Participants' 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 participants to complete the instruments, estimated to be 13 minutes at the Cycle 1 Day 1 and Cycle 3 Day 1 visits, 15 minutes at the Cycle 6 Day 1 visit, and 8 minutes at the Treatment Continuation, end-of-treatment, and follow-up visits.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Participants 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.
- Participants 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 participant to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the participant to complete the item or confirm that the item was intentionally left blank.

4.5.8.2 Description of Clinical Outcome Assessment Instruments

Patient Preference Questionnaire

The PPQ is a generic preference questionnaire designed to ask patients about which route of administration they preferred after receiving both the SC and IV formulations. Question 1 asks patients to report their preference for the route of administration (IV, SC, or no preference). Question 2 asks patients to rate the strength of their preference (if any) on a 3-point scale (very strong, fairly strong, not very strong). Question 3 asks patients to provide two main reasons for their preference (see Appendix 4).

The PPQ will be completed immediately after 3 cycles of each treatment (i.e., Day 1 of Cycle 6 of the Treatment Crossover Period) to allow participants to have experience with both routes of administration and to determine if additional treatment by one route or another modified their preference. Please refer to Appendix 1 for instructions regarding when participants who prematurely discontinue study treatment should complete the PPQ.

Therapy Administration Satisfaction Questionnaires

Participant-reported treatment satisfaction with atezolizumab IV and atezolizumab SC will be evaluated using the TASQ-IV and TASQ-SC, respectively (see Appendix 4).

Each TASQ will be completed by the participant as outlined in the schedule of activities (see Appendix 1).

EORTC QLQ-C30

The QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) (see Appendix 4). It consists of 30 questions that assess five aspects of participant functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), global health status and quality of life (QoL), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a four-point scale that ranges from "not at all" to "very much", and the global health status and QoL items are scored on a seven-point scale that ranges from "very poor" to "excellent". The QLQ-C30 takes approximately 10 minutes to complete. The QLQ-C30 will be completed by the participant as outlined in the schedule of activities (see Appendix 1).

Healthcare Professional Questionnaires

Healthcare professional reported perception of time and resource use associated with atezolizumab SC will be assessed via two HCPQs (see Appendix 5). One HCPQ (HCPQ-Treatment Room) will be completed by an HCP involved in treatment preparation and/or administration in the treatment room where study drugs are administered. The other HCPQ (HCPQ-Drug Preparation Area) will be completed by an HCP involved in study drug preparation. Please refer to each HCPQ in Appendix 5 for

personnel qualifying as HCPs for each questionnaire. The HCPQs will be completed by the HCP as outlined in the schedule of activities (see Appendix 1).

EuroQol EQ-5D-5L

The EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see Appendix 6). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale (VAS) that measures health state. The EQ-5D-5L is designed to capture the participant's current health status. Published weighting systems allow for creation of a single composite score of the participant's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations. The EQ-5D-5L will be completed by the participant as outlined in the schedule of activities (see Appendix 1).

4.6 TREATMENT, PARTICIPANT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Participants must permanently discontinue study treatment (atezolizumab) if any of the following criteria are met:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual participant's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the participant's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1)

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

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the final dose of study treatment. An earlier visit may be used as the treatment discontinuation visit if a local assessment of tumor response indicates a loss of clinical benefit.

Refer to the schedule of activities (see Appendix 1) for details on follow-up assessments to be performed for participants who permanently discontinue atezolizumab. If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

4.6.2 Participant Discontinuation from the Study

Participants 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 participant from the study at any time.

Reasons for participant discontinuation from the study may include, but are not limited to, the following:

- Participant withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Participant non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for participant discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Participants who withdraw from the study will not be replaced.

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 participants
- Participant enrollment is unsatisfactory
- Development of atezolizumab SC formulation is discontinued

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 participants have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for participants 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 participants in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of participants 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 participants who experience anticipated adverse events, including criteria for treatment interruption or discontinuation, are provided in Appendix 9. Refer to Sections 5.2–5.7 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

Participants 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 participant 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: infusion-related reaction (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, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 9 of the protocol and Section 6 of the atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Guidelines for managing participants who experience anticipated adverse events are provided in Appendix 9.

5.1.2 Risks Associated with rHuPH20

rHuPH20 is co-formulated with atezolizumab. rHuPH20 should not be injected into or around an infected or acutely inflamed area because of the danger of spreading a localized infection. Refer to the rHuPH20 U.S. Package Insert for more details regarding the full safety profile of rHuPH20, including boxed warnings and contraindications (Hylenex recombinant U.S. Package Insert). Refer to Appendix 9 for adverse event management guidelines for 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 participant 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 participant'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 participant or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by a 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 an individual exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- 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 for 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 participant contact. All adverse events, whether reported by the participant or noted by study personnel, will be recorded in the participant'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 participant 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 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 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 participants 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 participant, 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 participant 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 5 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 participant'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).

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 cytokine release syndrome (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"). 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 participant experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded as a separate event on the Adverse Event eCRF, with associated signs and symptoms 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 9.

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between participant 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 participant 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., ALP 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 (e.g., 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

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

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of NSCLC

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of NSCLC on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of non–small cell lung cancer"). 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 investigator assessment according to local standard of care. 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 participant 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 participant requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 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.

Note: 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 and atezolizumab IV 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.

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

In addition, all special situations associated with atezolizumab SC or atezolizumab IV, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

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

5.3.5.13 Participant-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)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information 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 Medical Monitors and Emergency Medical Contacts

Contact Information for all sites

Investigators will be provided with contact information for the Medical Monitor. An Emergency Medical Call Center will *also* be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to 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 Participants

Female participants 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 final 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 participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

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 participant exposed to study treatment or the female partner of a male participant 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 PARTICIPANTS 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, or the event is assessed as stable by the investigator, or the participant is lost to follow-up, or the participant 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 adverse event reporting period (defined in Section 5.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Section 5.4.3.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge

summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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

In addition, if the investigator becomes aware of a serious adverse event 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.

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.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Atezolizumab IV and SC	Atezolizumab 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 primary study analysis will take place when all study participants have completed their last study treatment administration in the Treatment Cross-over Period. Summaries of secondary study endpoints, including PK and ADA measurements, participant-reported TASQ and EORTC QLQ-C30 responses, selection of treatment administration method for the Treatment Continuation Period, HCP reported HCPQ responses, and safety endpoints, up to Day 1, Cycle 7 will be included in the primary analysis.

The final study analysis that includes all secondary endpoints including all questionnaires, PK, ADA, and safety endpoints will be conducted after the end of the study (i.e., when all patients have received 16 cycles of atezolizumab or discontinued study treatment).

For the definition of study populations, please refer to the Statistical Analysis Plan (SAP). The definitions of primary and secondary objectives and the corresponding estimand definitions and further details about the planned analyses will be presented in the SAP.

6.1 DETERMINATION OF SAMPLE SIZE

The primary study objective is to estimate the proportion of participants who express a preference for atezolizumab SC compared with atezolizumab IV.

The planned total sample size of 175 participants is based on an assumed rate of 70% of participants preferring atezolizumab SC compared with atezolizumab IV. To achieve a distance of approximately ± 8% from the estimated proportion to 95% CI limits, a total of 126 participants are needed for the evaluation of preference. The final target sample size was increased to approximately 175 participants to allow for 28% of the participants not providing an evaluable preference assessment.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrolment, eligibility violations and participant disposition will be summarized for participants by treatment arm. Reasons for participant's study treatment discontinuation and participant's reasons for study discontinuation will be listed by participant and summarized. Major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

Median follow-up on treatment and on study, estimated with corresponding 95% CI by the reverse Kaplan-Meier approach, will be presented.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic variables and other baseline and disease characteristics will be summarized overall and by treatment sequence using descriptive statistics.

