

PROTOCOL

TITLE: A PHASE II, OPEN-LABEL, MULTICENTER,
SINGLE-ARM STUDY TO INVESTIGATE THE EFFICACY
AND SAFETY OF ATEZOLIZUMAB AS NEOADJUVANT
AND ADJUVANT THERAPY IN PATIENTS WITH STAGE
IB, II, IIIA OR SELECTED IIIB RESECTABLE AND
UNTREATED NON-SMALL CELL LUNG CANCER

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MEDICAL MONITOR: [REDACTED], PA-C, MMSc

SPONSOR: Genentech, Inc.

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PROTOCOL AMENDMENT APPROVAL

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Title
[REDACTED]

Approver's Name
[REDACTED]

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PROTOCOL AMENDMENT, VERSION 7: RATIONALE

The protocol has been amended to update the risks associated with the use of atezolizumab as per the Atezolizumab Investigator's Brochure v18. In addition, the protocol was updated to align text with the company's most recent model document. Sections throughout the protocol have been updated accordingly and include the following:

- The atezolizumab risk language was updated throughout to align with the Atezolizumab Investigator's Brochure v18 (Appendix 9).
 - Throughout the protocol, the term "immune-related hepatitis" was changed to "immune-mediated hepatitis."
- The following revisions were made to align text with the most recent internal model document:
 - A COVID-19 benefit-risk assessment was added as per a company policy enacted since version 6 of this protocol (Section 1.3).
 - Requirements for Medical Monitor approval of Investigator decisions concerning the handling of study treatment or other procedures were removed, and text was added indicating that Investigators may discuss situations with Medical Monitor for guidance (Sections 3.1.4 and 4.4.1; Appendices 1 and 2).
 - In the permitted therapies, the vaccinations (e.g., influenza, COVID-19) allowed were modified, and megestrol acetate (appetite stimulant) was added. In addition, the phrase "for adrenocortical insufficiency" was removed from the mineralocorticoid therapy (Section 4.4.1).
 - In the prohibited therapies, the text concerning live attenuated vaccines has been revised (Section 4.4.3).
 - Standard text concerning COVID-19 screening before and during study participation as well as text concerning the association between COVID-19 and cytokine-release syndrome (CRS) were added per a company policy enacted since version 6 of this protocol (Section 5.1).
 - Text concerning systemic immune activation was removed as this information is covered in Appendix 9 (Section 5.1.1).
 - The text concerning treatment interruptions was revised to include additional information concerning the acceptable length of treatment interruptions (Section 5.1.2.1).
 - A sentence was added to clarify how cases of late-onset cytokine reaction syndrome (CRS) are to be reported in the case report forms (Section 5.3.5.1).
 - The name of the reporting form, "Serious Adverse Event/Adverse Event of Special Interest Reporting" form, was changed to "Clinical Trial Adverse Event/Special Situations" form (Sections 5.4.2.1, 5.4.2.2, and 5.6).

- Language was added concerning collecting and reporting infant health information, if permitted by the site and both parents, of infants from a pregnancy occurring during the study or within 5 months after the final dose of atezolizumab (Sections 5.4.3.1 and 5.5.1).
- The phrase “and review” was added to source data verification (i.e., “source data verification and review”) (Section 7.3).
- In the final sentence concerning compliance, “and applicable local, regional, and nation laws” was added (Section 8.1).
- The term “a Child’s Informed Assent Form” was revised to “an Assent Form” (Section 8.2.).
- Additional references were added to support newly added text (Section 10).
- Minor updates were made to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) language (Appendix 6).

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

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PROTOCOL ACCEPTANCE FORM

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MEDICAL MONITOR: [REDACTED] PA-C, MMSc

SPONSOR: Genentech, Inc.

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 as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE: A PHASE II, OPEN-LABEL, MULTICENTER, SINGLE-ARM STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB AS NEOADJUVANT AND ADJUVANT THERAPY IN PATIENTS WITH STAGE IB, II, IIIA, OR SELECTED IIIB RESECTABLE AND UNTREATED NON-SMALL CELL LUNG CANCER

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TEST PRODUCT: Atezolizumab (RO5541267)

PHASE: II

INDICATION: Non-Small Cell Lung Cancer

SPONSOR: Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy and safety of atezolizumab in patients with non-small cell lung cancer (NSCLC). Specific primary and secondary objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
<ul style="list-style-type: none">To evaluate the efficacy of atezolizumab as neoadjuvant treatment for Stage IB, II, IIIA, and selected IIIB NSCLC	<ul style="list-style-type: none">Major pathologic response (defined as $\leq 10\%$ of viable tumor cells), scored by a pathologist, based on surgical resection as defined by prior studies (Hellmann et al. 2014)
Secondary Efficacy Objectives:	
<ul style="list-style-type: none">To evaluate the efficacy of atezolizumab as neoadjuvant treatment for Stage IB, II, IIIA, and selected IIIB NSCLCTo evaluate response to atezolizumab in patients with PD-L1-positive vs. PD-L1-negative tumorsTo evaluate the association of mutational load, neoantigen score, gene expression signatures, and response to atezolizumab	<ul style="list-style-type: none">Pathological response in PD-L1-positive and PD-L1-negative groupsInvestigator-assessed response rate per RECIST v1.1Response by:<ul style="list-style-type: none">Mutation loadNeoantigen scoreGene expression signatures

Objectives	Corresponding Endpoints
Exploratory Efficacy Objectives:	
<ul style="list-style-type: none"> To evaluate the efficacy of atezolizumab as neoadjuvant or adjuvant treatment 	<ul style="list-style-type: none"> OS and DFS
Safety Objectives:	
<ul style="list-style-type: none"> To evaluate the safety and tolerability of atezolizumab as neoadjuvant or adjuvant treatment 	<ul style="list-style-type: none"> Incidence of adverse events, with severity per NCI CTCAE v4.0
Exploratory Biomarker Objectives:	
<ul style="list-style-type: none"> To evaluate the immune response to atezolizumab and assess mechanisms of immune escape 	<ul style="list-style-type: none"> Assessment of immune response by flow cytometry, IHC, IF, and/or NGS, including but not limited to the characterization of T-cell subsets, NK cells, MDSC, and B cells in whole blood and tissue samples and to correlate with clinical outcome
<ul style="list-style-type: none"> To investigate changes in tumor cell infiltrate in tissue samples To study the association of gene expression or mutation profiles in tumor tissue and/or blood with clinical outcome Assessment of ctDNA in blood samples obtained pre-, post-neoadjuvant therapy and throughout surveillance after surgical resection and correlation with clinical outcome measures 	<ul style="list-style-type: none"> Pathological analyses of tissue samples pre- and post-neoadjuvant therapy, at disease progression or recurrence (if available)

ctDNA=circulating tumor DNA; DFS=disease-free survival; IF=immunofluorescence; IHC=immunohistochemistry; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0; NGS=next-generation sequencing; NK=natural killer (cells); NSCLC=non-small cell lung cancer; MDSC=myeloid-derived suppressor cell; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand 1; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; WES=whole exome sequencing.

This is a Phase II, open-label, single-arm study, designed to evaluate the efficacy of atezolizumab as a neoadjuvant therapy in patients with Stage IB, II, IIIA, or selected IIIB NSCLC scheduled for curative-intent resection by evaluating response to treatment. In addition, the safety of atezolizumab will be evaluated in this treatment setting. The study is also designed to investigate a number of laboratory correlative studies to further define the mechanism of anti-tumor activity of atezolizumab and several potential predictive biomarkers, which will help identify patients who are more likely to respond to treatment, and to aid in the design of future clinical trials. A strong correlation between PD-L1 expression and response to the anti-PD-1/PD-L1 antibodies has been demonstrated, indicating that PD-L1 is potentially useful as a predictive biomarker. Finally, the study will also include DFS and OS as exploratory endpoints.

Approximately 180 patients with NSCLC will be enrolled in this study at approximately 15 study centers in the United States. The study will be conducted in two parts, a Neoadjuvant Atezolizumab Therapy Phase and an Adjuvant Atezolizumab Therapy Phase. During the Neoadjuvant Atezolizumab Therapy Phase, approximately 180 patients with pathologically documented Stage IB, II, IIIA, and selected IIIB NSCLC and are eligible for surgical resection

with curative intent will be enrolled to receive two doses of atezolizumab as neoadjuvant therapy. Primary and secondary efficacy analyses, safety analyses, and exploratory biomarker analyses will be conducted on this cohort.

All patients who undergo surgery will enter a Surveillance period and will be monitored for disease recurrence using extended chest CT and serial blood samples for biomarker assessments for up to 2 years after surgery. Patients who do not undergo surgery will move to Survival Follow-up.

Patients who undergo surgery and receive adjuvant atezolizumab therapy will enter the Adjuvant Atezolizumab Therapy Phase. The Adjuvant Atezolizumab Therapy Phase is exploratory and will evaluate atezolizumab adjuvant therapy for up to a maximum of 12 months (up to 18 cycles) in patients who demonstrate clinical benefit (evidence of pathologic response or absence of radiographic progression) from the Neoadjuvant Atezolizumab Therapy Phase. After surgical resection, patients may receive SOC adjuvant chemotherapy (with or without radiation) before starting atezolizumab adjuvant therapy. Any adjuvant treatment (optional SOC chemotherapy \pm radiotherapy and/or adjuvant atezolizumab) will be done concomitantly with Surveillance.

For clarity of assessments during the Surveillance phase, patients will be grouped by adjuvant treatment:

- Subgroup A: No Adjuvant Treatment
- Subgroup B: Adjuvant Atezolizumab Treatment
- Subgroup C: SOC Chemotherapy (\pm Radiotherapy) Only
- Subgroup D: SOC Chemotherapy (\pm Radiotherapy) + Adjuvant Atezolizumab Treatment

Neoadjuvant treatment (Neoadjuvant Atezolizumab Therapy Phase) with atezolizumab 1200 mg q21d (one cycle=21 days) will be given for a maximum of 2 cycles, and adjuvant treatment (Adjuvant Atezolizumab Therapy Phase) with atezolizumab 1200 mg q21d will be given for maximum of 12 months.

Patients could be asked to consent to an optional prescreening tumor biopsy, which will then be used for tissue analysis if the patient is eligible to participate in the study based on pathologically documented NSCLC and other eligibility criteria. This prescreening consent form also includes optional collection of bronchial brushing samples and lymph nodes (see Section 4.5.8 and Appendix 3 for details of sample collection).

Additionally, patients whose disease progresses or recurs anytime between the neoadjuvant phase and end of surveillance period will be asked to consent to an optional tissue biopsy (tumor and lymph node, if available) at the time of progression/recurrence. Images will be collected at the time of progression and reviewed.

Patients will be closely monitored for safety and tolerability throughout the study. Safety assessments will include collection and monitoring of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Tumor tissue samples, normal lung parenchyma, whole blood samples, and optional lymph node samples will be collected for biomarker assessments.

After Surveillance completion, patients will enter the Survival Follow-up period and will be followed per SOC, but information on cancer-treatment, recurrence and survival will be collected every 6 months for up to 3 years after the patient receives the last dose of atezolizumab on study. Patients who discontinue the study due to adverse events will be followed until resolution or stabilization of the adverse event.

Neoadjuvant Atezolizumab Therapy Phase

During this phase of the study, patients will have their NSCLC assessed by CT scan of the chest (with IV contrast), PET/CT, and brain MRI (preferably with gadolinium). The CT and PET CT images will be collected and reviewed for further analyses. Brain imaging may be omitted for patients with clinical Stage IB tumors but should be obtained for patients with clinical Stages II, IIIA, and selected IIIB tumors. If brain MRI is not feasible for technical or patient-related reasons (e.g., pacemaker, severe claustrophobia), brain CT scan with IV contrast should be

obtained. Tumor biopsy, whole blood samples, optional lymph node samples, and optional bronchial brushings will be obtained before treatment with atezolizumab. Either archival or newly collected sections of tumor biopsy will be formalin-fixed and fresh frozen. Optional lymph nodes will be sectioned for preparation in media and formalin-fixed.

Pretreatment whole blood will be used for IMMUNOME, and processed for plasma, serum, normal control DNA, and peripheral blood mononuclear cells (PBMC) for correlative studies.

Patients will receive two doses of atezolizumab administered 3 weeks apart before surgical resection. Patients who have radiologic progression prior to the second dose will be discontinued from atezolizumab and the patient will not have surgical resection as part of this study.

Surgical Resection

Following induction therapy in the Neoadjuvant Atezolizumab Therapy Phase, patients will undergo surgical resection of the primary tumor and associated lymph nodes.

Repeat chest CT scan, PET/CT scan, and MRI of the brain will be obtained prior to surgical resection and collected for review.

Resection may be accomplished via an open or minimally invasive procedure (i.e., thoracotomy, sternotomy, clamshell or hemclamshell incisions; or video assisted thoracic surgery (VATS) or robotically assisted VATS.

Pathologic complete resection of the primary tumor (R0) should be performed. Anatomic resection via segmentectomy, lobectomy, bilobectomy or pneumonectomy is strongly preferred although wedge resection is acceptable for very small (2 cm or less) tumors located peripherally where wedge resection permits a wide margin (at least 1 cm in all directions).

Hilar and mediastinal lymph node dissection or sampling should be performed. For right sided resections, this involves at least lymph nodes from levels 4R, 7, 10R, and 11R. For left sided resections, this involves at least lymph nodes from levels 5/6, 7, 10L, and 11L. Patients in whom a complete resection is not achieved will be discontinued from the study and will be replaced.

Pathologic specimens will undergo standard histopathologic and immunohistochemical evaluation for lung cancer. Tumor, normal lung parenchyma, and draining lymph nodes will be harvested immediately after resection. Sections of tumor will be fresh frozen and formalin-fixed for correlative studies. Sections of lymph nodes will be freshly prepared in media and formalin-fixed for correlative studies. Sections of adjacent normal lung tissue will be formalin-fixed for correlative studies. Sections of tumor, adjacent normal lung tissue, and lymph node may be freshly dissociated for correlative studies.

Whole blood samples will be collected at the time of surgical resection for correlative studies. The blood will be used for IMMUNOME and processed for PBMC, plasma, and serum for correlative studies.

At the postoperative follow-up visit, patients whose tumors have not demonstrated evidence of pathologic response or who have radiographic progression will have an end-of-study treatment (atezolizumab) visit, after which they will enter Surveillance for 2 years then Survival Follow-up for 1 year.

Whole blood will be collected at postoperative follow-up visit and will be processed for plasma, serum, and PBMC for correlative studies.

Surveillance

All patients who undergo surgery will enter the Surveillance Period. During Surveillance, patients will be monitored by extended chest CT scans (including liver and adrenals). Whole blood will be collected for plasma and serum, and PBMCs (at selected timepoints) every 6 weeks to 3 months for 2 years for correlative studies. Upon completion of Surveillance, patients enter Survival Follow-up. Patients whose disease progresses or recurs during Surveillance will discontinue from Surveillance and enter Survival Follow-up.

For patients previously enrolled under Protocol Version 3 or earlier:

- If the patient re-consents under Protocol Version 4 > 3 months after the Post-surgery Visit: patient will not enter Surveillance and will follow the schedule of activities from Protocol Version 3.

- If the patient re-consents under Protocol Version 4 at any time between Screening and the Post-surgery Visit: patient will be offered to enter Surveillance and follow Protocol Version 4 schedule of activities.
- If the patient re-consents under Protocol Version 4 ≤ 3 months after the Post-surgery Visit: patient will be offered to enter Surveillance and follow Protocol Version 4 schedule of activities only if post-surgery baseline chest CT scan is available. If chest CT scan is not available, patient will follow the schedule of activities from Protocol Version 3.

Adjuvant Atezolizumab Therapy Phase

Patients whose tumors have evidence of pathologic response or lack of radiographic progression will be eligible for the Adjuvant Atezolizumab Therapy Phase, which will occur during the Surveillance period.

During this part of the study, patients will receive adjuvant atezolizumab for up to a maximum of 12 additional months (up to 18 cycles). Adjuvant atezolizumab treatment may be started directly after surgery or after adjuvant SOC chemotherapy (with or without radiation). Choice of adjuvant SOC chemotherapy will be at the discretion of the treating physician, depending on the disease stage, as deemed clinically appropriate. It is highly recommended that any adjuvant treatment be initiated within 120 days after surgery. Additionally, it is recommended that patients who receive SOC Chemotherapy (\pm Radiotherapy) initiate adjuvant atezolizumab within 60 days of SOC Chemotherapy \pm Radiotherapy (whichever occurs last). If adjuvant treatment is planned to start outside of the recommended window, *Investigators may discuss it with the Medical Monitor.*

Whole blood samples will be collected prior to infusion on adjuvant Cycle 1, Day 1. Subsequent blood samples will be collected during Surveillance and 30 days after the last dose for correlative studies. The blood will be processed for PBMC, plasma, and serum.