6.4 PRIMARY ENDPOINT ANALYSIS

The primary objective of this study is to evaluate participant preference for atezolizumab SC based on the proportion of participants indicating an overall preference for atezolizumab SC compared with atezolizumab IV in Question 1 of the PPQ. Question 1 of the PPQ is as follows: "All things considered, which route of administration did you prefer?".

A point estimate with associated 95% CI for the proportion of participants who preferred atezolizumab SC will be calculated.

6.5 SECONDARY ENDPOINT ANALYSES

Participant assessed satisfaction with atezolizumab SC and atezolizumab IV will be based on participant responses to Question 1 of the TASQ-SC and TASQ-IV respectively. In addition, responses of the TASQ-SC and TASQ-IV will be summarized by domain (physical impact, psychological impact, impact on activities of daily living, convenience and satisfaction).

The proportion of participants who select each treatment administration route for the Treatment Continuation Period will be summarized for all participants who complete the Treatment Cross-over Period.

EORTC QLQ-C30 scores including change from baseline, will be summarized by treatment arm and by time.

Healthcare professional perception of time/resource use and convenience with atezolizumab SC will be assessed by summarizing responses to individual questions of the HCPQs.

The percentage of participants with continuing clinical benefit after 16 cycles of atezolizumab will be summarized (stratified by disease stage at study entry).

6.5.1 Safety Analyses

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

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

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

appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data (if available) will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs (if available) will be summarized.

To evaluate the safety of switching from atezolizumab SC to atezolizumab IV and from atezolizumab IV to atezolizumab SC, adverse event summaries will also be produced for the Treatment Cross-over Period by treatment arm and treatment period. An adverse event will be allocated to the treatment received on or before the adverse event start date.

Adverse events that started during the first three cycles of the Treatment Cross-over Period and continued into subsequent cycles (even if the adverse event changed severity grade) will be summarized under the route of administration during which it first occurred. These adverse events will be flagged in listings.

6.6 PHARMACOKINETIC ANALYSES

Samples will be collected for PK analyses and to compare exposure in this study with that attained in previous studies. Serum concentrations of atezolizumab will be reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by treatment arm and cycle, when appropriate and as data allow. Individual and median serum atezolizumab concentrations will be plotted by treatment arm and day. Atezolizumab concentration data may be pooled with data from other studies using an established population PK model to derive PK parameters such as clearance, volume of distribution, and area under the curve, as warranted by the data. Potential correlations of relevant PK parameters with safety outcomes may be explored.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all participants with at least one ADA assessment. Participants will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, participants 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 postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Participants are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety and PK endpoints may be analyzed and reported via descriptive statistics.

6.8 INTERIM ANALYSES

None.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) 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 CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

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

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

At the end of the study, the investigator will receive participant 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 participant 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, participant-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO and HCPQ data (if applicable), Informed Consent Forms, laboratory test results, medication inventory records, and images, must be retained by the Principal Investigator for 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 study results have been reported 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 Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent

forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each participant the objectives, methods, and potential risks associated with each optional procedure. Participants 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 participant's agreement to participate in optional procedures. Participants who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the participant or the participant's legally authorized representative before his or her participation in the study. The case history or clinical records for each participant 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 participant to participate. The final revised IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each participant 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 participant or the participant's legally authorized representative. All signed and dated Consent Forms must remain in each participant'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 participant 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 participant 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 participant, 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 participant recruitment materials must be approved by the IRB/EC.

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

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

8.4 CONFIDENTIALITY

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 participant enrolled in the study through assignment of a unique participant identification number. This means that participant names are not included in data sets that are transmitted to any Sponsor location.

Participant 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 participant, unless permitted or required by law.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant'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

participants 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 (see Section 9.6).

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 participant 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 participant 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 has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring participant safety and data integrity. Prior to study initiation, the Sponsor identified potential risks associated with critical trial processes and data and implemented plans for evaluating and controlling these risks. Risk evaluation and control included the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. 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 are 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, participants' 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.

Approximately 40–50 sites globally will participate to randomize approximately 175 participants. 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 and PK analyses), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.6 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 healthcare 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/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be made available upon request. 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 participants 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 participants 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 participants 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

Treatment cycle	Screening [a]	Treatment Cross-over Period						Treatment Continuation Period	End of treatment visit [c]	Follow-up telephone call [d]
		1	2	3	4	5	6	Cycle 7 onwards [b]		
Day	–28 to –1	1 (±3 days)						1 (±3 days)	≤ 30 days from last study dose	90 days from last study dose
Informed consent [e] Prescreening for PD-L1 and EGFR/ALK testing, if applicable [f] Main ICF for study participation	x									
If central testing is required, archival/fresh tumor tissue for PD-L1 and EGFR and/or ALK [g]	x									
PD-L1 expression and EGFR and ALK mutational status [h]	x									
Demographics	x									
Medical history and baseline conditions	x									
Vital signs [i]	x	x	x	x	x	x	x	x	x	
Weight	x	x	x	x	x	x	x	x	x	
Height	x									
Complete physical examination [j]	x								x	
Limited physical examination [k]		x	x	x	x	x	x	x		
ECOG Performance Status	x	x	x	x	x	x	x	x	x	
ECG [l]	x	x	x	x	x	x	x	x		

Appendix 1: Schedule of Activities

Treatment cycle	Screening [a]	Treatment Cross-over Period						Treatment Continuation Period	End of treatment visit [c]	Follow-up telephone call [d]
		1	2	3	4	5	6	Cycle 7 onwards [b]		
Day	–28 to –1	1 (±3 days)						1 (±3 days)	≤ 30 days from last study dose	90 days from last study dose
Hematology [m]	x [n,o]	x	x	x	x	x	x	x	x	
Chemistry [p]	x [n,o]	x	x	x	x	x	x	x	x	
Pregnancy test [q]	x [n]	x	x	x	x	x	x	x	x	(x) [r]
Coagulation (INR, aPTT)	x [n]									
TSH, free T3 (or total T3), free T4 [s]	x	x [s]							x	
Viral serology [t]	x									
Urinalysis [u]	x	x [v]								
Participant-reported outcomes										
PPQ [w]							X			
TASQ-SC [x]				Arm A only			Arm B only			
TASQ-IV [x]				Arm B only			Arm A only			
EORTC QLQ-C30 [y]		x		x			x	x [y]	x	
EQ-5D-5L [y]		x		x			x	x [y]	x	
HCP-reported outcomes										
HCPQ-Treatment Room [z]		x	x	x	x	x	x			
HCPQ-Drug Preparation Area [z]		x	x	x	x	x	x			

Appendix 1: Schedule of Activities

Treatment cycle	Screening [a]	Treatment Cross-over Period						Treatment Continuation Period	End of treatment visit [c]	Follow-up telephone call [d]
		1	2	3	4	5	6	Cycle 7 onwards [b]		
Day	–28 to –1	1 (±3 days)						1 (±3 days)	≤ 30 days from last study dose	90 days from last study dose
Concomitant medications [aa]	x	Collect on an ongoing basis								
Adverse events [bb]	x	Collect on an ongoing basis								x
Study treatment administration										
Atezolizumab SC [cc]		Arm A only			Arm B only			According to participant choice [dd]		
Atezolizumab IV [cc]		Arm B only			Arm A only					
Tumor assessment	x [ee]	x [ff]								
PK samples		See Appendix 2 for detailed schedule								
ADA samples		See Appendix 2 for detailed schedule								

ADA=anti-drug antibody; aPTT=activated partial thromboplastin time; eCRF=electronic Case Report Form; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCPQ=Healthcare Professional Questionnaire; HCV=hepatitis C virus; INR=International Normalized Ratio; NA=not applicable; PK=pharmacokinetic; PPQ=Patient Preference Questionnaire; TASQ-IV/SC=Therapy Administration Satisfaction Questionnaire for Intravenous Administration / Subcutaneous Administration; TSH=thyroid-stimulating hormone.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results of standard-of-care assessments performed prior to obtaining informed consent may be used (see specific assessments for allowed interval); such assessments do not need to be repeated for screening. Participants who do not meet the criteria for participation in this study may qualify for two re-screening opportunities (for a total of three screenings per participant) at the investigator's discretion, as described in Section 3.1.1.