Optional bronchial brushings samples may be collected from patients undergoing bronchoscopy or EBUS at prescreening or screening and approximately 3–4 months after starting adjuvant atezolizumab treatment (Group D only).

For all patients whose disease progresses or recurs (confirmed by imaging) at any time between neoadjuvant treatment and surveillance may undergo an optional tissue biopsy (tumor and lymph node, if available) for correlative studies, which will require a separate ICF signature. A blood sample will also be collected at the time of disease progression/recurrence.

All patients will enter Survival Follow-up, which will cover new anti-cancer treatment, DFS, and OS for up to 3 years after the last dose of atezolizumab.

Data Review

A review committee will be used to review data as specified in the Pathology Review Charter and Steering Committee Charter. This committee will include Genentech study team members, study investigators, and may also include external consultants, as needed.

Number of Patients

Approximately 180 patients with NSCLC will be enrolled in this study at approximately 15 study centers in the United States.

Target Population

Inclusion Criteria

Neoadjuvant Atezolizumab Therapy Phase

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Able to comply with the study protocol, in the investigator's judgment
- Pathologically documented NSCLC

- Stage IB, II, IIIA, or selected IIIB, including T3N2 or T4 (by size criteria, not by mediastinal invasion) NSCLC (based on the 8th edition of the American Joint Committee on Cancer [AJCC] Non-Small Cell Lung Cancer Staging system). Note: Patients may be enrolled based on clinical stage, but documentation of nodal involvement by endobronchial ultrasound (EBUS) or mediastinoscopy for patients with clinical Stage II and IIIA disease is encouraged.
- Measurable disease, as defined by RECIST v1.1
- NSCLC must have a solid or subsolid appearance on CT scan and cannot have a purely ground glass opacity (GGO) appearance. For subsolid lesions, the tumor size (i.e., clinical T stage) should be measured based on the solid component only, exclusive of the GGO component
- Evaluated by the operating attending surgeon prior to study enrollment to verify that the primary tumor and any involved lymph nodes are technically completely resectable
- Adequate pulmonary function to be eligible for surgical resection with curative intent
 - Pulmonary function tests (PFTs) must have been performed within 6 months of planned resection and repeated at screening and should include lung volumes, spirometry, and a diffusion capacity. Abnormal PFTs may be further evaluated with quantitative ventilation/perfusion scanning or cardiopulmonary exercise testing. Postoperative percent predicted forced expiratory volume in 1 second (FEV1) and diffusion capacity must be $\geq 40\%$ and/or maximal oxygen consumption ($\text{VO}_2 \text{ max}$) should be $> 10 \text{ mL/kg/min}$.
- Adequate cardiac function to be eligible for surgical resection with curative intent
 - If clinically indicated, patients with underlying ischemic or valvular heart disease should be evaluated preoperatively by a cardiologist.
- Availability of at least 2 cores of a pre-treatment formalin-fixed, paraffin-embedded (FFPE) biopsy and at least 1 core of fresh frozen biopsy of the primary tumor (archival sample) or willing to undergo an additional core needle biopsy (CNB; preferred method) or EBUS, or bronchoscopy (acceptable alternative) to provide newly collected samples.
 - For core biopsies, needle sizes of 16–18 gauge are preferred. If a 19 gauge or smaller needle is used, consider adding another pass. In addition, to ensure a quality tissue sample, a rapid on-site evaluation (ROSE) methodology is highly recommended to evaluate the adequacy of the sample.
 - If sample is collected during EBUS, at least 3 passes are requested (19–22 gauge needle can be used)
- ECOG Performance Status of 0 or 1
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first dose of atezolizumab:
 - $\text{ANC} \geq 1500/\mu\text{L}$
 - Platelet count $\geq 100,000/\mu\text{L}$
 - Hemoglobin $\geq 9.0 \text{ g/dL}$; patients may be transfused to meet this criterion.
 - $\text{AST and ALT} \leq 2.5 \times \text{upper limit of normal (ULN)}$
 - Serum bilirubin $\leq 1.5 \times \text{ULN}$
 - Serum creatinine $< 3.0 \text{ mg/dL}$
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $< 1\%$ per year during the treatment period and for at least 5 months after the last dose of atezolizumab. Women must refrain from donating eggs during this same period.
 - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

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

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

Adjuvant Atezolizumab Therapy Phase

- ECOG Performance Status of 0 or 1
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained per SOC prior to the starting adjuvant atezolizumab in the Adjuvant Atezolizumab Therapy Phase:
 - ANC $\geq 1500/\mu\text{L}$
 - Platelet count $\geq 100,000/\mu\text{L}$
 - Hemoglobin $\geq 9.0 \text{ g/dL}$; patients may be transfused to meet this criterion
 - AST and ALT $\leq 2.5 \times \text{ULN}$
 - Serum bilirubin $\leq 1.5 \times \text{ULN}$
 - Serum creatinine $< 3.0 \text{ mg/dL}$

Exclusion Criteria

Neoadjuvant Atezolizumab Therapy Phase

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

- NSCLC that is clinically T4 by virtue of mediastinal organ invasion or Stage IIIB by virtue of N3 disease
- Any prior therapy for lung cancer, including chemotherapy, hormonal therapy, or radiotherapy, within 3 years
- Patients with prior lung cancer that have been in remission for < 3 years
- Prior treatment with anti-PD-1 or anti-PD-L1 therapies or pathway-targeting agents
- Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation
- Major surgical procedure within 28 days prior to Cycle 1, Day 1
- Malignancies other than the disease under study within 3 years prior to Cycle 1, Day 1, with the exception of patients with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per SOC management (e.g., Rai Stage 0 chronic lymphocytic leukemia, prostate cancer with Gleason score ≤ 6 , and prostate-specific antigen (PSA) $\leq 10 \text{ ng/mL}$, etc.)
- Treatment with systemic immunosuppressive medications (e.g., prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1

- Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea or premedication for contrast dye allergy) are eligible.
- The use of inhaled corticosteroids for chronic obstructive pulmonary disease (COPD) and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
- History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis
 - Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible.
 - Patients with controlled type 1 diabetes mellitus on a stable insulin regimen are eligible.
 - Patients with eczema, psoriasis, or lichen simplex chronicus or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible provided they meet the following conditions:
 - Rash must cover < 10% of body surface area (BSA)
 - Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, fluocinolone 0.01%, desonide 0.05%, alclometasone dipropionate 0.05%)
 - No acute exacerbations of underlying condition within the last 12 months (requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
- History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest CT scan
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, fatty liver, and inherited liver disease
- History of HIV infection
- Active hepatitis B (chronic or acute) defined as having a positive hepatitis B surface antigen (HBsAg) test at screening
 - Patients with past or resolved hepatitis B infection (defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test) are eligible.
- Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test and a positive HCV RNA test at screening
- Active tuberculosis
- Administration of a live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks before Cycle 1, Day 1 or at any time during the study
 - Influenza vaccination should be given during influenza season only (approximately October to March).
- Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1
 - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or COPD) are eligible.
- Treatment with an investigational agent for any condition within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer)
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Pregnant or lactating, or intending to become pregnant during the study

- Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of atezolizumab.

Adjuvant Atezolizumab Therapy Phase

- Progressive or recurrent disease as documented by CT (per RECIST v1.1 criteria) at the end of SOC adjuvant therapy
 - Patients with radiographic progression and no evidence of pathologic response of the study during the neoadjuvant phase are not eligible for the Adjuvant Atezolizumab Therapy Phase.

End of Study

The end of this study is defined as the date when the last data point required for survival follow-up is received from the last patient. This is expected to occur approximately 3 years after the last patient receives the last dose of adjuvant atezolizumab.

The Neoadjuvant Atezolizumab Therapy Phase will end when the last data point required for primary efficacy analysis (i.e., pathology evaluation at time of surgery) is obtained. This is expected to occur approximately 30 days after the last patient's surgery.

The Surveillance period will end 2 years after the post-surgery visit.

After completing neoadjuvant or adjuvant treatment with atezolizumab, patients will be followed for survival for up to 3 years. For patients that undergo surgery and enter Surveillance, time in surveillance will overlap with time in survival follow-up.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 6 years.

Investigational Medicinal Products

Test Product (Investigational Drug)

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

The dose of atezolizumab in this study will be 1200 mg administered by IV infusion q21d (one cycle=21 days).

In the Neoadjuvant Atezolizumab Therapy Phase, neoadjuvant treatment with atezolizumab 1200 mg will be given q21d (± 2 days) for a maximum of 2 cycles. In the Adjuvant Atezolizumab Therapy Phase, adjuvant treatment with atezolizumab 1200 mg will be given q21d (± 3 days) for maximum of 12 months.

Administration of atezolizumab will be performed on an outpatient basis in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

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

The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. If the patient had an infusion-related reaction during previous infusion, the subsequent infusion must be administered over 60 (± 15) minutes.

For the first infusion, the patient's vital signs should be measured within 60 minutes before the infusion and during and after the infusion, if clinically indicated. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and at the end of the infusion, as clinically indicated.

Patients may need to remain in the clinic post-infusion for monitoring of side effects, if needed.

Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Guidelines for the management of infusion-related reactions are provided in the protocol.

Statistical Methods

Efficacy Analyses

The primary and secondary efficacy analyses will include all enrolled patients who have received at least one dose of the study drug and who do not have EGFR or ALK mutant tumors (efficacy population).

Primary Efficacy Endpoint

The effectiveness of the atezolizumab will be assessed by major pathologic response rate in the efficacy population, excluding patients who have not received surgery after neoadjuvant treatment with atezolizumab. A statistical test of a single proportion of major pathologic response rate will be tested against the alternative that the rate is 15%. If the null hypothesis is rejected then this is evidence that the response rate exceeds 5% when atezolizumab is given before resection. The one-sided 95% confidence interval (CI) for major pathologic response will be reported.

Determination of Sample Size

The primary objective of this study is to determine the major pathologic response rate. If there is evidence that the major pathologic response rate is at least 15% then there will be further consideration for the testing of atezolizumab in neoadjuvant lung cancer. This is a single-arm study, and all patients will be treated with atezolizumab. The primary endpoint is assessed by a statistical test of a single proportion of responders against the simple alternative of 5% response. This design provides 95% statistical power to detect a difference of 10% (15% vs. 5%) at a significance level of 0.05 (1-sided test, variance of the test statistic calculated under the alternative hypothesis). To achieve this, approximately 180 patients will be enrolled in this study. At the final analysis (after 180 patients are enrolled), if there are at least 17 patients who respond then the statistical test rejects the null hypothesis of a 5% response rate in favor of a higher response rate.

This study includes one interim analysis to assess futility after 90 patients are assessed. The non-binding futility interim boundary satisfies conditional power of 0.30. Thus, the probability that the statistical test at the final analysis will be significant at the specified power and test level is at least 0.30, conditional on the data available at the time of the interim analysis. At the interim analysis, if there are seven or fewer responders out of 90 patients then the conditional power of the study drops below 0.30, and enrollment into the study may be terminated.

Differential response by PD-L1 status (positive vs. negative) will also be assessed. While the composition of PD-L1 status in this patient population is not known, the study will aim to include at least 60 PD-L1-positive patients. With 60 patients, the one-sided 95% CI excludes 20% if the major pathologic response rate is 30% (18 responders out of 60 patients). Final enrollment numbers may be expanded accordingly.

Interim Analyses

The interim analyses described below will be performed. The study will continue during the interim analyses.

Planned Interim Safety Analysis

There is not yet extensive data on the safety of thoracic surgical resections after treatment with checkpoint inhibitors. Therefore, after the first 30 patients who complete protocol-specified atezolizumab treatment and have undergone the planned surgical resection of their tumor, the patient cohort will be evaluated for tolerability and safety of the neoadjuvant regimen. If, at the time of the safety interim analysis, three or more patients have experienced Grade 5 adverse events related to protocol treatment, then the study will be discontinued.

Planned Interim Efficacy Analysis

The study includes one interim analysis to assess futility after 90 patients are assessed. The non-binding futility interim boundary satisfies conditional power at a cut-off of 0.30.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
BSA	body surface area
CNB	core needle biopsy
COPD	chronic obstructive pulmonary disease
COVID-19	<i>coronavirus disease 2019</i>
CR	complete response
CRO	contract research organization
CRS	<i>cytokine release syndrome</i>
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C _{trough}	trough concentration
DFS	disease-free survival
DLT	dose-limiting toxicity
EBUS	endobronchial ultrasound
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	U.S. Food and Drug Administration
FEV ₁	forced expiratory volume in 1 second
FFPE	formalin-fixed, paraffin-embedded
GGO	ground glass opacity
HLH	hemophagocytic lymphohistiocytosis
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICH	International Conference on Harmonisation
IF	immunofluorescence
IFN	<i>interferon</i>
IHC	immunohistochemistry
IL	<i>interleukin</i>
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
ITT	intent-to-treat
IRB	Institutional Review Board

Abbreviation	Definition
IV	Intravenous
IxRS	interactive voice/web response system
K-M	Kaplan-Meier
MAS	macrophage activation syndrome
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	<i>National Comprehensive Cancer Network</i>
NCI	National Cancer Institute
NGS	next-generation sequencing
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PFT	pulmonary function test
PK	pharmacokinetic
PR	partial response
q21d	every 21 days
q3w	every 3 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RT-PCR	reverse transcriptase polymerase chain reaction
SARS-Cov-2	<i>severe acute respiratory syndrome coronavirus 2</i>
SD	stable disease
SITC	<i>Society for Immunotherapy for Cancer</i>
SOC	standard of care
TKI	tyrosine kinase inhibitor
TNF	tumor necrosis factor
UBC	urothelial bladder cancer
UC	urothelial cancer
ULN	upper limit of normal
VATS	video assisted thoracic surgery
VO ₂	maximal oxygen consumption
WES	whole-exome sequencing

1. BACKGROUND

1.1 BACKGROUND ON NON-SMALL CELL LUNG CANCER

Lung cancer is the leading cause of cancer death worldwide. In the United States about 200,000 cases are diagnosed each year with approximately 150,000 deaths occurring and a progressive increase in mortality with age (Siegel et al. 2015). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers and is divided into squamous cell carcinoma, large cell carcinoma, and adenocarcinoma subtypes. The majority of patients present with advanced metastatic disease that cannot be cured with current therapies. A minority of patients (about 25%) present with localized disease that is sometimes (about 50%) cured by surgical resection. Of those not cured by surgical resection, the majority recur in distant sites that could not be detected prior to surgical resection. For these Stage IB–IIIA patients, the addition of systemic chemotherapy before or after surgery improved 5-year survival rates by about 5% (Pignon et al. 2008). Chemotherapy before surgery (neoadjuvant) results in slightly higher response rates compared to chemotherapy for advanced stages but there are essentially no complete responses (CRs). Recently, immunotherapy with antibodies that bind to checkpoint inhibitors such as programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) have been shown to produce long lasting responses in some patients with advanced NSCLC who were refractory to standard chemotherapy (Rizvi et al. 2015).

Subsequent randomized clinical trials showed that these antibodies produce superior survival compared to docetaxel chemotherapy in patients who progressed after systemic platinum doublet chemotherapy (Borghaei et al. 2015; Brahmer et al. 2015; Fehrenbacher et al. 2016). The clinical benefits were greater in patients with high PD-L1 expression although survival was similar to docetaxel even in patients lacking PD-L1 expression. Early studies with these antibodies in the first line therapy setting showed even better results especially in patients with high PD-L1 expression (Gettinger 2015; Garon et al. 2015). Because PD-L1 expression is a continuous variable and not a perfect predictive biomarker, many investigators are exploring other potential biomarkers of predictive therapeutic benefit. The number of mutations determined by whole-exome sequencing (WES) has been shown to perform as another potential predictive biomarker (Rizvi et al. 2015). The expression of many other genes and proteins is being explored, but this is complicated by the lack of tissue and a limited understanding of its association with objective response rates (ORR) and survival.

1.2 BACKGROUND ON ATEZOLIZUMAB

PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors PD-1 and B7.1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer (Blank et al. 2005; Keir et al. 2008). Binding of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of

T cells. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen-presenting cells can mediate downregulation of immune responses, including inhibition of T-cell activation and cytokine production (Butte et al. 2007; Yang et al. 2011).

Overexpression of PD-L1 on tumor cells and the tumor microenvironment has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvestigate tumor-specific T-cell immunity.

Atezolizumab (Tecentriq[®], formerly MPDL3280A) is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids), and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptors, PD-1 and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells. Direct targeting of PD-L1 leaves the PD-L2-PD-1 interaction intact, potentially avoiding effects on immune homeostasis.

Atezolizumab (Tecentriq[®]) is approved for the treatment urothelial carcinoma, non-small cell lung cancer, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

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

1.2.1 Summary of Nonclinical Studies

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were thus undertaken with atezolizumab.

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent

with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway and supported entry into clinical studies in patients.

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

1.2.2 Clinical Experience with Atezolizumab

Atezolizumab clinical data are available from multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies (see the Atezolizumab Investigator's Brochure for study descriptions).

Single agent safety and efficacy data in patients with lung cancer are presented below from the following studies:

- Study PCD4989g: A Phase Ia, multicenter, first-in-human, open label, dose escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion given every 3 weeks (q3w) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.
- Study GO28753 (POPLAR): A randomized, Phase II, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in PD-L1-unselected patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen.
- Study GO28754 (BIRCH): A Phase II, multicenter, single-arm study assessing the clinical benefit of atezolizumab as a single agent in PD-L1-selected patients with locally advanced or metastatic NSCLC
- Study GO28915 (OAK): A randomized, Phase III, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in PD-L1-unselected patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen.

1.2.2.1 Clinical Safety

Single-Agent Clinical Safety in Patients with Non-Small Cell Lung Cancer in Study PCD4989g

Study PCD4989g is a Phase Ia dose escalation and expansion study, in which atezolizumab is being used as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies, and provides significant data (with 629 safety-evaluable patients across all cancer types as of the data cutoff date of 15 December 2015) for the safety profile of atezolizumab as monotherapy.

Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of adverse events have been determined.

The safety profile of atezolizumab as a single agent is observed to be consistent across different indications, including small-cell lung cancer, NSCLC, urothelial bladder cancer

(UBC), renal cell carcinoma (RCC), melanoma, gastric cancer, colorectal cancer, head and neck cancer, breast cancer, and sarcoma.

Of the 629 patients across all cancer types in Study PCD4989g, 619 patients (98.4%) experienced at least one adverse event, including 444 patients (70.6%) who experienced one treatment-related adverse event. Commonly reported events (reported in $\geq 10\%$ of all patients) included fatigue, nausea, decreased appetite, diarrhea, constipation, dyspnea, pyrexia, and cough (see [Table 1](#)).

A total of 89 safety-evaluable patients with NSCLC received atezolizumab in Study PCD4989g. A total of 88 patients (98.9%) experienced at least one adverse event, including 67 patients (75.3%) with treatment-related adverse events, 35 (39.3%) patients with Grade 3–4 adverse events, 36 patients (40.4%) with serious adverse events, 5 patients (5.6%) who discontinued study drug due to an adverse event, and 1 death (1.1%).

The safety profile of the NSCLC cohort was consistent with the overall safety profile of all safety-evaluable patients in Study PCD4989g, as well as with the safety-evaluable patients with NSCLC who received atezolizumab monotherapy in other studies.

Table 1 Adverse Events Reported in $\geq 10\%$ of Patients in Study PCD4989g

Preferred Term	All Grades n (%)
Any adverse event ($\geq 10\%$ incidence)	592 (94.1%)
Fatigue	248 (39.4%)
Nausea	175 (27.8%)
Decreased appetite	166 (26.4%)
Diarrhea	141 (22.4%)
Constipation	136 (21.6%)
Dyspnea	135 (21.5%)
Pyrexia	134 (21.3%)
Cough	127 (20.2%)
Vomiting	124 (19.7%)
Anemia	121 (19.2%)
Back Pain	111 (17.6%)
Headache	104 (16.5%)
Asthenia	101 (16.1%)
Arthralgia	95 (15.1%)
Pruritus	89 (14.1%)
Rash	82 (13.0%)
Abdominal pain	77 (12.2%)
Edema peripheral	72 (11.4%)
Urinary tract infection	67 (10.7%)
Insomnia	66 (10.5%)
Dizziness	63 (10.0%)

Single-Agent Clinical Safety in Patients with Non-Small Cell Lung Cancer in Study GO28753 (POPLAR)

As of the 1 December 2015 data cutoff date, 142 patients with NSCLC were treated with atezolizumab as a fixed dose of 1200 mg IV q3w and 135 patients were treated with docetaxel 75 mg/m² IV q3w in Study GO28753. The frequency of patients with any reported adverse event regardless of attribution was 96% in both arms. Fewer patients in the atezolizumab arm (41%) experienced Grade 3–4 adverse events compared with the docetaxel arm (53%). For Grade 3–4 adverse events that were assessed as treatment-related, the difference was greater between the two arms (12% vs. 39%, respectively). The most common atezolizumab-related Grade 3 adverse events were pneumonia (2%) and increased aspartate aminotransferase (2%). No

atezolizumab-related Grade 4 events have been reported. Treatment-related adverse events reported in at least 10% of patients in either treatment arm are listed in [Table 2](#).

Table 2 Treatment-Related Adverse Events Reported in at Least 10% of Patients in Either Treatment Arm in Study GO28753 (POPLAR)

MedDRA Preferred Term	Atezolizumab (n = 142) No. (%)	Docetaxel (n = 135) No. (%)
Fatigue	55 (38.7%)	54 (40.0%)
Decreased appetite	49 (34.5%)	28 (20.7%)
Nausea	32 (22.5%)	45 (33.3%)
Cough	40 (28.2%)	33 (24.4%)
Dyspnoea	39 (27.5%)	27 (20.0%)
Constipation	31 (21.8%)	32 (23.7%)
Diarrhoea	25 (17.6%)	38 (28.1%)
Alopecia	3 (2.1%)	52 (38.5%)
Anaemia	25 (17.6%)	27 (20.0%)
Pyrexia	24 (16.9%)	16 (11.9%)
Vomiting	20 (14.1%)	18 (13.3%)
Asthenia	15 (10.6%)	22 (16.3%)
Arthralgia	22 (15.5%)	12 (8.9%)
Insomnia	22 (15.5%)	11 (8.1%)
Rash	16 (11.3%)	16 (11.9%)
Back pain	16 (11.3%)	11 (8.1%)
Myalgia	9 (6.3%)	18 (13.3%)
Musculoskeletal pain	19 (13.4%)	7 (5.2%)
Weight decreased	16 (11.3%)	9 (6.7%)
Haemoptysis	15 (10.6%)	8 (5.9%)
Pneumonia	17 (12.0%)	4 (3.0%)
Neuropathy peripheral	3 (2.1%)	16 (11.9%)
Neutropenia	2 (1.4%)	17 (12.6%)

Single-Agent Clinical Safety in Patients with Non-Small Cell Lung Cancer in Study GO28754 (BIRCH)

As of the 1 December 2015 data cutoff date, 659 patients with NSCLC have been treated with atezolizumab as a fixed dose of 1200 mg IV q3w. In Study GO28754, 93.8% patients experienced at least one adverse event, 65% of patients experienced one treatment-related adverse event, and 12% of patients experienced Grade ≥ 3 treatment-related adverse event.

Single-Agent Clinical Safety in Patients with Non-Small Cell Lung Cancer in Study GO28915 (OAK)

As of the July 2016 data cutoff date, 609 patients with NSCLC were treated with atezolizumab as a fixed dose of 1200 mg IV q3w and 578 patients were treated with docetaxel 75 mg/m² IV q3w in Study GO28915. Fewer patients in the atezolizumab arm (37%) experienced Grade 3–4 adverse events compared with the docetaxel arm (54%). For Grade 3–4 adverse events that were assessed as treatment-related, the difference was greater between the two arms (15% vs. 43%, respectively). Rates of immune-mediated adverse events were low in patients treated with atezolizumab—pneumonitis (1%), hepatitis (0.3%), and colitis (0.3%). Adverse event-related discontinuation rates were 8% with atezolizumab arm vs. 19% for docetaxel arm.

For additional information, refer to the Atezolizumab Investigator's Brochure.

Single-Agent Clinical Safety in Patients Undergoing Surgery

Based on the mechanism of action and known safety profile of atezolizumab, no major complications (pre or post-surgery) are anticipated. The most commonly reported immune-mediated events with atezolizumab are dermatologic reactions and laboratory abnormalities (changes in liver function tests and thyroid function tests). Given the protocol design, short timeframe from atezolizumab administration to surgery, and the known longer time to onset of such events, these events are considered unlikely in the Neoadjuvant Atezolizumab Therapy Phase of this study (see Section 1.3).

1.2.2.2 Clinical Activity

Anti-tumor activity, including Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)-based responses, have been observed in patients with different tumor types (including NSCLC, RCC, melanoma, gastric cancer, UBC, colorectal cancer, head and neck cancer, breast cancer, and sarcoma) treated with atezolizumab in Study PCD4989g.

Refer to the Atezolizumab Investigator's Brochure for details on clinical activity in all patients treated to date, regardless of tumor type.

Single-agent data from Studies PCD4989g and GO28754 (BIRCH), and data from the randomized Study GO28753 (POPLAR) in patients with advanced NSCLC are summarized below.

Single-Agent Clinical Activity in Patients with Non-Small Cell Lung Cancer in Study PCD4989g

As of the 02 December 2014 cutoff date, 88 patients with NSCLC in Study PCD4989g who received their first dose of atezolizumab by 21 October 2013 were evaluable for efficacy. The median age was 60.5 years; the group represented a heavily pre-treated patient population. RECIST responses (confirmed) were observed in 20 of 88 (22.7%) patients, inclusive of squamous and non-squamous histologies and across all treatment

cohorts (treatment dose levels: 1 to 20 mg/kg). A total of 8 of the 20 responding patients have continued to respond at the time of the clinical data cutoff.

Single-Agent Clinical Activity in Patients with Non-Small Cell Lung Cancer in Study GO28753 (POPLAR)

In Study GO28753 (POPLAR), demographic characteristics were comparable between the atezolizumab and docetaxel treatment arms in the intent-to-treat (ITT) population. The median age was 62 years in both treatment arms, and the majority of patients had one prior therapy (65% for atezolizumab and 67% for docetaxel), non-squamous histology (66% for atezolizumab and 66% for docetaxel), and Eastern Cooperative Oncology Group (ECOG) performance status of 1 (68% for atezolizumab and 68% for docetaxel). More females were enrolled in the docetaxel arm (35% vs. 47%).

At the primary analysis on 8 May 2015, there were 287 efficacy-evaluable patients (ITT population), 143 in the docetaxel arm and 144 in the atezolizumab arm. Median OS was 12.6 months for atezolizumab compared with 9.7 months for docetaxel (HR of 0.73; 95% CI: 0.53, 0.99). Increasing improvement in OS was associated with increasing PD-L1 expression. Survival was similar to docetaxel in patients lacking PD-L1 expression and improved with atezolizumab in both responders and non-responders. Progression-free survival (PFS) and ORR were similar between the two treatment arms in the ITT population (Fehrenbacher et al. 2016).

Single-Agent Clinical Activity in Patients with Non-Small Cell Lung Cancer in Study GO28754 (BIRCH)

In the BIRCH study, 659 PD-L1-selected patients with advanced NSCLC were treated with atezolizumab; 139 patients were naïve to prior chemotherapy (Cohort 1) and 520 patients had received at least one prior platinum-based chemotherapy regimen (Cohorts 2 and 3). ORR was 19% in Cohort 1 and 17% in the other two cohorts. The majority of responses were ongoing and duration of response and OS data were not mature (Besse et al. 2015).

Single-Agent Clinical Activity in Patients with Non-Small Cell Lung Cancer in Study GO28915 (OAK)

In the OAK study, demographic characteristics were comparable between the atezolizumab and docetaxel treatment arms in the ITT population. The majority of patients had one prior therapy (75% in both arms), non-squamous histology (74% in both arms), history of tobacco use (80% for atezolizumab and 83% for docetaxel), and ECOG Performance Status of 1 (64% for atezolizumab and 62% for docetaxel).

At the primary analysis, there were 850 efficacy-evaluable patients (ITT population): 425 in the docetaxel arm and 425 in the atezolizumab arm. Median OS in the ITT population was 13.8 months for atezolizumab compared with 9.6 months for docetaxel (HR of 0.73; 95% CI: 0.62, 0.87, $p=0.0003$). OS benefit was seen regardless of PD-L1 expression (HR of 0.75 in <1% PD-L1 expression population; 0.41 in $\geq 50\%$ tumor cell or

≥ 10% immune cell expression population) and was consistent across subgroups, including histology (HR of 0.73 for both), in patients with asymptomatic central nervous system metastases (HR of 0.54) and never smokers (HR of 0.71). PFS and ORR were similar between the two treatment arms in the ITT population (Rittmeyer et al. 2017).

1.2.2.3 Clinical Pharmacokinetics and Immunogenicity

On the basis of available preliminary PK data (0.03–20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥ 1 mg/kg. For the 1-mg/kg and 20-mg/kg dose groups, the mean apparent clearance and the mean volume of distribution under steady-state conditions had a range of 3.20 to 4.44 mL/kg and 48.1 to 65.7 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

Development of anti-therapeutic antibodies (ATAs) has been observed in patients in all cohorts in Study PCD4989g and was associated with changes in PK (namely, a reduction of atezolizumab C_{min} to below the PK assay lower limit of quantification), in some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses from 10 to 20 mg/kg. Patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between the detection of ATAs and adverse events, infusion reactions, or efficacy has been observed.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

It is hypothesized that administration of atezolizumab, an engineered IgG1 monoclonal antibody targeting PD-L1, will demonstrate a good safety profile and produce objective responses in clinical Stage IB-IIIA NSCLC, especially in tumors which express PD-L1 prior to resection. PD-L1 expression by tumor and immune cells results in impaired anti-tumor immune responses by inhibiting T-cell proliferation, cytokine production, and cytotoxic activity. As a result there is significant interest in developing therapeutics to block the immunosuppressive effects of PD-L1 and to identify patients who will benefit from this treatment strategy.

While the addition of adjuvant cisplatin based chemotherapy following surgical resection of early stage NSCLC has produced significant survival benefits (Pignon et al. 2008), rates of local and distant disease relapse leading to death remain unacceptably high. Studies show that neoadjuvant chemotherapy has approximately the same benefit as adjuvant (Felip et al. 2010). Thus, it is critical to investigate the use of atezolizumab and similar agents in treating early stage resectable disease where one can assess the immune environment before and after treatment. It is also critical to develop highly predictive biomarkers of benefit and to study the evolution of immune-related markers with treatment with atezolizumab.

There will be two parts to this study: the first part (Neoadjuvant Atezolizumab Therapy Phase) will evaluate the ability of atezolizumab, an engineered IgG1 monoclonal

antibody targeting PD-L1, to produce pathologic responses in the neoadjuvant setting in patients with early stage NSCLC who have a pretreatment biopsy.

The subsequent resection of tumors from these patients will allow determination of pathologic response rates and potential predictive biomarkers from the pretreatment biopsy and evolution of cancer-/immune-related markers associated with response in the tumor biopsy specimen after treatment.

The primary endpoint of the study will be major pathologic response rate (defined as $\leq 10\%$ of viable tumor cells) determined from the surgical resection (Hellmann et al. 2014). In addition, response rates according to RECIST v1.1 will be determined from chest CT scans obtained before and after the atezolizumab therapy and before surgical resection. The images will be collected for further analyses.

The Neoadjuvant Atezolizumab Therapy Phase will only include patients with Stage IB, II, IIIA, or selected IIIB disease and who are deemed suitable for surgical resection without metastatic disease but with sufficient material for initial biopsy to analyze biomarkers. Clinical staging of NSCLC is based on computed tomography (CT) of the chest and upper abdomen, positron emission tomography (PET) and brain CT or magnetic resonance imaging (MRI) to rule out metastatic disease and assess the potential for curative-intent resection. Resection represents the best chance for prolonged survival for patients with non-advanced NSCLC.

After surgical resection, routine clinical surveillance will involve repeated radiographic imaging and monitoring of clinical symptoms for disease recurrence. All patients that complete surgical resection, will be monitored for disease recurrence using extended CT scans with IV contrast every 6 weeks to 3 months. Blood samples will be obtained along with chest CT scans to explore the association of blood-based biomarkers, such as ctDNA positivity with clinical outcome, for up to 2 years. Early detection of biomarkers that predict relapse of disease may help identify personalized treatment options to limit disease recurrence for patients in the future. Blood-based assay approaches, such as detection of circulating tumor DNA (ctDNA), may represent an innovative tool to complement disease surveillance in NSCLC.

Following resection, the risk for relapse correlates with clinical and pathological stage, but the addition of cisplatin based adjuvant chemotherapy improves survival for patients with Stage II and IIIA disease (Pignon et al. 2008), and potentially for some Stage IB patients with lesions greater than 4 cm (Butts et al. 2010).