[b] For up to a total of 16 cycles for patients with early-stage NSCLC or until loss of clinical benefit, as determined by the investigator according to local standard of care, for patients with advanced NSCLC.

[c] Participants who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after their final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[d] *Safety follow-up should occur approximately 90 days after the last dose of study treatment. Thereafter, participants will be contacted for survival status and to collect details of new anti-cancer therapy, if any.*

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

[f] Participants have the option to sign the Prescreening ICF to consent to central PD-L1, EGFR, and/or ALK tissue testing during prescreening, prior to signing the main ICF for study participation. Consent may be obtained more than 28 days before initiation of study treatment.

[g] Refer to Sections 4.1.1.2 and 4.1.1.3 for description of when central testing is required and Section 4.5.6 for tissue sample requirements.

[h] For details of PD-L1 expression and EGFR and ALK mutational status testing requirements see Sections 4.1.1.2, 4.1.1.3, 4.1.2, and 4.5.6.

[i] Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Refer to Table 3 for details of the timings of vital sign assessments.

[j] A complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[k] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints.

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

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[n] Specified screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[o] If screening laboratory assessments were performed within 4 days prior to Day 1 of Cycle 1, they do not have to be repeated.

[p] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH.

[q] All women of childbearing potential will have a serum pregnancy test at screening, within 14 days prior to initiation of study treatment. Urine pregnancy tests (or serum, if urine is not feasible) will be performed at specified subsequent visits during treatment, at the treatment discontinuation visit, and 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 urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[r] In accordance with 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.

[s] 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.).

[t] At screening, participants will be tested for HIV, HBsAg, HBsAb, total HBcAb, and HCV antibody. If a participant has negative HBsAg and HBsAb tests and a positive total HBcAb test at screening, an HBV DNA test must also be performed. If a participant has a positive HCV antibody test at screening, an HCV RNA test must also be performed.

[u] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[v] Urinalysis should be performed as clinically indicated during study treatment.

[w] The Patient Preference Questionnaire (PPQ) must be completed following study treatment administration on Day 1 of Cycle 6 of the Treatment Cross-over Period. Participants who discontinued study treatment prior to study treatment Cycle 6 should complete the questionnaire at the time of discontinuation as long as they have received at least one dose of atezolizumab SC and atezolizumab IV post-randomization.

[x] Participants in Arm A will complete the Therapy Administration Satisfaction Questionnaire for SC administration (TASQ-SC) immediately following study treatment administration on Day 1 of Cycle 3 of the Treatment Cross-over Period and the Therapy Administration Satisfaction Questionnaire for IV administration (TASQ-IV) immediately following study treatment administration on Day 1 of Cycle 6 of the Treatment Cross-over Period. Participants in Arm B will complete the TASQ-IV and TASQ-SC immediately following study treatment administration on Day 1 of Cycle 3 and 6 of the Treatment Cross-over Period, respectively.

[y] During the study treatment periods, participants must complete the EORTC QLQ-30 and EQ-5D-5L before the participant and clinician receives any information on disease status and prior to treatment administration on the scheduled visit day. EORTC QLQ-C30 and EQ-5D will be administered at Cycle 7, 10, 13, and 16 of the Treatment Continuation Period.

[z] Each Healthcare Professional Questionnaire (HCPQ) will be completed by the applicable HCP after each study treatment preparation and/or administration for each participant. Applicable HCPs are described in each of the questionnaires (HCPQ-Treatment Room, HCPQ-Drug

Preparation Area). Instructions for which questions should be completed in each questionnaire at each timepoint are indicated in the introduction to each questionnaire.

[aa] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[bb] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest 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 (see Section 5.6).

[cc] Participants 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. For administration instructions, please check the Pharmacy Manual.

[dd] After Cycle 6, participants will select the route of administration (SC or IV) they would like to receive from Cycle 7 onwards.

[ee] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening, so long as they meet criteria outlined in Section 4.5.5. Screening assessments must include CT scans with contrast or MRI scans of the chest, abdomen, pelvis, and brain. 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 participants with impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and brain should be performed. A CT scan with contrast or MRI scan of the brain must be done at screening to evaluate CNS metastasis in all participants (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the brain 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.

[ff] Participants will undergo tumor assessments as per local standard of care.

Appendix 2
Schedule of Pharmacokinetic and Immunogenicity Samples

Cycle	Day	Time/maximum window	PK sample	ADA sample
1	1	Predose	Atezolizumab (serum)	Atezolizumab (serum)
	4	Between 72 and 96 hours postdose	Atezolizumab (serum)	-
2–6, 8, and 16	1	Predose	Atezolizumab (serum)	Atezolizumab (serum)
Treatment discontinuation visit	At visit	At visit	Atezolizumab (serum)	Atezolizumab (serum)

ADA=anti-drug antibody; PK=pharmacokinetic.

Appendix 3
PK and ADA Sampling Instructions for Investigators

Body Sites for PK and ADA for Atezolizumab 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 participant 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 participant 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 2) and prior to any infusion or injection is given (for predose samples). Our recommendation is to plan the first dose accordingly so that these key days fall into a day when the participant can attend the clinic.

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

Appendix 4
Participant-Reported Outcome Measures

PATIENT PREFERENCE QUESTIONNAIRE

You have now received *Tecentriq* (atezolizumab) in two different ways:

1. through a thin plastic tube and a needle that was put directly into a vein in your arm, called an intravenous or IV infusion.
2. through a syringe attached to a thin plastic tube and a needle, or just a syringe with a needle, injected under the skin in your thigh, called a subcutaneous or SC injection.

Please answer the following questions about your experiences and your preferences.

There are no right or wrong answers.

1) All things considered, which route of administration did you prefer?

☐ IV ☐ SC ☐ No preference

2) If you have a preference for one of the administration routes, how strong is this preference?

☐ Very strong ☐ Fairly strong ☐ Not very strong

3) If you have a preference for one of the administration routes, what are the **TWO** main reasons for your preference?

☐ Feels less emotionally distressing

☐ Requires less time in the clinic

☐ Lower level of injection-site pain

☐ Feels more comfortable during administration

☐ Other reason; please specify: .....

Please use the space below for any other comments you would like to add:

.....

.....

Appendix 4: Patient-Reported Outcome Measures

Study Number:	Subject Number:	Visit Name: Cycle ☐☐ Day ☐☐
Site Number:	Date of Assessment:	

THERAPY ADMINISTRATION SATISFACTION QUESTIONNAIRE (TASQ-SC)*

Instructions: Cancer treatment can be given through an injection in your thigh.

Please answer the questions based on your most recent SC injection.

1. How satisfied or dissatisfied were you with the SC injection?

Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

2. How much pain did you experience at the site of the SC injection?

None	Mild	Moderate	Severe	Very Severe

3. How much swelling did you experience at the site of the SC injection?

None	Mild	Moderate	Severe	Very Severe

4. How much redness did you experience at the site of the SC injection?

None	Mild	Moderate	Severe	Very Severe

5. When receiving the SC injection, how restricted did you feel?

Not at all	A little bit	Somewhat	Quite a bit	Very much

6. How convenient is it for you to get your SC injection?

Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient

7. How bothered are you by the amount of time it takes to have the SC injection?

Not at all bothered	A little bothered	Moderately bothered	Quite bothered	Very bothered

8. Does setting up the SC injection mean you lose or gain time for other things?

Lost a lot of time	Lost some time	Neither lost nor gained time	Gained some time	Gained a lot of time

Respondent Initials: _____ Date: _____

Appendix 4: Patient-Reported Outcome Measures

Study Number:	Subject Number:	Visit Name: Cycle ☐☐ Day ☐☐
Site Number:	Date of Assessment:	

9. When you receive the SC injection treatment, are you able to talk to your nurse and/or doctor as much as you would like about your illness? (please only check ONE answer)

- ☐ Yes, I had more than enough time to talk to my nurse and/or doctor.
- ☐ Yes, but I would have liked more time to talk to my nurse and/or doctor.
- ☐ It does not matter to me if I have time to talk to my nurse and/or doctor during my treatment.
- ☐ No, I did not have enough time to talk to my nurse and/or doctor.
- ☐ No, I did not talk to my nurse and/or doctor at all.

10. Does the SC injection impact the amount of time you have to talk to your nurse and/or doctor about your illness and other concerns?

Yes No

11. There are two ways to get cancer treatment:

a) IV infusion given through a port or small tube

b) SC (subcutaneous) injection in your thigh

Which would you prefer?

a) IV

b) SC

c) no preference

12. Would you recommend the way you received the treatment (SC injection) to another patient?

Definitely yes Probably yes I don't know Probably not Definitely not

Respondent Initials: _____ Date: _____

Appendix 4: Patient-Reported Outcome Measures

Study Number:	Subject Number:	Visit Name: Cycle ☐☐ Day ☐☐
Site Number:	Date of Assessment:	

THERAPY ADMINISTRATION SATISFACTION QUESTIONNAIRE (TASQ-IV)*

Instructions: Cancer treatment can be given through a port or a thin plastic tube and a needle that was put directly into a vein in your arm, called an intravenous or IV infusion.

Please answer the questions based on your most recent IV infusion.

1. How satisfied or dissatisfied were you with the IV infusion?

Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

2. How much pain did you experience at the IV site?

None	Mild	Moderate	Severe	Very Severe

3. How much swelling was there at the IV site?

None	Mild	Moderate	Severe	Very Severe

4. How much redness did you experience at the IV site?

None	Mild	Moderate	Severe	Very Severe

5. When receiving the IV infusion, do you feel restricted?

Not at all	A little bit	Somewhat	Quite a bit	Very much

6. How convenient is it for you to have your IV infusion?

Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient

7. How bothered are you by the amount of time it takes to have the infusion?

Not at all bothered	A little bothered	Moderately bothered	Quite bothered	Very bothered

8. Does setting up the IV infusion mean you lose or gain time for other things?

Lost a lot of time	Lost some time	Neither lost nor gained time	Gained some time	Gained a lot of time

Respondent Initials: _____ Date: _____

Appendix 4: Patient-Reported Outcome Measures

Study Number:	Subject Number:	Visit Name: Cycle ☐☐ Day ☐☐
Site Number:	Date of Assessment:	

9. When you receive the IV infusion treatment, are you able to talk to your nurse and/or doctor as much as you would like about your illness? (please only check ONE answer)

- ☐ Yes, I had more than enough time to talk to my nurse and/or doctor.
- ☐ Yes, but I would have liked more time to talk to my nurse and/or doctor.
- ☐ It does not matter to me if I have time to talk to my nurse and/or doctor during my treatment.
- ☐ No, I did not have enough time to talk to my nurse and/or doctor.
- ☐ No, I did not talk to my nurse and/or doctor at all.

10. Does the IV infusion impact the amount of time you have to talk to your nurse and/or doctor about your illness and other concerns?

Yes No

11. There are two ways to get cancer treatment:

a) IV infusion given through a port or small tube

b) SC (subcutaneous) injection in your thigh

Which would you prefer?

a) IV

b) SC

c) no preference

12. Thinking about the IV treatment, would you recommend the way you received the treatment (IV infusion) to another patient?

Definitely yes Probably yes I don't know Probably not Definitely not

Respondent Initials: _____ Date: _____

Appendix 4: Patient-Reported Outcome Measures

EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE QUESTIONNAIRE C30

Do not reproduce or distribute: The Sponsor will provide sites with all instruments to be completed in this study.

Appendix 4: Patient-Reported Outcome Measures

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ | | | | ⌋
Your birthdate (Day, Month, Year): ⌊ | | | | | | | | ⌋
Today's date (Day, Month, Year): 31 ⌊ | | | | | | | | ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 5
Healthcare-Professional Reported Outcome Measures

HEALTHCARE PROFESSIONAL QUESTIONNAIRE-TREATMENT ROOM

Healthcare Professional Experiences and Preferences for either Atezolizumab Subcutaneous Injection or Atezolizumab Intravenous Infusion for the Treatment of Participants with Non–Small Cell Lung Cancer

HEALTHCARE PROFESSIONAL SURVEY – TREATMENT ROOM

This Qualitative Survey is to be completed by healthcare professionals (HCPs) that have had experience with administering both atezolizumab subcutaneous (SC) injections and atezolizumab intravenous (IV) infusions as part of the MO43576 clinical study.

An HCP is defined as any personnel involved in SC and IV processes. Assessment of patient chair time (see Table 1) includes atezolizumab IV or atezolizumab SC administration time and should be based on "time of day" measurements (min/h). Active HCP time will be measured for chronologically listed, pre-selected tasks (Table 2) for atezolizumab IV and atezolizumab SC processes, both in the Care Unit (time for administration) and drug preparation area (DPA, time for preparation). Active HCP time should be based on "stopwatch time" measurements (min/sec).

Table 1 Study definitions

Term	Definition
Patient chair time	Time between entry and exit of the infusion chair
Infusion duration	Time between initiation and completion of infusion
Active HCP time	Time actively dedicated by any staff member to pre-specified tasks
Treatment room	The place where atezolizumab IV or atezolizumab SC treatments are being administered
Drug preparation area	The place where atezolizumab IV reconstitution or atezolizumab SC is prepared before the actual drug administration takes place. Thus, "drug preparation area" can refer to the hospital pharmacy or to a special aseptic drug preparation area within the day oncology unit.