Therefore, this study will also include a second (exploratory) part, the Adjuvant Atezolizumab Therapy Phase, which will enroll patients who demonstrated clinical benefit (defined as evidence of pathologic response or absence of radiographic progression) with neoadjuvant atezolizumab, to receive up to 12 additional months of adjuvant atezolizumab. Patients can choose to receive standard-of-care (SOC) adjuvant

chemotherapy (with or without radiation) before receiving atezolizumab post-surgical resection.

There are little data to guide the duration of adjuvant immunotherapy in lung cancer. An ongoing Phase III study is evaluating 12 months of atezolizumab treatment after cisplatin-based chemotherapy in patients with completely resected Stage IB–IIIA NSCLC with high PD-L1 expression. Another Phase III study is currently recruiting patients with unresectable Stage III NSCLC to receive 1 year of consolidation anti-PD-1 therapy after definitive chemo-radiation. Adjuvant immunotherapy has also been explored in other solid tumors. Adjuvant immunotherapy treatment for 1 year with interferon alfa-2b prolongs the relapse-free interval and OS of high-risk resected melanoma patients (Kirkwood et al. 1996). One year of adjuvant anti-PD1 therapy is considered standard of care for resected melanoma based on the data from the CHECKMATE-238 study (Weber et al. 2017).

Follow-up of all patients will allow for exploration of atezolizumab treatment, as well as non-protocol specified, post-study cancer treatment, on long term survival outcomes, disease-free survival [DFS], overall survival [OS]) and further improve our understanding of predictive biomarkers.

Blood samples, tumor biopsies, normal lung parenchyma, lymph node samples, and bronchial brushings will also be obtained for secondary and exploratory laboratory studies to evaluate potential predictive and prognostic biomarkers and to assess the immune response to atezolizumab as detailed in Section 2.

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

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

Severe SARS-CoV-2 infection appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN)- γ (Merad and Martin 2020). While it is not known, there may be a

potential for an increased risk of an enhanced inflammatory response if a patient develops acute severe acute respiratory syndrome corona virus 2 (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 Comprehensive Cancer 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.

SITC 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 the efficacy and safety of atezolizumab in patients with NSCLC. Specific objectives and corresponding endpoints for the study are outlined in [Table 3](#).

Table 3 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
<ul style="list-style-type: none"> To evaluate the efficacy of atezolizumab as neoadjuvant treatment for Stage IB, II, IIIA, and selected IIIB NSCLC 	<ul style="list-style-type: none"> Major pathologic response (defined as $\leq 10\%$ of viable tumor cells), scored by a pathologist, based on surgical resection as defined by prior studies (Hellmann et al. 2014)
Secondary Efficacy Objectives:	
<ul style="list-style-type: none"> To evaluate the efficacy of atezolizumab as neoadjuvant treatment for Stage IB, II, IIIA, and selected IIIB NSCLC To evaluate response to atezolizumab in patients with PD-L1-positive vs. PD-L1-negative tumors To evaluate the association of mutational load, neoantigen score, gene expression signatures, and response to atezolizumab 	<ul style="list-style-type: none"> Pathological response in PD-L1-positive and PD-L1-negative groups Investigator-assessed response rate per RECIST v1.1 Response by: <ul style="list-style-type: none"> Mutation load Neoantigen score Gene expression signatures
Exploratory Efficacy Objectives:	
<ul style="list-style-type: none"> To evaluate the efficacy of atezolizumab as neoadjuvant or adjuvant treatment 	<ul style="list-style-type: none"> OS and, DFS
Safety Objectives:	
<ul style="list-style-type: none"> To evaluate the safety and tolerability of atezolizumab as neoadjuvant or adjuvant treatment 	<ul style="list-style-type: none"> Incidence of adverse events, with severity per NCI CTCAE v4.0
Exploratory Biomarker Objectives:	
<ul style="list-style-type: none"> To evaluate the immune response to atezolizumab and assess mechanisms of immune escape 	<ul style="list-style-type: none"> Assessment of immune response by flow cytometry, IHC, IF, and/or NGS, including but not limited to the characterization of T-cell subsets, NK cells, MDSC, and B cells in whole blood and tissue samples and to correlate with clinical outcome
<ul style="list-style-type: none"> To investigate changes in tumor cell infiltrate in tissue samples To study the association of gene expression or mutation profiles in tumor tissue and/or blood with clinical outcome Assessment of ctDNA in blood samples obtained pre-, post-neoadjuvant therapy and throughout surveillance after surgical resection and correlation with clinical outcome measures 	<ul style="list-style-type: none"> Pathological analyses of tissue samples pre- and post-neoadjuvant therapy, at disease progression or recurrence (if available)

Table 3 Objectives and Corresponding Endpoints (cont.)

ctDNA=circulating tumor DNA; DFS=disease-free survival; IF=immunofluorescence; IHC=immunohistochemistry; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0; NGS=next-generation sequencing; NK=natural killer (cells); NSCLC=non-small cell lung cancer; MDSC=myeloid-derived suppressor cell; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand 1; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; WES=whole exome sequencing.

3. STUDY DESIGN**3.1 DESCRIPTION OF THE STUDY****3.1.1 Overview of Study Design**

This is a Phase II, open-label, single-arm study, designed to evaluate the efficacy of atezolizumab as a neoadjuvant therapy in patients with Stage IB, II, IIIA, or selected IIIB NSCLC scheduled for curative-intent resection by evaluating response to treatment. In addition, the safety of atezolizumab will be evaluated in this treatment setting. The study is also designed to investigate a number of laboratory correlative studies to further define the mechanism of anti-tumor activity of atezolizumab and several potential predictive biomarkers, which will help identify patients who are more likely to respond to treatment, and to aid in the design of future clinical trials. A strong correlation between PD-L1 expression and response to the anti-PD-1/PD-L1 antibodies has been demonstrated (Brahmer et al. 2010; Garon et al. 2015; Vansteenkiste et al. 2015), indicating that PD-L1 is potentially useful as a predictive biomarker. Finally, the study will also include DFS and OS as exploratory endpoints.

Approximately 180 patients with NSCLC will be enrolled in this study at approximately 15 study centers in the United States. The study will be conducted in two parts, a Neoadjuvant Atezolizumab Therapy Phase and an Adjuvant Atezolizumab Therapy Phase. During the Neoadjuvant Atezolizumab Therapy Phase, approximately 180 patients with pathologically documented Stage IB, II, IIIA, and selected IIIB NSCLC and are eligible for surgical resection with curative intent will be enrolled to receive two doses of atezolizumab as neoadjuvant therapy. Primary and secondary efficacy analyses, safety analyses, and exploratory biomarker analyses will be conducted on this cohort.

All patients who undergo surgery will enter a Surveillance period and will be monitored for disease recurrence using extended chest CT and serial blood samples for biomarker assessments for up to 2 years after surgery. Patients who do not undergo surgery will move directly to Survival Follow-up.

Patients who undergo surgery and receive adjuvant atezolizumab therapy will enter the Adjuvant Atezolizumab Therapy Phase (see Section 3.1.4). The Adjuvant Atezolizumab Therapy Phase is exploratory and will evaluate atezolizumab adjuvant therapy for up to a maximum of 12 months (up to 18 cycles) in patients who demonstrate clinical benefit

(evidence of pathologic response or absence of radiographic progression) from the Neoadjuvant Atezolizumab Therapy Phase. After surgical resection, patients may receive SOC adjuvant chemotherapy (with or without radiation) before starting atezolizumab adjuvant therapy. Any adjuvant treatment (optional SOC chemotherapy \pm radiotherapy and/or adjuvant atezolizumab) will be done concomitantly with Surveillance.

For clarity of assessments during the Surveillance period, patients will be grouped by adjuvant treatment (See [Figure 2](#) and [Appendix 2](#)):

- Subgroup A: No Adjuvant Treatment
- Subgroup B: Adjuvant Atezolizumab Treatment
- Subgroup C: SOC Chemotherapy (\pm Radiotherapy) Only
- Subgroup D: SOC Chemotherapy (\pm Radiotherapy) + Adjuvant Atezolizumab Treatment

Neoadjuvant treatment (Neoadjuvant Atezolizumab Therapy Phase) with atezolizumab 1200 mg q21d (one cycle=21 days) will be given for a maximum of 2 cycles, and adjuvant treatment (Adjuvant Atezolizumab Therapy Phase) with atezolizumab 1200 mg q21d will be given for maximum of 12 months.

Patients could be asked to consent to an optional prescreening tumor biopsy, which will then be used for tissue analysis if the patient is eligible to participate in the study based on pathologically documented NSCLC and other eligibility criteria. This prescreening consent form also includes optional collection of bronchial brushing samples and lymph node samples (see Section [4.5.8](#) and [Appendix 3](#) for details of sample collection).

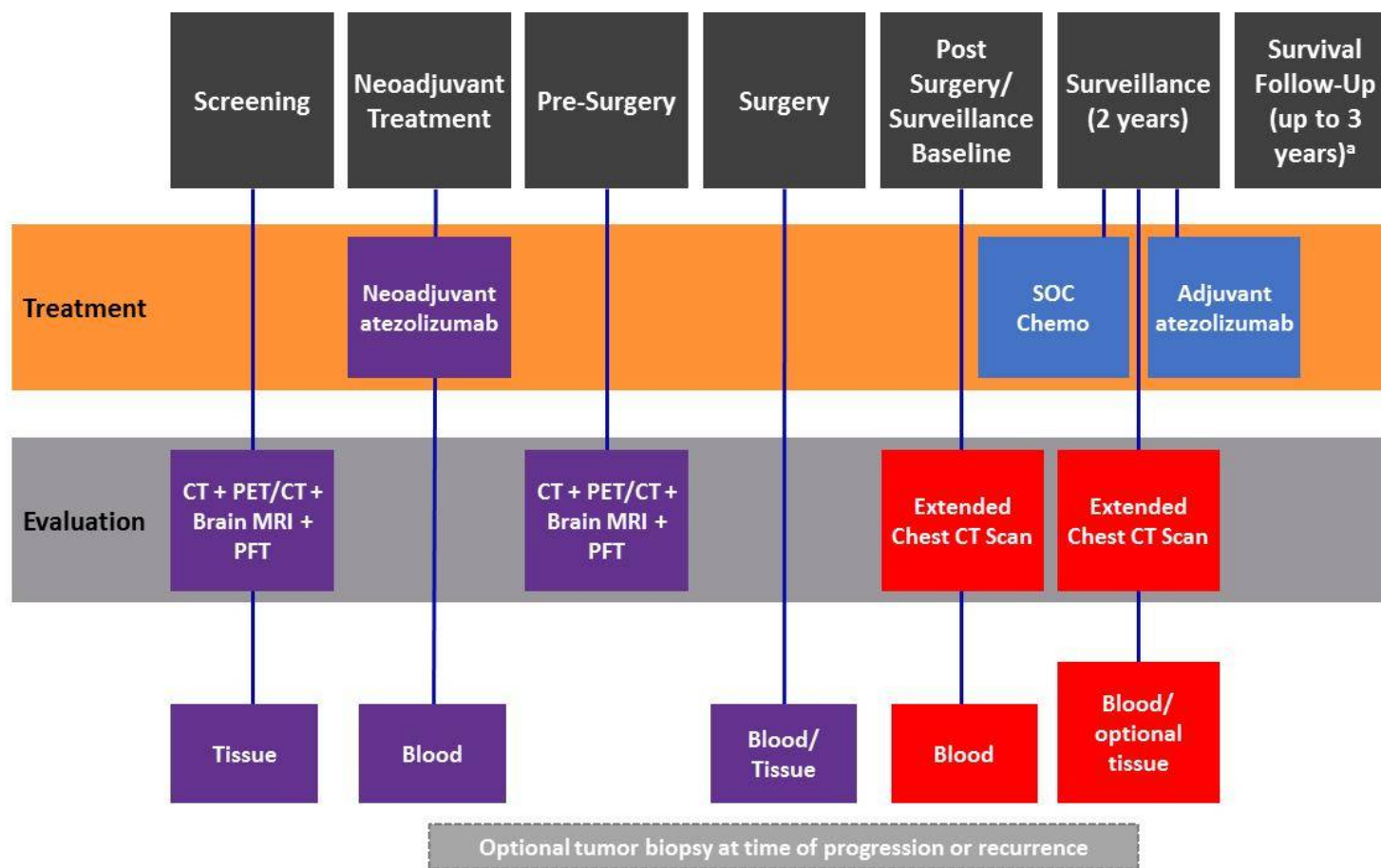
Additionally, patients whose disease progresses or recurs anytime between the neoadjuvant phase and end of Surveillance period will be asked to consent to an optional tissue biopsy (tumor and lymph node, if available) at the time of progression/recurrence. Images will be collected at the time of progression and reviewed.

Patients will be closely monitored for safety and tolerability throughout the study. Safety assessments will include collection and monitoring of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Tumor tissue samples, normal lung parenchyma, whole blood samples, and optional lymph node samples will be collected for biomarker assessments.

After Surveillance completion, patients will enter the Survival Follow-up period and will be followed per SOC, but information on off-protocol cancer treatment, recurrence and survival will be collected every 6 months for up to 3 years (see [Appendix 2](#)) after the patient receives the last dose of atezolizumab on study. Patients who discontinue the study due to adverse events will be followed until resolution or stabilization of the adverse event.

A schedule of activities is provided in [Appendix 1](#).

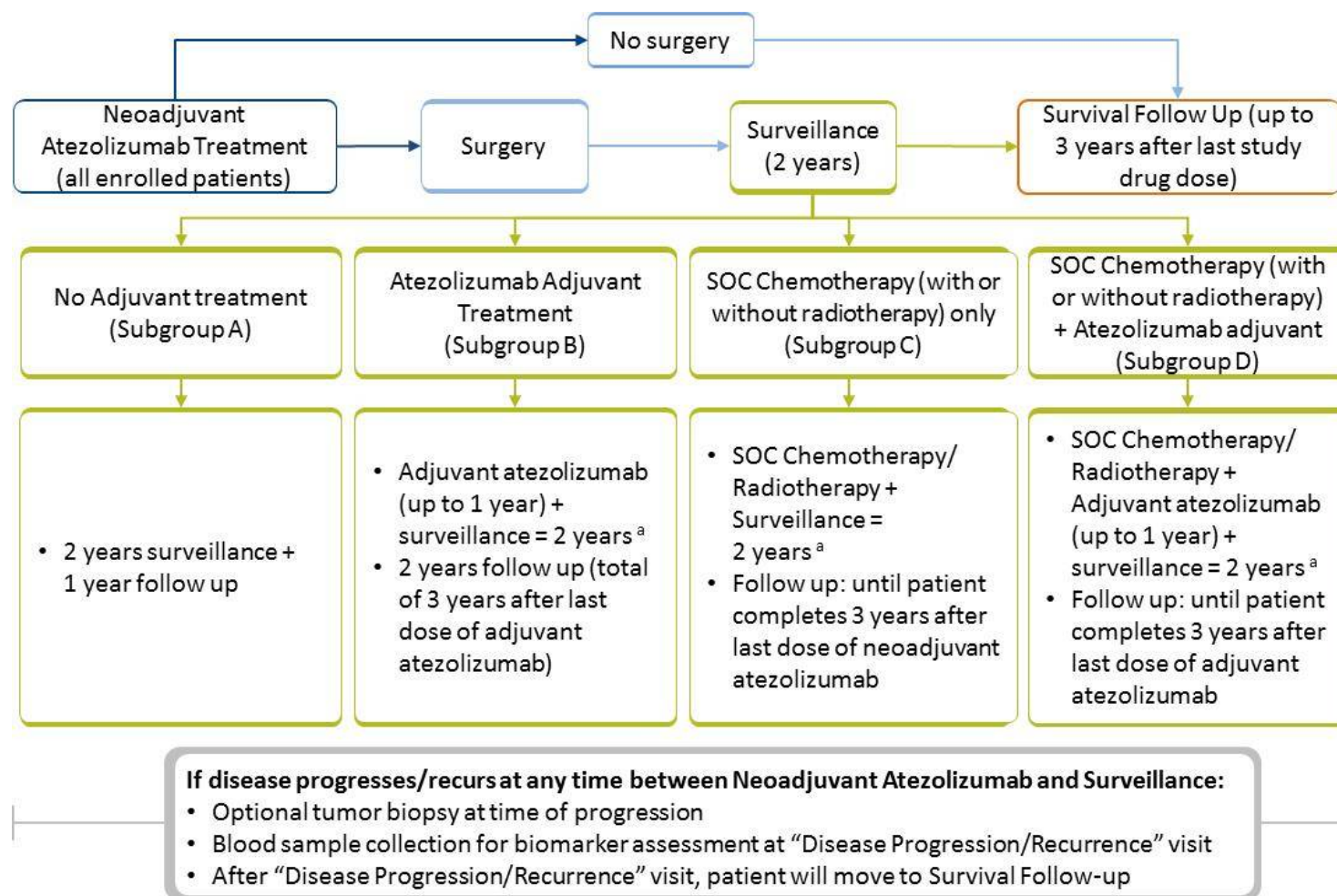
Figure 1 Study Schema



CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography; PFT=pulmonary function test; SOC=standard of care.