Table 2 Chronological listing of observed tasks

Task	Atezo IV	Atezo SC
Drug preparation area		
• Collection of atezolizumab (includes IV consumables and time to reach aseptic preparation area; and SC vial checks), reconstitution of IV atezolizumab, SC filling, sign-off of prepared IV atezolizumab bags/dispensed SC formulation	x	x
Treatment room		
• Installation of venous catheter/line flushing	x	
• Bringing IV bag to patient chair	x	
• Atezolizumab SC vial check and filling (if not done in drug preparation area)		x
• Connection of winged infusion set and priming		x
• Atezolizumab IV infusion initiations	x	
• Atezolizumab SC administration and immediate monitoring		x
• Patient monitoring during infusion	x	
• Disconnecting infusion/flushing line/disposing of materials	x	
• Disposing of atezolizumab SC vials, winged sets and syringes		x
• Patient monitoring post-infusion/post-injection (only "active" monitoring time in the treatment room to be collected)	x	x

[1] Generic task flow is represented, which may deviate from center practice.

[2] In the drug preparation area, the total time for all tasks combined should be recorded.

[3] In all centers, SC injection administration includes immediate monitoring for injection-related reactions.

IV, intravenous; SC, subcutaneous.

This survey will take approximately 5 minutes to complete.

You are being invited to complete this survey because your center is a MO43576 clinical study site.

Questions 1a–1f should be completed for every participant after administration of every cycle during the Treatment Cross-over Period of the study (Cycles 1–6, i.e., 3 cycles of atezolizumab IV followed by 3 cycles of atezolizumab SC or vice versa).

Questions 2–8 should be completed for each participant after administration of study treatment Cycle 6.

The objective of this survey is to obtain feedback from key HCPs within the care unit where atezolizumab is prepared and dispensed. We are interested in the following:

1. to understand perceived changes in the management of atezolizumab treatments at the healthcare center, as a result of the use of atezolizumab SC injection compared to atezolizumab IV infusion
2. to survey healthcare personnel's treatment preferences and perceptions of the time required to complete tasks associated with atezolizumab SC injection compared to atezolizumab IV infusion

Your confidentiality will be respected, and none of the information we receive will be used in a way that could identify you.

Study ID: _____

Site ID: _____

Participant ID: _____

Cycle Number: _____

Date of treatment: _____ **(dd/mm/yyyy)**

Healthcare Professional Respondent (please indicate):

☐ Nurse

☐ Pharmacy Technician/Pharmacist

☐ Oncologist

☐ Pulmonologist/Pneumologist

Other (specify): _____

DATE OF COMPLETION: / / (dd/mm/yyyy)

Experience with atezolizumab SC injection and atezolizumab IV infusion administration

Please complete Questions 1a–1f for each patient treatment cycle.

1a. Please indicate which treatment the estimates relate to:

☐ Atezolizumab SC (proceed to Q1e) ☐ Atezolizumab IV (proceed to Q1b)

1b. Did the patient have existing IV access?

☐ YES (proceed to Q1d) ☐ NO (proceed to Q1c)

1c. If new IV access was needed for this cycle of treatment, please indicate what type of IV access was provided and how long (in minutes) this took to set up (atezolizumab IV patients only)?

☐ central venous catheter

☐ PICC, peripherally inserted central catheter

☐ peripheral vein cannulation

..... (please estimate to the nearest minute)

1d. What type of existing IV access did the patient have?

☐ central venous catheter

☐ PICC, peripherally inserted central catheter

☐ peripheral vein cannulation

1e. How long (in minutes) did it take to administer the treatment, i.e., total infusion duration?

..... (please estimate to the nearest minute)

1f. How long (in minutes) was the patient in the Treatment Room for in total?

..... (please estimate to the nearest minute)

Please indicate any factors during the treatment in the Treatment Room that may have affected the timing estimate (if any):

.....

.....

.....

.....

.....

Impact on Clinical Management and Clinical Efficiency

2. If all atezolizumab IV infusions are switched to atezolizumab SC injections, please indicate how strongly you agree or disagree with each of the following statements[1]. When answering question 2, please only consider atezolizumab IV and atezolizumab SC and not other IV treatment options.

	One "X" only					
	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree	Not applicable
a. Patients will be moved outside of the infusion unit to receive atezolizumab SC injections (e.g. physician consultation room)						
b. Atezolizumab SC route will allow more flexible treatment scheduling (i.e. patient visits not confined to availability of infusion beds/chairs, patient visits not confined to certain atezolizumab treatment days)						
c. More patients will be treated in the infusion unit						
d. Waiting list for any atezolizumab IV treatment at the infusion unit will be reduced						
e. Staff resources will be re-distributed to other departments of the hospital (i.e. less staffing required within the infusion unit)						
f. There will still be sufficient interaction time between HCPs and patients (e.g. for patient education)						
g. Staff will spend more time for further professional education/development.						
h. Staff will dedicate more time to attending to administrative tasks for atezolizumab patients (e.g. efficient chart completion, appointment scheduling, returning patient phone calls, etc.)						
i. Patients will spend less time in the care unit						
j. Administration by atezolizumab SC injection is preferred by patients						
Please use this box to add any additional comments you have:						

1. Statements are hypotheses and not actual claims

[Please consider the standard practice at your site, even if the process deviates somewhat from what is described below.]

Looking back over the atezolizumab treatment sessions, please indicate based on your opinion which administration method:

3. Was most convenient for the patient

☐ Atezolizumab IV ☐ Atezolizumab SC ☐ no difference ☐ unsure

4. Was the best for optimizing patient care within your treatment center

☐ Atezolizumab IV ☐ Atezolizumab SC ☐ no difference ☐ unsure

5. Took the least amount of time from start of preparation to finish of administration (excluding observation period)

☐ Atezolizumab IV ☐ Atezolizumab SC ☐ no difference

6. Required least resource use for administration, for example nursing time, facility costs, equipment, etc.?

☐ Atezolizumab IV ☐ Atezolizumab SC ☐ no difference

7. Was preferred by patients?

☐ Atezolizumab IV ☐ Atezolizumab SC ☐ no difference ☐ unsure

8. How frequently would you offer or recommend atezolizumab SC administration to your patients in the future?

☐ always ☐ sometimes ☐ never

Please provide a reason for your choice of response to Q8:

.....
.....
.....
.....
.....

HEALTHCARE PROFESSIONAL QUESTIONNAIRE-DRUG PREPARATION ROOM

Healthcare Professional Experiences and Preferences for either Atezolizumab Subcutaneous Injection or Atezolizumab Intravenous Infusion for the Treatment of Participants with Non–Small Cell Lung Cancer

HEALTHCARE PROFESSIONAL SURVEY – PHARMACY/DRUG PREPARATION AREA

This Qualitative Survey is to be completed by healthcare professionals (HCPs) that have had experience with preparing both atezolizumab subcutaneous (SC) injections and atezolizumab intravenous (IV) infusions as part of the MO43576 clinical study.

An HCP is defined as any personnel involved in SC and IV processes. Assessment of patient chair time (see Table 1) includes atezolizumab IV or atezolizumab SC administration time and should be based on "time of day" measurements (min/h). Active HCP time will be measured for chronologically listed, pre-selected tasks (see Table 2) for atezolizumab IV and atezolizumab SC processes, both in the Care Unit (time for administration) and drug preparation area (DPA, time for preparation). Active HCP time should be based on "stopwatch time" measurements (min/sec).

Table 1 Study definitions

Term	Definition
Patient chair time	Time between entry and exit of the infusion chair
Infusion duration	Time between initiation and completion of infusion
Active HCP time	Time actively dedicated by any staff member to pre-specified tasks
Treatment room	The place where atezolizumab IV or atezolizumab SC treatments are being administered
Drug preparation area	The place where atezolizumab IV reconstitution or atezolizumab SC is prepared before the actual drug administration takes place. Thus, "drug preparation area" can refer to the hospital pharmacy or to a special aseptic drug preparation area within the day oncology unit.