^a Refer to [Appendix 2](#).

Figure 2 Surveillance Flow Chart with Treatment Subgroups



^a Total Surveillance period = 2 years. If patient discontinues treatment for any reason, they should remain in Surveillance until they complete 2 years and then move to Survival Follow-up.

3.1.2 Neoadjuvant Atezolizumab Therapy Phase

During this phase of the study, patients will have their NSCLC assessed by CT scan of the chest (with IV contrast), PET/CT, and brain MRI (preferably with gadolinium). The CT and PET CT images will be collected and reviewed for further analyses. Brain imaging may be omitted for patients with clinical Stage IB tumors but should be obtained for patients with clinical Stages II, IIIA, and selected IIIB tumors. If brain MRI is not feasible for technical or patient-related reasons (e.g., pacemaker, severe claustrophobia), brain CT scan with IV contrast should be obtained. Tumor biopsy, whole blood samples, optional lymph node samples and optional bronchial brushings will be obtained before treatment with atezolizumab. Either archival or newly collected sections of tumor biopsy will be formalin-fixed and fresh frozen (see Section 4.1.1). Optional lymph nodes will be sectioned for preparation in media and formalin-fixed.

Pretreatment whole blood will be used for IMMUNOME, and processed for plasma, serum, normal control DNA, and peripheral blood mononuclear cells (PBMC) for correlative studies.

Patients will receive two doses of atezolizumab administered 3 weeks apart before surgical resection. Patients who have radiologic progression prior to the second dose will be discontinued from atezolizumab and the patient will not have surgical resection as part of this study.

Surgical Resection

Following induction therapy in the Neoadjuvant Atezolizumab Therapy Phase, patients will undergo surgical resection of the primary tumor and associated lymph nodes.

Repeat chest CT scan, PET/CT scan, and MRI of the brain will be obtained prior to surgical resection and collected for review.

Resection may be accomplished via an open or minimally invasive procedure (i.e., thoracotomy, sternotomy, clamshell or hemiclamshell incisions; or video assisted thoracic surgery (VATS) or robotically assisted VATS.

Pathologic complete resection of the primary tumor (R0) should be performed. Anatomic resection via segmentectomy, lobectomy, bilobectomy or pneumonectomy is strongly preferred although wedge resection is acceptable for very small (2 cm or less) tumors located peripherally where wedge resection permits a wide margin (at least 1 cm in all directions).

Hilar and mediastinal lymph node dissection or sampling should be performed. For right sided resections, this involves at least lymph nodes from levels 4R, 7, 10R, and 11R. For left sided resections, this involves at least lymph nodes from levels 5/6, 7, 10L, and 11L. Patients in whom a complete resection is not achieved will be discontinued from the study and will be replaced.

Pathologic specimens will undergo standard histopathologic and immunohistochemical evaluation for lung cancer. Tumor, normal lung parenchyma, and draining lymph nodes will be harvested immediately after resection. Sections of tumor will be fresh frozen and formalin-fixed for correlative studies (see [Appendix 3](#)). Sections of lymph nodes will be freshly prepared in media and formalin-fixed for correlative studies. Sections of adjacent normal lung tissue will be formalin-fixed for correlative studies. Sections of tumor, adjacent normal lung tissue and lymph node may be freshly dissociated for correlative studies.

Whole blood samples will be collected at the time of surgical resection for correlative studies. The blood will be used for IMMUNOME and processed for PBMC, plasma, and serum for correlative studies.

At the postoperative follow-up visit, patients whose tumors have not demonstrated evidence of pathologic response or who have radiographic progression will have an end-of-study treatment (atezolizumab) visit, after which they will enter Surveillance for 2 years then Survival Follow-up for 1 year.

Whole blood will be collected at postoperative follow-up visit and will be processed for plasma, serum, and PBMC for correlative studies.

3.1.3 Surveillance

All patients who undergo surgery will enter the Surveillance Period. During Surveillance, patients will be monitored by extended chest CT scans (including liver and adrenals). Whole blood will be collected for plasma and serum, and PBMCs (at selected timepoints), every 6 weeks to 3 months for 2 years for correlative studies (see [Appendix 2](#) for details). Upon completion of Surveillance, patients enter Survival Follow-up. Patients whose disease progresses or recurs during Surveillance will discontinue from Surveillance and enter Survival Follow-up.

For patients previously enrolled under Protocol Version 3 or earlier:

- If the patient re-consents under Protocol Version 4 >3 months after the Post-surgery Visit: patient will not enter Surveillance and will follow the schedule of activities from Protocol Version 3 (see [Appendix 11](#)).
- If the patient re-consents under Protocol Version 4 at any time between Screening and the Post-surgery Visit: patient will be offered to enter Surveillance and follow Protocol Version 4 schedule of activities.
- If the patient re-consents under Protocol Version 4 \leq 3 months after the Post-surgery Visit: patient will be offered to enter Surveillance and follow Protocol Version 4 schedule of activities only if post-surgery baseline chest CT scan is available. If chest CT scan is not available, patient will follow the schedule of activities from Protocol Version 3 (see [Appendix 11](#)).

3.1.4 Adjuvant Atezolizumab Therapy Phase

Patients whose tumors have evidence of pathologic response or lack of radiographic progression will be eligible for the Adjuvant Atezolizumab Therapy Phase, which will occur during the Surveillance period.

During this part of the study, patients will receive adjuvant atezolizumab for up to a maximum of 12 additional months (up to 18 cycles). Adjuvant atezolizumab treatment may be started directly after surgery or after adjuvant SOC chemotherapy (with or without radiation). Choice of adjuvant SOC chemotherapy will be at the discretion of the treating physician, depending on the disease stage, as deemed clinically appropriate. It is highly recommended that any adjuvant treatment be initiated within 120 days after surgery. Additionally, it is recommended that patients who receive SOC Chemotherapy (\pm Radiotherapy) initiate adjuvant atezolizumab within 60 days of SOC Chemotherapy \pm Radiotherapy (whichever occurs last). If adjuvant treatment is planned to start outside of the recommended window, *Investigators may discuss it with the Medical Monitor.*

Whole blood samples will be collected prior to infusion on adjuvant Cycle 1, Day 1. Subsequent blood samples will be collected during Surveillance (see Section 3.1.3) and 30 days after the last dose for correlative studies. The blood will be processed for PBMC, plasma, and serum.

Optional bronchial brushings samples may be collected from patients undergoing bronchoscopy or EBUS at prescreening or screening and approximately 3–4 months after starting adjuvant atezolizumab treatment (Group D only).

For all patients whose disease progresses or recurs (confirmed by imaging) at any time between neoadjuvant treatment and surveillance may undergo an optional tissue biopsy (tumor and lymph node, if available) for correlative studies, which will require a separate ICF signature (see Section 4.5.1). A blood sample will also be collected at the time of disease progression/recurrence.

All patients will enter Survival Follow-up, which will cover new anti-cancer treatment, DFS, and OS for up to 3 years after the last dose of atezolizumab (See Appendix 2 for details regarding time in Survival Follow-up).

3.1.5 Data Review

A review committee will be used to review data as specified in the Pathology Review Charter and Steering Committee Charter. This committee will include Genentech study team members, study investigators, and may also include external consultants, as needed.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last data point required for survival follow-up is received from the last patient. This is expected to occur approximately 3 years after the last patient receives the last dose of adjuvant atezolizumab.

The Neoadjuvant Atezolizumab Therapy Phase will end when the last data point required for primary efficacy analysis (i.e., pathology evaluation at time of surgery) is obtained. This is expected to occur approximately 30 days after the last patient's surgery.

The Surveillance period will end 2 years after the Post-surgery Visit.

After completing neoadjuvant or adjuvant treatment with atezolizumab, patients will be followed for survival for up to 3 years. For patients that undergo surgery and enter Surveillance, time in Surveillance will overlap with time in Survival Follow-up (see [Appendix 2](#)).

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 6 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Dose and Schedule

The fixed dose of 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) was selected on the basis of both nonclinical studies described in Section [1.2.1](#) and available clinical data from Study PCD4989g as described below.

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

The atezolizumab dose is also informed by available clinical activity, safety, pharmacokinetics, and immunogenicity data. Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg q21d. The MTD of atezolizumab was not reached, and no DLTs have been observed at any dose in Study PCD4989g. Currently available PK and ATA data suggest that the 15-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent) for Phase II and Phase III studies would be sufficient to both maintain $C_{trough} \geq 6$ µg/mL and further safeguard against both interpatient variability and the potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, moving further to the 20-mg/kg

atezolizumab q3w regimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15-mg/kg atezolizumab q3w level.

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

Refer to the Atezolizumab Investigator's Brochure for details regarding nonclinical and clinical pharmacology of atezolizumab.

3.3.2 Rationale for Patient Population

While the addition of adjuvant cisplatin based chemotherapy following surgical resection of early stage NSCLC has produced significant survival benefits (Pignon et al. 2008), rates of local and distant disease relapse leading to death remain unacceptably high. Studies show that neoadjuvant chemotherapy has approximately the same benefit as adjuvant (Felip et al. 2010). Recently, immunotherapy with antibodies that bind to checkpoint inhibitors such as PD-1 and PD-L1 have been shown to produce long lasting responses in some patients with advanced NSCLC who were refractory to standard chemotherapy (Brahmer et al. 2015). Therefore this study population was chosen to primarily determine the ability of atezolizumab to produce objective responses in patients undergoing curative intent surgery for Stage IB-IIIA NSCLC. This study will also explore impact of adjuvant atezolizumab on long term survival outcomes.

3.3.3 Rationale for Biomarker Assessments

It is currently thought atezolizumab functions through preventing suppression of CD8 cytotoxic T-cell function, but the details of this process as well as the impact of atezolizumab on additional immune cell populations is thus far undefined. Cancer can escape the immune system through multiple mechanisms including the manipulation of cells with immunosuppressive phenotypes. In addition, it has been shown that elements of both the innate and adaptive immune systems have anti-tumor functions. As a result, it is necessary to study the global immune modulatory effects of atezolizumab to further elucidate its mechanism of action in different patients with lung cancer.

Furthermore, it has been hypothesized that atezolizumab efficacy shown in smoking-associated lung cancer and melanoma is due to the high mutational burden of these diseases, leading to the generation of immune stimulating neoantigens. Recently, it has been shown that somatic mutations present within tumor cells are capable of eliciting tumor specific T-cell responses (Tran et al. 2014). The identification of somatic mutations in NSCLC producing immune stimulating mutant peptides may help to better select patients for treatment with atezolizumab and provide information about potential vaccine immunotherapy approaches. As mentioned previously, the number of mutations determined by WES has been shown to perform as another predictive biomarker (Rizvi

et al. 2015). Therefore, WES will be performed with comparison to control normal DNA to enable direct determination of mutational load and the spectrum of mutations present using tumor tissue and/or blood. In addition, atezolizumab is proposed to reverse exhaustive status of T-cell responses against cancer that was associated with PD-1 expression (Barber et al. 2006; Dong et al. 2002). The impact of such mutations on treatment with atezolizumab and similar agents is unknown, and their identification could help identify patients for treatment.

Tumor tissue samples will be obtained pre-treatment, at resection and at disease progression/recurrence (if available) for, including, but not limited to immunohistochemistry, immunofluorescence microscopy, next generation sequencing (e.g. RNA sequencing, whole exome sequencing, TCR sequencing). Furthermore, digital pathology and machine-learning approaches may be applied in this study to derive predictive histological signatures or to explore the applicability for digital assessment of major pathological response. Adjacent normal lung tissue may be obtained at resection to allow comparisons with the tumor immune microenvironment.

Whole blood and lymph nodes will be obtained to analyze, including but not limited to, changes in the phenotype and function of immune cell subtypes by flow cytometry and may be used, but not limited to assess T-cell receptor clonality by NGS, gene expression profiling and monitoring of anti-tumor immunity using functional assays.

After surgical resection, routine clinical surveillance involves repeated radiographic imaging and monitoring of clinical symptoms for disease recurrence. Blood-based biomarkers can help to better understand disease recurrence and improve the development of future adjuvant treatment options (Chaudhuri et al. 2017). Blood samples obtained during Surveillance will be used for serial ctDNA analysis by NGS and may include, but is not limited to, immune profiling by NGS or flow cytometry and functional T-cell assays.

Patients whose disease progresses or recurs anytime between the neoadjuvant phase and end of Surveillance will be asked to consent to an optional tissue biopsy (tumor and lymph node, if available) at the time of progression or recurrence. The biopsy may be used to explore if radiographic findings are consistent with histological presence of tumor and/or if the appearance of recurrence was caused by tumor immune infiltration. In addition, the tissue may be used for biomarker research to explore mechanisms of resistance and recurrence to therapy. This exploratory biomarker analysis will not be used for any treatment-related decisions.

See Section 2 for details for secondary and exploratory laboratory analyses.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 180 patients with histologically documented Stage IB, II, IIIA, and selected IIIB NSCLC and are eligible for surgical resection with curative intent will be enrolled in the Neoadjuvant Atezolizumab Therapy Phase of this study. Approximately 50 patients who complete neoadjuvant atezolizumab therapy are expected to continue on to the Adjuvant Atezolizumab Therapy Phase.

4.1.1 Inclusion Criteria

Neoadjuvant Atezolizumab Therapy

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age \geq 18 years
- Able to comply with the study protocol, in the investigator's judgment
- Pathologically documented NSCLC
 - Stage IB, II, IIIA, or selected IIIB, including T3N2 or T4 (by size criteria, not by mediastinal invasion) NSCLC (based on the 8th edition of the American Joint Committee on Cancer [AJCC] Non-Small Cell Lung Cancer Staging system; see [Appendix 4](#)). Note: Patients may be enrolled based on clinical stage, but documentation of nodal involvement by endobronchial ultrasound (EBUS) or mediastinoscopy for patients with clinical Stage II and IIIA disease is encouraged.
- Measurable disease, as defined by RECIST v1.1
- NSCLC must have a solid or subsolid appearance on CT scan and cannot have a purely ground glass opacity (GGO) appearance. For subsolid lesions, the tumor size (i.e., clinical T stage) should be measured based on the solid component only, exclusive of the GGO component
- Evaluated by the operating attending surgeon prior to study enrollment to verify that the primary tumor and any involved lymph nodes are technically completely resectable
- Adequate pulmonary function to be eligible for surgical resection with curative intent
 - Pulmonary function tests (PFTs) must have been performed within 6 months of planned resection and repeated at screening and should include lung volumes, spirometry, and a diffusion capacity. Abnormal PFTs may be further evaluated with quantitative ventilation/perfusion scanning or cardiopulmonary exercise testing. Postoperative percent predicted forced expiratory volume in 1 second (FEV1) and diffusion capacity must be \geq 40% and/or maximal oxygen consumption (VO₂ max) should be $>$ 10 mL/kg/min.