Table 2 Chronological listing of observed tasks

Task	Atezo IV	Atezo SC
Drug preparation area		
• Collection of atezolizumab (includes IV consumables and time to reach aseptic preparation area; and SC vial checks), reconstitution of IV atezolizumab, SC filling, sign-off of prepared IV atezolizumab bags/dispensed SC formulation	x	x
Treatment room		
• Installation of venous catheter/line flushing	x	
• Bringing IV bag to patient chair	x	
• Atezolizumab SC vial check and filling (if not done in drug preparation area)		x
• Connection of winged infusion set and priming		x
• Atezolizumab IV infusion initiations	x	
• Atezolizumab SC administration and immediate monitoring		x
• Patient monitoring during infusion	x	
• Disconnecting infusion/flushing line/disposing of materials	x	
• Disposing of atezolizumab SC vials, winged sets and syringes		x
• Patient monitoring post-infusion/post-injection (only "active" monitoring time in the treatment room to be collected)	x	x

[1] Generic task flow is represented, which may deviate from center practice.

[2] In the drug preparation area, the total time for all tasks combined should be recorded.

[3] In all centers, SC injection administration includes immediate monitoring for injection-related reactions.

IV, intravenous; SC, subcutaneous.

This survey will take approximately 5 minutes to complete.

You are being invited to complete this survey because your center is a MO43576 clinical study site.

Questions 1a and 1b should be completed for every patient after administration of every cycle during the Treatment Cross-over Period of the study (Cycles 1–6, i.e., 3 cycles of atezolizumab IV followed by 3 cycles of atezolizumab SC or vice versa).

Question 2–4 should be completed for each patient after administration of study treatment Cycle 6.

The objective of this survey is to obtain feedback from key HCPs within the pharmacy/drug preparation area where atezolizumab is prepared and dispensed. We are interested in the following:

1. to understand perceived changes in the management of atezolizumab treatments at the healthcare center, as a result of the use of atezolizumab SC injection compared to atezolizumab IV infusion
2. to survey healthcare personnel's treatment preferences and perceptions of the time required to complete tasks associated with atezolizumab SC injection compared to atezolizumab IV infusion

Your confidentiality will be respected, and none of the information we receive will be used in a way that could identify you.

Study ID: _____

Site ID: _____

Participant ID: _____

Cycle Number: _____

Date of treatment: _____ **(dd/mm/yyyy)**

Healthcare Professional Respondent (please indicate):

☐ Nurse

☐ Pharmacist/Pharmacy technician

☐ Oncologist

Other (specify): _____

DATE OF COMPLETION: / / (dd/mm/yyyy)

Experience with atezolizumab SC and atezolizumab IV infusion Dispensing and Preparation

Please complete Questions 1a and 1b for each patient treatment cycle.

1a. Please indicate which treatment preparation the estimates relate to:

☐ Atezolizumab SC ☐ Atezolizumab IV

1b. How long did it take to prepare the treatment for use?

..... (please estimate to the nearest minute)

Please indicate any factors during the preparation that may have affected the timing estimate (if any):

.....
.....
.....
.....
.....

2. If all atezolizumab IV infusions are switched to atezolizumab SC injections, please indicate how strongly you agree or disagree with each of the following statements[1]. When answering question 3, please only consider atezolizumab IV and atezolizumab SC and <u>not</u> other IV treatment options.

	One "X" only					
	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree	Not applicable
a. Staff will have increased availability for other tasks in the pharmacy (e.g. reconstituting other drugs, performing more frequent or timely inventory checks, more timely responses to queries from other departments, etc.)						
b. Administrative procedures around atezolizumab SC will require less time (i.e. worksheet, release form, labels, etc.)						
c. Atezolizumab SC formulations will provide more flexibility for pharmacy staff in managing their workload						
d. Due to ready-to-use, atezolizumab SC formulations, potential dosing errors will be avoided						
e. Due to ready-to-use atezolizumab SC formulations, there will be less drug wastage (e.g. IV bag already reconstituted but not used, or not used/leftover drug in IV vial)						
f. Without having to reconstitute the drug, less storage space for atezolizumab SC related supplies will be required in the pharmacy						
g. Preparation procedures and associated time staff time commitment will be reduced						
h. It will ease drug administration for patients with difficult venous access						
Please use this box to add any additional comments you have:						

1. Statements are hypotheses and not actual claims

Looking back over the atezolizumab drug preparation sessions, please indicate which administration method:

3. Was quickest from start to end of preparation to finish of administration (excluding observation period)

☐ Atezolizumab IV ☐ Atezolizumab SC ☐ no difference

4. Required less resource use for preparation and administration, for example nursing time, facility costs, equipment, etc.?

☐ Atezolizumab IV ☐ Atezolizumab SC ☐ no difference

Appendix 6
EuroQol EQ-5D-5L

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

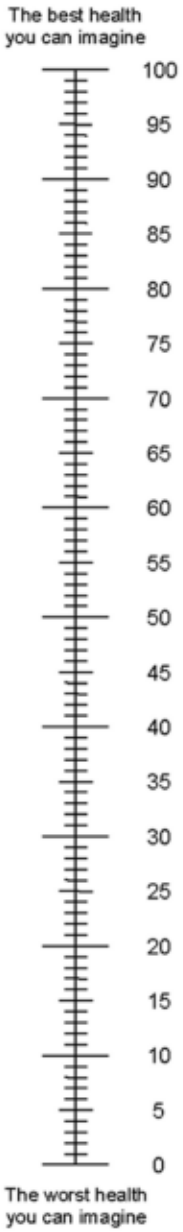
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 7
Preexisting Autoimmune Diseases and Immune Deficiencies

Participants should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Participants 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 participants with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Participants 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 participants 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 as needed.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Anti-phospholipid 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 8
Anaphylaxis Precautions

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

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

1. Stop the study treatment administration, if possible.
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 and IV fluids as required by participant status and as directed by the physician in charge.
6. Continue to observe the participant and document observations.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Although *toxicities* observed with atezolizumab have been mild and self-limiting, *they* 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.

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in participants experiencing toxicity considered to be related to study treatment. *Management guidelines for patients who experience adverse events associated with atezolizumab are provided in* Table 1. 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.

Table **1** *Dose Modification and* **Management Guidelines** *for Patients Who Experience Adverse* **Events** *Associated with Atezolizumab*

GENERAL GUIDANCE

Early Recognition and Close Monitoring:
Patients and family caregivers should receive timely and up-to-date information 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. Irrespective of severity grade, patients presenting with adverse events should be monitored closely and referred promptly to specialists for evaluation. Initiate treatment as per institutional guidelines and supportive care measures as deemed necessary.

Adverse Event Management Guidance–Use of Corticosteroids and/or Immunosuppressants:
For Grade 1 events, atezolizumab therapy should be continued with close monitoring of the affected organ function (including but not limited to TSH, liver function tests, blood glucose, creatinine, urine protein, amylase, and lipase), with exceptions specified below. For Grade ≥2 events, initiate treatment with high-dose corticosteroids (1–2 mg/kg/day oral prednisone/IV methylprednisolone or equivalent) as clinically indicated (see the table below). If symptoms do not improve within 48 hours of high-dose corticosteroid use, other immunosuppressants may be considered. 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. For toxicities not described below, refer to the current standard clinical practice/management guidelines of immune checkpoint inhibitor-related toxicities including but not limited to those provided by a professional society (e.g., NCCN, ESMO, SITC, and ASCO).