- Adequate cardiac function to be eligible for surgical resection with curative intent
 - If clinically indicated, patients with underlying ischemic or valvular heart disease should be evaluated preoperatively by a cardiologist.
- Availability of at least 2 cores of a pre-treatment formalin-fixed, paraffin-embedded (FFPE) biopsy and at least 1 core of fresh frozen biopsy of the primary tumor (archival sample) or willing to undergo an additional core needle biopsy (CNB; preferred method), EBUS, or bronchoscopy (acceptable alternatives) to provide newly collected samples.
 - For core biopsies, needle sizes of 16–18 gauge are preferred. If a 19 gauge or smaller needle is used, consider adding another pass. In addition, to ensure a quality tissue sample, a rapid on site evaluation (ROSE) methodology is highly recommended to evaluate the adequacy of the sample.
 - If sample is collected during EBUS, at least 3 passes are requested (19–22 gauge needle can be used)
- ECOG Performance Status of 0 or 1 (see [Appendix 7](#))
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first dose of atezolizumab:
 - ANC $\geq 1500/\mu\text{L}$
 - Platelet count $\geq 100,000/\mu\text{L}$
 - Hemoglobin ≥ 9.0 g/dL; patients may be transfused to meet this criterion.
 - AST and ALT $\leq 2.5 \times$ upper limit of normal (ULN)
 - Serum bilirubin $\leq 1.5 \times$ ULN
 - Serum creatinine < 3.0 mg/dL
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $< 1\%$ per year during the treatment period and for at least 5 months after the last dose of atezolizumab. Women must refrain from donating eggs during this same period.
 - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Adjuvant Atezolizumab Therapy Phase

Patients must meet the following criteria to be eligible to continue to receive atezolizumab adjuvant therapy:

- ECOG Performance Status of 0 or 1 (see [Appendix 7](#))
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained per SOC prior to the starting adjuvant atezolizumab in the Adjuvant Atezolizumab Therapy Phase:
 - ANC $\geq 1500/\mu\text{L}$
 - Platelet count $\geq 100,000/\mu\text{L}$
 - Hemoglobin ≥ 9.0 g/dL; patients may be transfused to meet this criterion
 - AST and ALT $\leq 2.5 \times \text{ULN}$
 - Serum bilirubin $\leq 1.5 \times \text{ULN}$
 - Serum creatinine < 3.0 mg/dL

4.1.2 Exclusion Criteria

Neoadjuvant Atezolizumab Therapy Phase

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

- NSCLC that is clinically T4 by virtue of mediastinal organ invasion or Stage IIIB by virtue of N3 disease
- Any prior therapy for lung cancer, including chemotherapy, hormonal therapy, or radiotherapy, within 3 years
- Patients with prior lung cancer that have been in remission for < 3 years
- Prior treatment with anti-PD-1 or anti-PD-L1 therapies or pathway-targeting agents
- Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation
- Major surgical procedure within 28 days prior to Cycle 1, Day 1
- Malignancies other than the disease under study within 3 years prior to Cycle 1, Day 1, with the exception of patients with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per SOC management (e.g., Rai Stage 0 chronic lymphocytic leukemia, prostate cancer with Gleason score ≤ 6 , and prostate-specific antigen (PSA) ≤ 10 ng/mL, etc.)
- Treatment with systemic immunosuppressive medications (e.g., prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1
 - Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea or premedication for contrast dye allergy) are eligible.

- The use of inhaled corticosteroids for chronic obstructive pulmonary disease (COPD) and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
- History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis
 - Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible.
 - Patients with controlled type 1 diabetes mellitus on a stable insulin regimen are eligible.
 - Patients with eczema, psoriasis, or lichen simplex chronicus or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible provided they meet the following conditions:
 - Rash must cover < 10% of body surface area (BSA)
 - Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, fluocinolone 0.01%, desonide 0.05%, alclometasone dipropionate 0.05%)
 - No acute exacerbations of underlying condition within the last 12 months (requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
- History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest CT scan
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, fatty liver, and inherited liver disease
- History of HIV infection
- Active hepatitis B (chronic or acute) defined as having a positive hepatitis B surface antigen (HBsAg) test at screening
 - Patients with past or resolved hepatitis B infection (defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test) are eligible.
- Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test and a positive HCV RNA test at screening
- Active tuberculosis

- Administration of a live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks before Cycle 1, Day 1 or at any time during the study
 - Influenza vaccination should be given during influenza season only (approximately October to March).
- Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1
 - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or COPD) are eligible.
- Treatment with an investigational agent for any condition within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer)
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Pregnant or lactating, or intending to become pregnant during the study
 - Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of atezolizumab

Adjuvant Atezolizumab Therapy Phase

- Progressive or recurrent disease as documented by CT scan (per RECIST v1.1 criteria) at the end of SOC adjuvant therapy
 - Patients with radiographic progression/recurrence and no evidence of pathologic response of the study during the Neoadjuvant Phase are not eligible for the Adjuvant Atezolizumab Therapy Phase

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label single-arm study. Eligible patients will be enrolled to the study to receive atezolizumab treatment.

Patients may be re-screened for enrollment during the screening period, if necessary, at the discretion of the investigator.

After written informed consent has been obtained, all required screening test results are available, and eligibility has been confirmed, the study site personnel will obtain the patient's unique identification number by registering the patient in an interactive voice/web response system (IxRS).

4.3 STUDY TREATMENT

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

4.3.1 Formulation, Packaging, and Handling

Atezolizumab will be supplied by the Sponsor. Atezolizumab is provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free, clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

Atezolizumab must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

Atezolizumab will be delivered in 250 mL 0.9% NaCl IV infusion bags with product contacting surfaces of polyvinyl chloride (PVC) or polyolefin (PO), and IV infusion lines with product contacting surfaces of PVC or polyethylene (PE) and 0.2 µm in-line filters (filter membrane of polyethersulfone [PES]). No incompatibilities have been observed between atezolizumab and these infusion materials (bags and infusion lines).

For further details on drug preparation, storage, and administration; see the pharmacy manual and the Atezolizumab Investigator's Brochure.

4.3.2 Dosage, Administration, and Compliance

Dosage

The dose of atezolizumab in this study will be 1200 mg administered by IV infusion q21d (one cycle=21 days).

In the Neoadjuvant Atezolizumab Therapy Phase, neoadjuvant treatment with atezolizumab 1200 mg will be given q21d (± 2 days) for a maximum of 2 cycles. In the Adjuvant Atezolizumab Therapy Phase, adjuvant treatment with atezolizumab 1200 mg will be given q21d (± 3 days) for maximum of 12 months.

Administration

Administration of atezolizumab will be performed on an outpatient basis in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

Premedication may be administered for any atezolizumab infusions after Cycle 1 (see Section [4.4.1](#) for details).

The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion

may be delivered over 30 (\pm 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (\pm 10) minutes. If the patient had an infusion-related reaction during previous infusion, the subsequent infusion must be administered over 60 (\pm 15) minutes.

For the first infusion, the patient's vital signs should be measured within 60 minutes before the infusion and during and after the infusion, if clinically indicated. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and at the end of the infusion, as clinically indicated.

Patients may need to remain in the clinic post-infusion for monitoring of side effects, if needed.

Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

The management of infusion-related reactions will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) infusion-related event, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate
- In the event that a patient experiences a moderate infusion-related event (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the patient should have his or her infusion immediately interrupted and should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the infusion-related event
- For severe or life-threatening infusion-related events (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening infusion-related events will not receive further infusion and will be further managed as clinically indicated until the event resolves
- For anaphylaxis precautions, see [Appendix 8](#).

Dose modifications of atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation are provided in [Section 5.1.2](#).

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

4.3.4 Post-Trial Access to Atezolizumab

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide atezolizumab or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing atezolizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of atezolizumab until the following visit: 1) For patients who will receive adjuvant atezolizumab treatment – until the adjuvant atezolizumab completion/ discontinuation visit, or 2) For patients who will not receive adjuvant atezolizumab treatment – until the Post-surgery Visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

In general, investigators should manage a patient's care with supportive therapies, as clinically indicated per standard clinical practice.

Premedication may be administered for atezolizumab infusions at the discretion of the treating physician. After the first cycle, patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist per 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](#) for anaphylaxis precautions.

Concomitant medications should be avoided with the exception of analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. For immune-related adverse events (IRAEs), patients should be carefully monitored for clinically significant systemic IRAEs or organ-specific IRAEs. Serological, immunological, and histological data should be used to support the diagnosis of immune-mediated toxicity. Corticosteroid therapy should be initiated if considered clinically necessary; use of corticosteroids as pre-medication for patients with CT IV contrast allergy is allowed.

The following therapies should continue while patients are in 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 low-molecular-weight heparin or warfarin at a stable dose level)
- *Vaccinations (such as influenza, COVID-19)*
 - *Live, attenuated vaccines are not permitted (see Section [4.4.3](#)).*
- *Megestrol acetate administered as an appetite stimulant*
- Inhaled or low-dose corticosteroids administered for COPD or asthma
- Mineralocorticoids (e.g., fludrocortisone)
- Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency

Surgical Resection

Following induction therapy, patients will undergo surgical resection of the primary tumor and associated lymph nodes. Pathologic complete resection of the primary tumor (R0) should be performed. See Section [3.1.3](#).

Standard-of-Care Chemotherapy (with or without Radiation) after Surgical Resection

After surgical resection of their tumor, patients may receive SOC chemotherapy (with or without radiation). Choice of SOC adjuvant therapy will be at the discretion of the treating physician, depending on the stage of their disease, as deemed clinically appropriate. (It is highly recommended that any adjuvant treatment be initiated within 120 days after surgery. Additionally, it is recommended that patients who receive SOC Chemotherapy (\pm Radiotherapy) initiate adjuvant atezolizumab within 60 days of SOC Chemotherapy \pm Radiotherapy (whichever occurs last). If adjuvant treatment is planned to start outside of the recommended window, *Investigators may discuss it with the Medical Monitor*).

4.4.2 Cautionary Therapy

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. Guidelines for management of immune-mediated adverse events are described in Section 5.1.

4.4.3 Prohibited Therapy

Use of the following therapies is prohibited during the study and within the timeframe (neoadjuvant phase, surgery phase, and adjuvant phase) as specified below:

- Any non-protocol-specified therapy intended for the treatment of cancer, whether health authority-approved or experimental
- Immunostimulatory agents, including but not limited to IFN- α , IFN- γ , or IL-2. These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions
- Live, attenuated vaccine (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*
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents), except as below:
 - Acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea)
 - Inhaled corticosteroids for COPD and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency
- Investigational therapy

4.5 STUDY ASSESSMENTS

Please see [Appendix 1](#) for the schedule of activities to be performed during each part of the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms (ICFs) for enrolled

patients and for patients who are not subsequently enrolled will be maintained at the study site.

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

The following ICFs will be available:

An optional prescreening ICF may be requested for patients undergoing SOC biopsy if the patient does not have adequate available archival tumor tissue as required by the protocol. If available, lymph node sample collection is also requested during the prescreening tumor biopsy. For patients undergoing bronchoscopy or EBUS, optional (but highly encouraged) bronchial brushings are also included in the prescreening ICF. If these procedures are done as part of the prescreen, they may not need to be repeated at the time of screening.

A separate ICF will be required for all patients planning to enter the main study, regardless of prescreening ICF signature status.

For patients whose disease progresses or recurs: An ICF for an optional tissue biopsy (tumor and lymph node, if available) is provided with the main ICF.

4.5.2 Prescreening Tumor Biopsy

A prescreening tumor biopsy could be conducted for patients who do not have an adequate tumor specimen, in the opinion of the investigator. This prescreening biopsy will be used to diagnose the patient and for tissue analysis. This biopsy will not need to be repeated at study screening if the sample taken is adequate, as specified in the inclusion criteria (see Section 4.1.1). If available, lymph node sample collection is also requested during the prescreening tumor biopsy. For patients undergoing bronchoscopy or EBUS, optional (but highly encouraged) bronchial brushings may also be collected at this time.

If a patient has an adequate archival tumor biopsy to yield required FFPE and fresh-frozen samples, no prescreening biopsy will be needed.

4.5.3 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including histology, grade, stage, prior cancer therapies and procedures), smoking history, asbestos, pleural or pericardial effusion, ascites requiring intervention, exposure, HPV infection and HPV subtypes, associated syndromes, *Helicobacter pylori* infection, relevant mutations, and reproductive status (women). In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic

remedies, nutritional supplements) used by the patient within 7 days prior to screening will be recorded.

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

4.5.4 Physical Examinations

A complete physical examination should be performed at screening and at the pre-surgery visit. The examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. 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.

4.5.5 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

In the Neoadjuvant Atezolizumab Therapy Phase, the patient's vital signs should be measured within 60 minutes before the infusion, and during the infusion and after the infusion, if clinically indicated.

Blood oxygen saturation by pulse oximetry will be measured in the Neoadjuvant Atezolizumab Therapy Phase as specified in [Appendix 1](#).

In the adjuvant atezolizumab therapy phase, vital signs should be measured as per standard clinical practice.

4.5.6 Tumor and Response Evaluations

Neoadjuvant Atezolizumab Therapy Phase

During the Neoadjuvant Atezolizumab Therapy Phase, the patient's tumor will be staged at screening by contrast-enhanced (if patient is not contrast-allergic) helical CT scan of the chest, PET-CT, and brain MRI, preferably with gadolinium (for Stage II or IIIA disease). If brain MRI is not feasible for technical or patient-related reasons (e.g., pacemaker, severe claustrophobia), brain CT scan with IV contrast should be obtained. All scans will be repeated prior to surgery to confirm surgical eligibility.

At the investigator's discretion, scans may be repeated at any time if progressive disease is suspected.

Radiographic responses will be assessed by the investigator per RECIST v1.1 after two cycles of neoadjuvant atezolizumab.

Pathologic responses will be assessed from surgically resected tumor by the site pathologist.

All radiologic digital imaging (including CT and CT/PET scans plus all supporting radiologic interpretation or reports) will be submitted for central review. The timepoints are:

- Time of biopsy
- Pre-surgery
- Post-surgery
- Or at any time of disease progression

Surveillance

For all patients who enter surveillance, extended Chest CT scans (including liver and adrenals) will be performed approximately every 6 weeks to 3 months for up to 2 years (see [Appendix 2](#)); all other non-protocol specified tumor assessments will be performed per standard clinical practice.

For patients that receive any adjuvant treatment (Subgroups B, C, and D): In order to align adjuvant treatment with Surveillance assessments, timing of the initial post-baseline extended chest CT scan and blood draws will be flexible (see [Appendix 2](#)). For patients in Subgroup D: Extended Chest CT Scan and blood drawn are required at C1D1 (± 5 days) of adjuvant atezolizumab phase. If C1D1 falls in between surveillance visits, an extra extended Chest CT scan needs to be done and subsequent surveillance visits will be adjusted accordingly (at every 3 months after adjuvant atezolizumab C1D1).

All radiologic digital imaging (including CT and CT/PET scans plus all supporting radiologic interpretation or reports) will be submitted for central review. The timepoints are:

- Post-surgery (or new baseline)
- Surveillance timepoints
- Or at any time of disease progression

Adjuvant Atezolizumab Therapy Phase

For patients who enroll in the Adjuvant Atezolizumab Therapy Phase, extended chest CT scans (including liver and adrenals) will be required after SOC adjuvant therapy and before initiation of atezolizumab to confirm lack of disease progression/recurrence, then for Surveillance, as outlined in [Appendix 2](#); all other non-protocol specified tumor assessments will be performed per standard clinical practice.

Radiographic responses will be assessed by the investigator per RECIST v1.1 during the adjuvant therapy phase (adjuvant atezolizumab, SOC chemotherapy, and/or both).

Follow-Up

After completion of neoadjuvant or adjuvant atezolizumab treatment (whichever occurs last), new anti-cancer treatment, recurrence and survival information will be obtained and documented approximately every 6 months for up to 3 years. For patients that undergo surgery and enter Surveillance, time in surveillance will overlap with time in survival follow-up (see [Appendix 2](#)). This information may be obtained at clinic visits or by telephone, mail, or email.

4.5.7 Other Disease-Specific Assessments

Neoadjuvant Atezolizumab Therapy Phase: Pathologic responses will be scored by a pathologist based on the surgical resection as defined by prior studies (Hellmann et al. 2014).

Adjuvant Atezolizumab Therapy Phase: All other non-protocol specified tumor and laboratory assessments will be per standard clinical practice.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology: CBC, including WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum): sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH
- Coagulation: international normalized ratio (INR), activated partial thromboplastin time (aPTT), prothrombin time (PT)
- Viral serology: HIV, HBsAg, antibodies against HBsAg, hepatitis B core antigen, and HCV antibody (anti-HCV)
 - HBV DNA is required if a patient has a positive anti-HBc antibody test.
- Pregnancy test: All women of childbearing potential will have a serum pregnancy test at screening.
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood)
- Thyroid function testing (TSH, free T3, free T4)
- C-reactive protein (CRP)

Samples listed below for biomarker analyses will be sent to one or several central laboratories for storage and/or analysis (see [Table 4](#)). Analyses may include, but are not limited to the analysis of DNA, RNA, and proteins using immunohistochemistry, next generation sequencing, functional T-cell assays, and flow cytometry. Additional assays

may be performed as technology and science are rapidly evolving. For sampling procedures, sample processing, storage conditions, and shipment instructions, refer to the laboratory manual.