Action to be Taken with Atezolizumab:
For Grade 1 events, atezolizumab therapy should be continued. Consider withholding atezolizumab for most Grade 2 toxicities unless specified below. Withhold for all Grade 3 toxicities. Permanently discontinue for Grade 4 toxicities, with the exception of endocrinopathies that are controlled by hormone-replacement therapy. Atezolizumab can be withheld for up to 12 weeks after event onset. If atezolizumab is withheld for >12 weeks, the patient should be discontinued from atezolizumab. However, atezolizumab may be withheld for >12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment.
For events, symptoms, and/or laboratory values that resolve to Grade 1 or better, resume atezolizumab. For events that do not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event, with exceptions listed below. The decision to rechallenge 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.

Appendix 9: Management of Adverse Events Associated with Atezolizumab

Event	*CTCAE Toxicity Grade or Condition*	*Action to be Taken with Atezolizumab*	*Adverse Event Management [guidance in addition to the general recommendations provided above]*
Pulmonary event	*Grade 1*	• *For pneumonitis, consider withholding and resuming on radiographic evidence of improvement.*	• *Re-evaluate on serial imaging.*
	Grade 2	• *Withhold.*	• *Consider bronchoscopy or BAL with or without transbronchial biopsy.* • *Initiate treatment with high-dose oral corticosteroids, followed by taper.*
	Grade 2 recurrent/not improving after 48–72 hours of corticosteroids or Grades 3–4	• *Permanently discontinue.* • *In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.*	• *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 high-dose IV corticosteroids, followed by taper when event resolves to Grade 1 or better.* • *If event does not improve, consider adding an immunosuppressive agent.*
Hepatic event	*Guidelines for patients **without** hepatocellular carcinoma*		
	Grade 2	***Events of >5 days' duration:*** • *Withhold.*	***All events:*** • *Monitor LFTs more frequently until return to baseline values.* ***Events of >5 days' duration:*** • *Initiate treatment with high-dose oral corticosteroids.*

	Grades 3–4	• *Permanently discontinue.*	• *Consider liver biopsy to establish etiology of hepatic injury.* • *Initiate treatment with high-dose oral corticosteroids, followed by taper when event resolves to Grade 1 or better.* • *If event does not improve, consider adding an immunosuppressive agent.*
	*Guidelines for patients **with** hepatocellular carcinoma*		
	AST/ALT is within normal limits at baseline and increases to >3 ×ULN to ≤10 ×ULN ***or*** *AST/ALT is >ULN to ≤3 ×ULN at baseline and increases to >5 ×ULN to ≤10 ×ULN* ***or*** *AST/ALT is >3 ×ULN to ≤5 ×ULN at baseline and increases to >8 ×ULN to ≤10 ×ULN*	• *Withhold.* • *If event resolves to baseline or to Grade 1 or better, resume.* • *If event does not resolve to baseline or to Grade 1 or better while withholding, permanently discontinue and contact the Medical Monitor.*	• *Monitor LFTs more frequently until return to baseline values.* • *For events of >5 days' duration, consider initiating treatment with high-dose oral corticosteroids.*
	AST or ALT increases to >10 ×ULN or	• *Permanently discontinue.*	• *Consider liver biopsy to establish etiology of hepatic injury.* • *Initiate treatment with high-dose oral corticosteroids, followed by taper when event resolves to baseline.*

	total bilirubin increases to >3 ×ULN		• *If event does not improve, consider adding an immunosuppressive agent.*
Diarrhea or colitis	*Grade 2*	• *Withhold.*	• *Initiate symptomatic treatment.* • *Endoscopy is recommended. This also applies to Grade 1 events if symptoms persist for >7 days.* • *If strong clinical suspicion for immune-mediated colitis, initiate empiric IV corticosteroids while waiting for definitive diagnosis.* • *For recurrent events or events that persist >5 days, initiate treatment with high-dose oral corticosteroids.* • *If event does not improve, consider adding an immunosuppressive agent.*
	Grade 3	• *Withhold.*	• *Order confirmatory biopsy.* • *Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper.* • *If event does not improve, consider adding an immunosuppressive agent.*
	Grade 4	• *Permanently discontinue.*	
Hypothyroidism	*Grade 2*	• *Consider withholding.* • *Resume when symptoms are controlled and thyroid function is improving.*	• *Initiate treatment with thyroid replacement hormone.*
	Grades 3–4	• *Withhold.* • *Resume when symptoms are controlled and thyroid function is improving.* • *Permanently discontinue and contact the Medical Monitor for life-threatening*	• *Initiate treatment with thyroid replacement hormone.* • *Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status).*

		immune-mediated hypothyroidism.	
Hyperthyroidism	*Grade 1 with TSH <0.1 mU/L or Grade 2*	• *Consider withholding.* • *Resume when symptoms are controlled and thyroid function is improving.*	• *Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed.*
	Grades 3–4	• *Withhold.* • *Resume when symptoms are controlled and thyroid function is improving.* • *Permanently discontinue and contact the Medical Monitor for life-threatening immune-mediated hyperthyroidism.*	
Symptomatic adrenal insufficiency	*Grades 2–4*	• *Withhold.* • *If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume.* • *If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding, permanently discontinue and contact the Medical Monitor.*	• *Perform appropriate imaging.* • *Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper.*
Hyperglycemia	*Grades 3–4 or patient has Type 1 diabetes*	• *Withhold.* • *Resume when symptoms resolve and glucose levels are stable.*	• *Initiate treatment with insulin.* • *Evaluate for diabetic ketoacidosis.*

Hypophysitis (pan-hypopituitarism)	*Grades 2–3*	• *Withhold.*	• *Perform brain MRI (pituitary protocol).* • *Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper.* • *Initiate hormone replacement if clinically indicated.*
	Recurrent hypophysitis or Grade 4	• *Permanently discontinue.*	
Ocular event	*Grade 1*	• *Continue.*	• *Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.*
	Persistent Grade 1 despite treatment or Grade 2	• *Withhold.*	
	Grades 3–4	• *Permanently discontinue.*	• *Initiate treatment with high-dose oral corticosteroids, followed by taper when event resolves to Grade 1 or better.*
Myocarditis or pericardial disorders	*Grades 2–4*	• *Permanently discontinue.* • *Atezolizumab should not be resumed after permanent discontinuation.*	• *Consider anti-arrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate.* • *Initiate treatment with higher-dose IV corticosteroids equivalent to 1 g/day IV methylprednisolone for 3–5 days and convert to high-dose oral corticosteroids upon improvement, followed by taper when event resolves to Grade 1 or better.* • *If event does not improve within 24 hours after initiating corticosteroids, consider adding an immunosuppressive agent.*

Amylase and/or lipase elevation	*Grade 2 with amylase and/or lipase >1.5–2.0 ×ULN*	• *Continue.*	• *For prolonged elevation (e.g., >3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone, followed by taper.*
	Grade 2 asymptomatic with amylase and/or lipase >2.0–5.0 ×ULN or Grades 3–4	• *Withhold.* • *For recurrent events, permanently discontinue.*	• *If no improvement, consider treatment with high-dose oral corticosteroids, followed by taper.*
Pancreatitis	*Grades 2–3*	• *Withhold.* • *For recurrent events, permanently discontinue.*	• *Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper.*
	Grade 4	• *Permanently discontinue.*	• *Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper when event resolves to Grade 1 or better.* • *If event does not improve, consider adding an immunosuppressive agent.*
Dermatologic event	*Grade 1*	• *Continue.*	• *Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).*
	Grade 2		• *Consider biopsy, if indicated.* • *Initiate treatment with topical corticosteroids.* • *Consider treatment with higher-potency topical corticosteroids if the event does not improve.* • *If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.*

	Grade 3	• *Withhold.*	• *If indicated, order a biopsy.* • *Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing to high-dose oral corticosteroids if event does not improve within 48–72 hours, followed by taper.*
	Grade 4	• *Permanently discontinue.*	
Stevens-Johnson syndrome or toxic epidermal necrolysis	*Any grade suspected event*	• *Withhold.*	• *Confirm diagnosis by referring the patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy.* • *Follow the applicable treatment/management guidelines of dermatologic events above.*
	Any grade confirmed event	• *Permanently discontinue.* • *Atezolizumab should not be resumed after permanent discontinuation.*	
Neuropathy, including facial paresis	*Grade 2*	• *Withhold.* *For facial paresis:* • *If event resolves fully, resume.* • *If event does not resolve fully while withholding, permanently discontinue.*	• *Investigate etiology.* *For facial paresis:* • *Initial observation OR initiate high-dose oral corticosteroids (if progressing from mild). Initiate treatment with gabapentin, pregabalin, or duloxetine, for pain.*
	Grades 3–4	• *Permanently discontinue.*	• *Proceed as per Guillain-Barré syndrome management.*
Myasthenia gravis and Guillain-Barré syndrome	*Any grade*	• *Permanently discontinue.* • *Atezolizumab should not be resumed after permanent discontinuation.*	• *Consider initiation of high-dose oral or IV corticosteroids, followed by taper.* • *Consider IVIG or plasmapheresis in patients with rapid progression with development of bulbar and/or respiratory symptoms.* • *In life-threatening cases, consider higher-dose IV methylprednisolone 1 g/day for 3–5 days and other immunosuppressive agents.*

Myelitis	*Grade 1*	• *Continue unless symptoms worsen or do not improve.*	• *Investigate etiology.*
	Grade 2	• *Permanently discontinue.*	• *Investigate etiology and rule out infection.* • *Initiate treatment with high-dose oral corticosteroids, followed by taper.*
	Grades 3–4	• *Permanently discontinue.* • *Atezolizumab should not be resumed after permanent discontinuation.*	• *Initiate non-opioid treatment (e.g., pregabalin, gabapentin, duloxetine) for pain.* • *Hospitalize patient.* • *Initiate treatment with IV corticosteroids equivalent to 1 g/day methylprednisolone.* • *If event does not improve or there is worsening of symptoms within 3 days, consider IVIG or plasmapheresis and manage as per institutional guidelines.*
Meningoencephalitis	*Any grade*	• *Permanently discontinue.* • *Atezolizumab should not be resumed after permanent discontinuation.*	• *Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper when event resolves to Grade 1 or better.* • *If event does not improve, consider adding an immunosuppressive agent.*
Renal event	*Grade 2*	• *Withhold.*	• *Initiate treatment with high-dose oral corticosteroids, followed by taper.*
	Grades 3–4	• *Permanently discontinue.*	• *Consider renal biopsy.* • *Initiate treatment with high-dose oral corticosteroids, followed by taper when the event resolves to Grade 1 or better.* • *If event does not improve, consider adding an immunosuppressive agent.*

Myositis	*Patients with possible myositis should be monitored for signs of myocarditis and myasthenia gravis.*		
	Grade 2	• *Withhold.*	• *Consider treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper.* • *If the event does not improve, consider adding an immunosuppressive agent.*
	Grade 3	• *Withhold.*	• *Initiate treatment with high-dose IV corticosteroids, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to oral corticosteroids upon improvement, followed by taper when event resolves to Grade 1 or better.* • *If event does not improve within 24–48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *Consider IVIG or plasmapheresis.*
	Recurrent Grade 3 or Grade 4	• *Permanently discontinue.* • *Atezolizumab should not be resumed after permanent discontinuation.*	
Suspected HLH [a]	*Not applicable*	• *Permanently discontinue.* • *Atezolizumab should not be resumed after permanent discontinuation.*	• *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, followed by taper when the event resolves to Grade 1 or better.* • *If the event does not respond to treatment within 24 hours, contact the Medical Monitor and initiate treatment as appropriate according to published guidelines.* [b]

IRR and CRS	*Grade 1 [c] fever [d] with or without constitutional symptoms*	• *Immediately interrupt infusion.* • *Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.* • *If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate.* • *If symptoms recur, discontinue infusion of this dose.*	• *Administer symptomatic treatment, [e] including maintenance of IV fluids for hydration.* • *In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2.* • *For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS.*
	Grade 2 [c] fever [d] with hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen [f] by nasal cannula or blow-by	• *Immediately interrupt infusion.* • *Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.* • *If symptoms recur, discontinue infusion of this dose.*	• *Administer symptomatic treatment. [e]* • *For hypotension, administer IV fluid bolus as needed.* • *Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.* • *Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS.* • *Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).* • *Consider anti-cytokine therapy.* • *Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact the Medical Monitor.* • *If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral*

			premedication with antihistamines, 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 [c] fever [d] with hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow oxygen [f] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• *Permanently discontinue. [g]*	• *Administer symptomatic treatment. [e]* • *For hypotension, administer IV fluid bolus and vasopressor as needed.* • *Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.* • *Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS.* • *Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).* • *Consider anti-cytokine therapy.* • *Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.*
	Grade 4 [c] fever [d] with hypotension requiring multiple vasopressors (excluding vasopressin)	• *Permanently discontinue. [g]*	• *Administer symptomatic treatment. [e]* • *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.*

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

ASCO =American Society of Clinical Oncology; ASTCT =American Society for Transplantation and Cellular Therapy; BAL =bronchoscopic alveolar lavage; BiPAP =bi-level positive airway pressure; CPAP =continuous positive airway pressure; CRS =cytokine release syndrome; CTCAE =Common Terminology Criteria for Adverse Events; ECMO =extracorporeal membrane oxygenation; eCRF =electronic Case Report Form; ESMO =European Society for Medical Oncology; HLH =hemophagocytic lymphohistiocytosis; ICU =intensive care unit; IRR =infusion-related reaction; IVIG =intravenous immunoglobulin; LFT =liver function test; MAS =macrophage activation syndrome; MRI =magnetic resonance imaging; NCCN =National Comprehensive Cancer Network; NCI =National Cancer Institute; SITC =Society for Immunotherapy of Cancer; VAD =ventricular assist device; ULN =upper limit of normal.

[a] *Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014).*

[b] *Refer to La Rosée (2015); Schram and Berliner (2015); La Rosée et al. (2019).*

[c] *Grading system for these management guidelines is based on ASTCT Consensus Grading Scale 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.*

[d] *Fever is defined as temperature ≥38 ℃ not attributable to any other cause. In patients who develop CRS and then receive antipyretic, 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.*

[e] *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.*

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

[g] *For subsequent infusions, 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 time may also be considered after assessing the benefit-risk ratio.*

[h] *Refer to Riegler et al. (2019).*

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Signature Page for Protocol - MO43576 - TECENTRIQ - v4 - Global/Core - Published
System identifier: RIM-CLIN-523023

Approval Task	[redacted] Company Signatory 27-Feb-2024 14:56:12 GMT+0000