- Archival or newly collected sample (fresh frozen tumor tissue and FFPE sample) for secondary and exploratory biomarker objectives.
 - If archival FFPE and fresh frozen tissue are not available, a new pre-treatment CNB (preferred), EBUS, or bronchoscopy (acceptable alternatives) will be required. The new samples will be obtained solely for the purpose of research studies (pre-treatment sample). The number of cores obtained will be determined by the radiologist performing the procedure, based on the patient's clinical condition at the time of biopsy, but will ideally include 5 core biopsies (minimum of 3 [2 FFPE, and 1 fresh frozen]). The additional 2 fresh frozen cores are optional.
 - For core biopsies, needle sizes of 16–18 gauge are preferred. If a 19 gauge or smaller needle is used please consider adding another pass. In addition, to ensure a quality tissue sample, a rapid on site evaluation (ROSE) methodology is highly recommended to evaluate the adequacy of the sample.
 - If sample is collected during EBUS, at least 3 passes are requested (a 19–22 gauge needle can be used)
- One representative block of the FFPE specimen and one fresh frozen tumor tissue sample collected from surgical resection for secondary and exploratory biomarker analyses
- FFPE lymph node obtained at surgical resection and/or obtained pre-treatment, optional. FFPE blocks are preferred. If blocks cannot be released, at least 10 positively charged FFPE slides should be provided. Collection should include involved and non-involved lymph nodes, if available.
- Optional: Fresh Tumor Tissue from resected specimens obtained at surgery
- Optional: Fresh Normal Lung Tissue from resected specimens obtained at surgical resection (only if collected together with a fresh tumor tissue samples)
- Optional: FFPE normal tumor from resected specimens obtained at surgery.
- Optional: Fresh lymph nodes obtained pre-treatment and at surgical resection. Collection at surgical resection is only performed, if a pre-treatment sample has been collected (pair for flow cytometry) and/or if also a fresh tumor tissue sample has been obtained at resection (pair for additional research). Collection can include involved and non-involved lymph nodes, if available.
- Whole blood samples at selected timepoints and at disease progression for exploratory biomarker analyses
- Blood sample for normal control DNA extraction for NGS pre-treatment
- Optional: Bronchial Brushings samples may be collected at screening after approximately 3–4 months of starting adjuvant atezolizumab treatment only for Immune-related biomarker research that may include, but is not limited to DNA and

RNA sequencing. See lab manual for exact nomenclature and specific areas to be sampled during procedure.

- Optional: FFPE tumor tissue (and lymph node, if available) biopsy at disease progression or recurrence for correlative studies. Tissue collection by CNB is preferred, but collection by EBUS, or bronchoscopy are acceptable alternatives.

Exploratory biomarker research may include, but will not be limited to, the biomarkers listed in [Table 4](#).

Table 4 Proposed Biomarkers for Exploratory Research

Sample Type	Proposed Biomarkers ^{a, d}
Whole blood DNA	<ul style="list-style-type: none"> • Normal germline control DNA for NGS
Whole blood flow cytometry	<ul style="list-style-type: none"> • Cellular IMMUNOME characterization by multicolor flow cytometry
Whole blood PBMC	<ul style="list-style-type: none"> • Gene expression analysis for cancer/ immune-related genes and biomarkers associated with common molecular pathways by NGS or RT-PCR • TCR sequencing and functional T-cell assays
Plasma/serum biomarker	<ul style="list-style-type: none"> • Circulating-free DNA by NGS • Serum markers by ELISA or proteomics
Fresh frozen tumor tissue	<ul style="list-style-type: none"> • Cancer/immune-related genes and biomarkers associated with common molecular pathways by NGS • Additional tumor- and immune-related analysis that may include TCR–sequencing
Fresh lymph nodes ^b	<ul style="list-style-type: none"> • Cellular IMMUNOME characterization by multicolor flow cytometry • Additional tumor- and immune-related analysis that may include RNA sequencing, TCR/BCR-sequencing, CyTOF
Fresh tumor tissue (optional)	<ul style="list-style-type: none"> • Tumor- and immune-related analysis that may include RNA sequencing, TCR/BCR sequencing, CyTOF
Fresh normal lung tissue (optional)	<ul style="list-style-type: none"> • Tumor- and immune-related analysis that may include RNA sequencing, TCR/BCR sequencing, CyTOF
FFPE tumor tissue	<ul style="list-style-type: none"> • PD-L1 expression • Immune markers • Additional tumor- and immune-related analysis that may include NGS, TCR-sequencing and proteomics
FFPE lymph node	<ul style="list-style-type: none"> • Gene expression analysis for cancer-/ immune-related genes and biomarkers associated with common molecular pathways by NGS • Additional tumor- and immune-related analysis that may include TCR–sequencing
Bronchial brushing (optional) ^c	<ul style="list-style-type: none"> • Tumor- and immune-related biomarker research that may include DNA and RNA sequencing
FFPE normal lung	<ul style="list-style-type: none"> • Additional immune related biomarker research

FFPE = formalin-fixed, paraffin-embedded; NGS = next-generation sequencing; PBMC = peripheral blood mononuclear cell; PD-L1 = programmed death ligand 1; TCR = T-cell receptor, BCR = B-cell receptor.

^a Proposed analysis may include but is not limited to the following biomarkers or assays

^b Lymph node sample at screening is optional, but highly encouraged. If the patient opts for lymph node sample collection at screening, lymph node sample collection will be required at time of surgical resection, if available. Residual material may be cryopreserved for additional exploratory research.

^c Encouraged for patients undergoing EBUS and/or bronchoscopy.

^d All specifics on Biomarker Collections can be found in the Laboratory Manual.

Residual material will be banked for future analyses related to NSCLC, atezolizumab's mode of action, or to increase understanding of response to atezolizumab and may include, but is not limited to, next generation sequencing.

Biological samples will be destroyed a maximum of 15 years after completion of the final Clinical Study Report, with the following exception:

- Blood samples collected and derivatives thereof will be stored until they are no longer needed or until they are exhausted.

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

Data arising from sample analysis, including data on germline mutations, will be subject to the confidentiality standards described below and in Section 8.4. Exploratory biomarker data will not be used for making a treatment decision.

4.5.8.1 Tissue Sample Prioritization

Analyses of samples will be prioritized as specified below. See [Table 4](#) for proposed analyses.

Pre- and Post-Treatment FFPE Biopsy Samples

1. Pathology analyses
2. PD-L1 IHC analysis
3. Multiplex IF analysis
4. Additional exploratory analyses

Pre- and Post-Treatment Fresh Frozen Biopsy Samples

1. RNA and DNA isolation for next generation sequencing
2. Additional exploratory analyses

Fresh Lymph Node Biopsy (if available)

1. Cellular IMMUNOME
2. Additional exploratory analyses

All other tissue samples (tumor, lymph node, bronchial brushings, adjacent normal lung) will be used for additional exploratory analyses.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance

Every effort should be made to obtain information on patients who withdraw from the study but do not withdraw consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

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

4.6.2 Atezolizumab Treatment Discontinuation

Patients must discontinue neoadjuvant or adjuvant atezolizumab treatment if they experience any of the following:

- Pregnancy
- Radiographic disease progression and/or symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status. Please note all radiographic images related to disease will be collected.
- Intolerable toxicity related to atezolizumab, including development of an irAE determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event. May contact Medical Monitor and Sponsor for further guidance.
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues on atezolizumab
- Use of another non-protocol-specified anti-cancer therapy

The primary reason for atezolizumab discontinuation should be documented on the appropriate eCRF.

If patient prematurely discontinues neo-adjuvant treatment for any reason other than progressive disease (after Cycle 1 and before surgery), they may proceed with surgery as part of the study and enter surveillance. If patient discontinues treatment for any

reason after surgery, they should remain in Surveillance until they complete 2 years and then move to Survival Follow-up. Patients who discontinue atezolizumab prematurely will not be replaced.

4.6.3 Study and Site Discontinuation

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

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

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

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 Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Atezolizumab is approved in the United States for the treatment of locally advanced or metastatic UC. The safety plan for patients in this study is based on clinical experience with atezolizumab in completed and ongoing studies. The anticipated important safety risks for atezolizumab are outlined below.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below. In addition, a pre-specified interim safety analysis will be conducted to evaluate the safety data during the study.

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional

guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

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

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: infusion-related reactions (IRRs) and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab.

Refer to [Appendix 9](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Management of Patients Who Experience Specific Adverse Events

Guidelines for management of patients who experience specific adverse events associated with atezolizumab, including infusion-related reactions and immune-mediated events (e.g., myocarditis and pulmonary, hepatic, gastrointestinal, endocrine, ocular, pancreatic, dermatologic, neurologic, and renal events), are provided in the [Appendix 9](#).

5.1.2.1 Atezolizumab Dose Modification and Treatment Interruption

Atezolizumab dose modification is not allowed in the Neoadjuvant Atezolizumab Therapy Phase. The following rules apply: 1) if atezolizumab is interrupted during infusion due to reaction, but resumed, *the* patient may proceed with all future study-related activities, 2) if atezolizumab is held (e.g., treatment is delayed) after *the* first dose due to tolerability concerns, the Investigator may choose to discontinue *the* patient from *the* study if medically indicated, *and* 3) if the patient receives less than prescribed dose of atezolizumab (e.g., if infusion cannot be completed), patient continuation in the study will require Medical Monitor approval. If the patient does not discontinue from study, they may proceed as per protocol. Investigator may contact Medical Monitor for further guidance. If the patient discontinues treatment, they will enter Survival Follow-up, as specified in Section [4.6](#).

Atezolizumab dose modification is not allowed during Adjuvant Atezolizumab Therapy Phase. However, atezolizumab may be temporarily suspended in patients experiencing toxicity considered to be related to atezolizumab for up to 12 weeks after the last dose if they experience toxicity that require a dose to be withheld. If atezolizumab is withheld because of toxicity for > 12 weeks after the last dose, then the patient will be discontinued from atezolizumab treatment and will be followed for safety and efficacy as specified in Section 4.6. If a patient must be tapered off corticosteroids used to treat adverse events, atezolizumab may be held for > 12 weeks after the last dose until corticosteroids are discontinued or reduced to prednisone dose of ≤ 10 mg/day (or equivalent).

Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator 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.

Guidelines for management of specific adverse events associated with atezolizumab are provided in the [Appendix 9](#).

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), except as described in Section 5.3.5.10
- 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 atezolizumab treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of atezolizumab treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization (see Section [5.3.5.11](#))
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [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)

See [Appendix 10](#) for list of adverse events of special interest.

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, 5.5, and 5.6.

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

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study drug**, 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 drug, all adverse events will be reported until 30 days after the last dose of atezolizumab (neoadjuvant or adjuvant, whichever occurs last). Serious adverse events and non-serious adverse events of special interest will be reported until 90 days after the last dose of atezolizumab (neoadjuvant or adjuvant, whichever occurs last). For patients participating in the Adjuvant Atezolizumab Therapy Phase, as outlined in Section 3.1.4, who will receive and complete SOC chemotherapy prior to adjuvant atezolizumab, all AE's will be reported from their first dose of neoadjuvant atezolizumab until 30 days after the last dose of adjuvant atezolizumab. Additionally, serious adverse events and non-serious adverse events of special interest will be reported until 90 days after the last dose of adjuvant atezolizumab for these patients. During the Surveillance Period, as outlined in Section 3.1.3, if a patient is not receiving atezolizumab, only serious adverse events associated with CT scans, blood sample collection, and the optional biopsy (collected at the time of disease progression) will be collected and reported (see Table 5).

Table 5 Reporting Requirements After Initiation of Study Drug (by Treatment Subgroup)

	Subgroup A	Subgroup B	Subgroup C	Subgroup D
Safety Reporting Requirements	No Adjuvant Treatment	Adjuvant Atezolizumab Treatment	SOC Chemotherapy (± Radiotherapy) only	SOC Chemotherapy (± Radiotherapy) plus Adjuvant Atezolizumab
AEs	From first dose of neoadjuvant atezolizumab until 30 days after last dose of neoadjuvant atezolizumab ^b	From first dose of neoadjuvant atezolizumab until 30 days after last dose of adjuvant atezolizumab ^{a, b}	From first dose of neoadjuvant atezolizumab until 30 days after last dose of neoadjuvant atezolizumab ^b	From first dose of Neoadjuvant atezolizumab until 30 days after last dose of Adjuvant atezolizumab ^{a, b}
SAEs/AESIs	From first dose of neoadjuvant atezolizumab until 90 days after last dose of neoadjuvant atezolizumab ^{b, c}	From first dose of neoadjuvant atezolizumab until 90 days after last dose of adjuvant atezolizumab ^{a, b, c}	From first dose of neoadjuvant atezolizumab until 90 days after last dose of neoadjuvant atezolizumab ^{b, c}	From first dose of neoadjuvant atezolizumab until 90 days after last dose of adjuvant atezolizumab ^{a, b, c}

AE=adverse event; AESI=adverse event of special interest; SAE=serious adverse event; SOC=standard of care.

^a No safety reporting interruption between neoadjuvant and adjuvant atezolizumab.

^b After informed consent has been obtained but prior to initiation of study drug, adverse events should be reported as outlined in Section 5.3.1. During Surveillance, but after patients have already completed atezolizumab treatment, AEs should be reported as outlined in Section 5.3.1.

^c Serious adverse events associated with CT scans, blood sample collection, and the optional biopsy (collected at the time of disease progression) will be collected and reported during the entire Surveillance period.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 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 (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also [Table 7](#)):

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

Table 7 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug 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 the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	<u>An adverse event will be considered related, unless it fulfills the criteria specified below.</u> Evidence exists that the adverse event has an etiology other than the study drug (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 the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

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

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

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., 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 is a change from baseline and meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in atezolizumab 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

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of NSCLC.

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"). If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of NSCLC, this is the only case when "disease progression" should be recorded on the Adverse Event eCRF.

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 Non-Small Cell Lung Cancer

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 non-small cell lung cancer 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, unless death is the outcome (see Section 5.3.5.8). These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression/recurrence, 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 drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

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

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

5.3.5.12 Adverse Events Associated with an Accidental Overdose or Medication Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. 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.

An overdose or incorrect administration of atezolizumab treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose, incorrect administration or medication error of study drug should be recorded 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).

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 drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

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

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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board (IRB)/Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

CRO Medical Monitor contact information:

Medical Monitor: [REDACTED], M.D. (Primary)

Telephone Nos.: [REDACTED]

Email: [REDACTED]

Genentech Medical Monitor contact information:

Medical Monitor: [REDACTED] (Secondary), PA-C, MMSc, MBA

Telephone No.: [REDACTED]

Email: [REDACTED]

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 Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, 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 Drug Initiation

After initiation of study drug, adverse events will be reported until 30 days after the last dose of atezolizumab (neoadjuvant or adjuvant, whichever occurs last). See [Table 5](#) for full details. Serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of atezolizumab (neoadjuvant or adjuvant, whichever occurs last). Only serious adverse events associated with CT scans, blood sample collection, and optional biopsy at the time of disease progression/recurrence that occur after the 90 day reporting window, but during the Surveillance period, will be collected and reported (see [Table 5](#)). 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 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 > 90 days after the last dose of atezolizumab are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the 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 drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

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 and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug 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). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.4.4 Reporting Requirements for Special Situations and Non-Serious Adverse Events Associated with a Special Situation

After initiation of study drug, special situations and adverse events associated with special situations will be reported until 90 days after the final dose of study drug. Investigators should record all case details that can be gathered on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system within 30 calendar days of awareness. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, *or* the event is assessed as stable by the investigator, *or* the patient is lost to follow-up, *or* the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or 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 patient'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, electronic mail, 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

The Sponsor should be notified if the investigator becomes aware of any serious adverse event or non-serious adverse event of special interest that occurs after the end

of the adverse event reporting period (defined as 90 days after the last dose of neoadjuvant or adjuvant atezolizumab, whichever occurs last; see [Table 5](#)), if the event is believed to be related to prior study drug treatment. These events 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.

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

- 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 objective of this study is to determine if atezolizumab 1200 mg q21d demonstrates efficacy in the neoadjuvant setting by producing a major pathologic response rate of at least 15%; major pathologic response is defined as $\leq 10\%$ of viable tumor cells (Hellmann et al. 2014). Tumors without radiographic response, but which demonstrate a major pathologic response (Hellmann et al. 2014) will be counted as a response.

Safety of atezolizumab in this treatment setting will also be assessed.

Details of the analyses are provided in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

The primary objective of this study is to determine the major pathologic response rate. If there is evidence that the major pathologic response rate is at least 15% then there will be further consideration for the testing of atezolizumab in neoadjuvant lung cancer. This is a single-arm study, and all patients will be treated with atezolizumab. The primary endpoint is assessed by a statistical test of a single proportion of responders against the

simple alternative of 5% response. This design provides 95% statistical power to detect a difference of 10% (15% vs. 5%) at a significance level of 0.05 (1-sided test, variance of the test statistic calculated under the alternative hypothesis). To achieve this, approximately 180 patients will be enrolled in this study. At the final analysis (after 180 patients are enrolled), if there are at least 17 patients who respond then the statistical test rejects the null hypothesis of a 5% response rate in favor of a higher response rate.

This study includes one interim analysis to assess futility after 90 patients are assessed. The non-binding futility interim boundary satisfies conditional power of 0.30. Thus, the probability that the statistical test at the final analysis will be significant at the specified power and test level is at least 0.30, conditional on the data available at the time of the interim analysis. At the interim analysis, if there are seven or fewer responders out of 90 patients then the conditional power of the study drops below 0.30, and enrollment into the study may be terminated. Table 8 summarizes the simulated probabilities of stopping at the interim and the final analysis for different values of major pathologic response. Note that simulated probabilities not identical to calculated probabilities due to the discrete nature of response.

Table 8 Simulated Probabilities of Stopping at the Interim and Final analysis for Different Values of Major Pathologic Response

True Major Pathologic Response Rate	Probability of Stopping at Interim	Probability of Continuing to Final	Simulated Power
0.05	0.84	0.16	3%
0.10	0.19	0.81	72%
0.15	0.01	0.99	99%

Note: Simulated probabilities are not identical to calculated probabilities due to the discrete nature of response.

Differential response by PD-L1 status (positive vs. negative) will also be assessed. While the composition of PD-L1 status in this patient population is not known, the study will aim to include at least 60 PD-L1-positive patients. With 60 patients, the one-sided 95% CI excludes 20% if the major pathologic response rate is 30% (18 responders out of 60 patients). Final enrollment numbers may be expanded accordingly.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic information such as age and race will be tabulated. Descriptive statistics, including means, standard deviations, and ranges for continuous parameters, as well as percentages and frequencies for categorical parameters, will be presented. Adverse events, Grade 3/4 adverse events, and serious adverse events will be tabulated.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all enrolled patients who have received at least one dose of the study drug and who do not have EGFR or ALK mutant tumors (efficacy population).

6.4.1 Primary Efficacy Endpoint

The effectiveness of the atezolizumab will be assessed by major pathologic response rate in the efficacy population, excluding patients who have not received surgery after neoadjuvant treatment with atezolizumab. A statistical test of a single proportion of major pathologic response rate will be tested against the alternative that the rate is 15%. If the null hypothesis is rejected then this is evidence that the response rate exceeds 5% when atezolizumab is given before resection. The one-sided 95% confidence interval (CI) for major pathologic response will be reported.

6.4.2 Secondary Efficacy Endpoints

The major pathologic response rates for PDL-1 negative and PDL-1 positive patients in the efficacy population will be presented separately. A comparison of the major pathologic rates between the PD-L1 positive and PD-L1 negative groups will be performed by calculating the lower bound of a one-sided 80% CI for the difference, major pathologic response for PDL-1 positive patients – major pathologic response for PDL-1 negative patients.

Similar analysis will be performed for the investigator-assessed response rate per RECIST v1.1.

Correlation of response will be performed for the following variables:

- Mutation load
- Neo-antigen score
- Gene expression signatures

Forest plot of major pathological response by demographic subgroups and disease status subgroups will be provided.

Available biomarker data will be used to assess response by different biomarker defined subgroups. Due to the limited sample size, the biomarker data analysis is for the exploratory research only

6.4.3 Exploratory Efficacy Endpoints

Changes in tumor and immune markers from baseline to surgery will be assessed in tissue samples. Also, changes in the circulating immuno-phenotype will be assessed.

DFS is defined as the time from the first date of no disease (i.e., date of surgery) to local or distant recurrence or death due to any cause, whichever occurs first. DFS will be analyzed only for patients who underwent surgery. After surgery, data for patients who withdraw from the study without documented disease recurrence or death and for whom there is evidence in the eCRF that disease follow-up evaluations were performed will be censored at the date of the last assessment when the patient is known to be free from disease recurrence (that is, last scan or collection of recurrence information when the patient is known to be free from disease recurrence). Patients without post-surgery assessments but known to be alive will be censored at the date of surgery plus one day.

Time to event analyses of OS and DFS will be calculated using the Kaplan-Meier method for all patients in the efficacy population and for subgroups of responders and non-responders and PDL-1 negative and positive.

6.5 SAFETY ANALYSES

The safety analyses will include all enrolled patients who have received at least one dose of study drug.

6.6 BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in order to explore the relationship between multiple pathological, immunological, and genomic characteristics of the cancers and clinical outcome in these patients. Biomarker analyses may include, but may not be limited to, the analyses described below.

Pathological Analyses:

- A detailed pathological evaluation will be performed on the surgically resected samples to obtain data as specified in Section [2](#).

Immunological Analyses

- Immunologic analyses by IHC, IF, and flow cytometry; and as specified in Section [2](#)

Genomic Analyses

- WES of DNA from tumor tissue and normal blood DNA, to identify mutations, for comparison of individual mutations with treatment response, and for association of total mutation burden with treatment response
- RNA-Seq analysis of pre-treatment CNB and post-neoadjuvant treatment surgical specimens to determine gene expression profile overall and signatures related to immune cell components for correlation with response
- ctDNA for association with treatment response and other endpoints

6.7 INTERIM ANALYSES

6.7.1 Planned Interim Analyses

The interim analyses described below will be performed. The study will continue during the interim analyses.

6.7.1.1 Planned Interim Safety Analysis

There is not yet extensive data on the safety of thoracic surgical resections after treatment with checkpoint inhibitors. Therefore, after the first 30 patients who complete protocol-specified atezolizumab treatment and have undergone the planned surgical resection of their tumor, the patient cohort will be evaluated for tolerability and safety of the neoadjuvant regimen. If, at the time of the safety interim analysis, three or more patients have experienced Grade 5 adverse events related to protocol treatment, then the study will be discontinued.

6.7.1.2 Planned Interim Efficacy Analysis

The study includes one interim analysis to assess futility after 90 patients are assessed. The non-binding futility interim boundary satisfies conditional power at a cut-off of 0.30.

6.7.2 Optional Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct an optional interim analysis, and the timing of the analysis, will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

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 the 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 Sponsor will perform oversight of the data management of this study. The CRO will produce an EDC Study Specification document that describes the quality checking to be performed on the data. 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.

Central laboratory data will be sent directly to the Sponsor and/or CRO, using the Sponsor's and/or CRO's standard procedures to handle and process the electronic transfer of these data.

Imaging data will be sent directly to the Sponsor and/or CRO, using the Sponsor's and/or CRO's standard procedures. Please refer to the imaging manual for specific instructions.

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, imaging, 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 PRO data (if applicable), Informed Consent Forms, laboratory test results, medication inventory records, and images, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

The Sponsor will retain study data for 25 years after the final 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 laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or

European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) *and applicable local, regional, and national laws.*

8.2 INFORMED CONSENT

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

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

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.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by Genentech, Inc. (a member of the Roche Group). Approximately 15 sites in the U.S. will participate in the study, and approximately 180 patients will be enrolled.

Enrollment will occur through an interactive voice/web-based response system (IxRS). Central laboratory facilities will be used for study assessments throughout the study (e.g., PD-L1 testing). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

A Data Review Committee will be the advisory committee, and study status will be discussed on an ongoing basis.

A contract research (CRO) will support coordination and medical monitoring activities.

9.5 PUBLICATION 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, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following Web site:
http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1 Schedule of Activities

Assessment	Screening ^a		Part 1 – Atezolizumab Neoadjuvant Treatment		Surgery			Neo- adjuvant Atezo Treatment Completion/ D/C ^d .	Surveillance				Disease Progression or Recurrence ^g	Survival Follow- up ^h
									All Subgroups	For Subgroups B and D only				
					Surveillance for All Treatment Subgroups See Appendix 2	Adjuvant Atezo Treatment ^{e,f}	Adjuvant Atezo Treatment ^{c,f}		Adjuvant Atezo Treatment Completion /D/C ^d					
(Window [Days])	Day –42 to –1	Day –14 to –1	C1D1 (Day 1 ± 3)	C2D1 (Day 22 ± 3) ⁱ	Day 36 (± 3)	Day 40 (± 10) ^j	4–6 weeks after surgery	30 (± 5) days after last dose	Every 6 weeks to 3 months for up to 2 years ^k	Adjuvant Cycle 1, Day 1, (± 5) days	Adjuvant Cycle 2–17, Day 1 (± 5) days ⁱ	30 (± 5) days after last dose	30 days after progression/ recurrence (± 5) days ^l	Up to 3 years
Informed consent (prescreening ICF and main ICF) ^m	x													
Prescreening biopsy	See footnote ⁿ													
Medical history and demographic data ^o	x													
Weight	x									x	x			
Height	x													
Complete physical examination ^p	x				x ^q									
Limited physical examination ^r						x		x		x	x ^s	x		

Appendix 1 Schedule of Activities (cont.)

Assessment	Screening ^a		Part 1 – Atezolizumab Neoadjuvant Treatment		Surgery			Neo- adjuvant Atezo Treatment Completion/ D/C ^d .	Surveillance				Disease Progression or Recurrence ^g	Survival Follow- up ^h
									All Subgroups	For Subgroups B and D only				
					Surveillance for All Treatment Subgroups See Appendix 2	Adjuvant Atezo Treatment ^{e,f}	Adjuvant Atezo Treatment ^{c,f}		Adjuvant Atezo Treatment Completion /D/C ^d					
(Window [Days])	Day –42 to –1	Day –14 to –1	C1D1 (Day 1 ± 3)	C2D1 (Day 22 ± 3) ⁱ	Day 36 (± 3)	Day 40 (± 10) ^j	4–6 weeks after surgery	30 (± 5) days after last dose	Every 6 weeks to 3 months for up to 2 years ^k	Adjuvant Cycle 1, Day 1, (± 5) days	Adjuvant Cycle 2–17, Day 1 (± 5) days ⁱ	30 (± 5) days after last dose	30 days after progression/ recurrence (± 5) days ^l	Up to 3 years
ECOG Performance Status ^t	x							x		x ^t	x ^t	x		
Vital signs ^u	x		x ^u	x		x		x		x ^u	x ^u	x		
Tumor and response evaluations ^v	x				x		x ^{w, x}		x ^w	x ^{y, x}	x			
Pathologic response assessment ^z							x							
Pulmonary function tests	x ^{aa}				x									
Hematology ^{bb}		x		x	x					x				
Chemistry ^{cc}		x		x	x					x				
Coagulation (aPTT and INR)		x												
Pregnancy test ^{dd}		x												

Appendix 1 Schedule of Activities (cont.)

Assessment	Screening ^a		Part 1 – Atezolizumab Neoadjuvant Treatment		Surgery			Neo- adjuvant Atezo Treatment Completion/ D/C ^d .	Surveillance				Disease Progression or Recurrence ^g	Survival Follow- up ^h
									All Subgroups	For Subgroups B and D only				
					Surveillance for All Treatment Subgroups See Appendix 2	Adjuvant Atezo Treatment ^{e,f}	Adjuvant Atezo Treatment ^{c,f}		Adjuvant Atezo Treatment Completion /D/C ^d					
(Window [Days])	Day –42 to –1	Day –14 to –1	C1D1 (Day 1 ± 3)	C2D1 (Day 22 ± 3) ⁱ	Day 36 (± 3)	Day 40 (± 10) ^j	Post- Surgery/ Surveillance Baseline ^c	30 (± 5) days after last dose	Every 6 weeks to 3 months for up to 2 years ^k	Adjuvant Cycle 1, Day 1, (± 5) days	Adjuvant Cycle 2–17, Day 1 (± 5) days ⁱ	30 (± 5) days after last dose	30 days after progression/ recurrence (± 5) days ^l	Up to 3 years
Urinalysis ^{ee}		x												
Thyroid function test (TSH, free T3, and free T4) ^{ff}		x			x		x			x	x ^{ff} (q3 cycles)			
C-reactive protein		x												
Viral serology ^{gg}		x												
Biomarker samples (tissue) ^{hh}	x ⁱⁱ					x							x ^{jj}	
Biomarker samples (blood-based) ^{hh, kk}			x			x	x ^x	x	x ^{ll}	x	x ^{mm}	x	x ^{jj}	
Optional bronchial brushing ⁿⁿ	x										x ^{oo}			
Atezolizumab administration ^{pp}			x	x						x	x			

Appendix 1 Schedule of Activities (cont.)

Assessment	Screening ^a		Part 1 – Atezolizumab Neoadjuvant Treatment		Surgery			Neo- adjuvant Atezo Treatment Completion/ D/C ^d .	Surveillance				Disease Progression or Recurrence ^g	Survival Follow- up ^h
									All Subgroups	For Subgroups B and D only				
					Surveillance for All Treatment Subgroups See Appendix 2	Adjuvant Atezo Treatment ^{e,f}	Adjuvant Atezo Treatment ^{c,f}		Adjuvant Atezo Treatment Completion /D/C ^d					
(Window [Days])	Day –42 to –1	Day –14 to –1	C1D1 (Day 1 ± 3)	C2D1 (Day 22 ± 3) ⁱ	Day 36 (± 3)	Day 40 (± 10) ^j	Post- Surgery/ Surveillance Baseline ^c	30 (± 5) days after last dose	Every 6 weeks to 3 months for up to 2 years ^k	Adjuvant Cycle 1, Day 1, (± 5) days	Adjuvant Cycle 2–17, Day 1 (± 5) days ⁱ	30 (± 5) days after last dose	30 days after progression/ recurrence (± 5) days ^l	Up to 3 years
Concomitant medications ^{qq}	x	x	x	x	x	x	x	x		x	x	x	x	
Adverse events ^{rr}	x	x	x	x	x	x	x	x		x	x	x	x	
Survival and recurrence follow- up ^h														x

atezo = atezolizumab; C1D1 = Cycle 1, Day 1; C2D1 = Cycle 2, Day 1; D/C = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; q = every; SOC = standard of care.

Notes: All assessments should be performed within the time windows specified for the scheduled visit. All designated procedures are required at each visit, even if visit is outside the recommended time window. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

- ^a Results of SOC assessments performed prior to obtaining informed consent and within 42 days prior to Day 1 (or within 14 days prior to Day 1 for laboratory tests) may be used; such assessments do not need to be repeated for screening.
- ^b Preferably, assessments at this visit should be performed by the surgeon, if feasible. If not feasible, the assessments may be performed by the Medical Oncologist.
- ^c It is acceptable for visit to occur outside the recommended window; all indicated procedures should be still be performed.

Appendix 1

Schedule of Activities (cont.)

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- ^d For the Adjuvant Atezolizumab Therapy Phase, all vital sign measurements and routine laboratory tests and tumor assessments, will be performed per SOC except biomarkers assessments and Extended Chest CT scan, which will occur per Surveillance schedule of activities ([Appendix 2](#)).
 - ^e Patients who prematurely discontinue neoadjuvant atezolizumab will return to the clinic 30 (+5) days after the last dose of atezolizumab treatment. If patients undergo surgery after neoadjuvant atezolizumab discontinuation/completion and will not receive adjuvant atezolizumab, the Treatment Discontinuation Visit assessments can be performed at the Post-Surgery Visit (even if it is more than 30 days after the last dose). If the patient will receive adjuvant atezolizumab, the Treatment Discontinuation Visit will occur when the patient completes/discontinues adjuvant atezolizumab treatment. Patients who do not complete surgery will then be followed for survival. Patients who complete surgery will enter the Surveillance period. The visit at which progressive disease or recurrence occurs may be used as the Treatment Discontinuation Visit.
 - ^f Any assessments not marked with an “x” should be performed as per SOC.
 - ^g Disease progression/recurrence must be confirmed by tumor imaging.
 - ^h Patients who prematurely discontinue neoadjuvant atezolizumab and do not undergo surgery will enter Survival Follow-Up for up to 3 years after the last dose of neoadjuvant atezolizumab. Patients who undergo surgery will enter the Surveillance period (See [Appendix 2](#)) and then will enter Survival Follow-Up. During Survival Follow-Up, information on recurrence, off-protocol cancer-related treatment and survival will be collected every 6 months for up to 3 years Surveillance. This information may be obtained at clinic visits or by telephone, mail, or email. The last Survival Follow-up Visit will serve as the Study Completion Visit.
 - ⁱ If C2D1 visit is delayed, all subsequent visits will be delayed accordingly.
 - ^j Delay in surgery due to an adverse event is permitted.
 - ^k Window for assessments may be altered to align with adjuvant therapy. Allowed timeframe for Surveillance assessments is outlined in [Appendix 2](#). Blood sample and extended chest CT from Post-surgery Visit will be a part of Surveillance assessments.
 - ^l Exceptions may be made; *Investigators may discuss them with the Medical Monitor.*
 - ^m Informed consent must be documented before any prescreening or screening procedure is performed.
 - ⁿ A prescreening biopsy can be conducted for patients who do not have an adequate archival tumor specimen. This biopsy will not need to be repeated at study screening. If a patient has an adequate archival tumor specimen, no additional biopsy will be needed.
 - ^o Includes clinically significant diseases, surgeries, cancer history (including histology, stage, prior cancer therapies and procedures), smoking history, asbestos, pleural or pericardial effusion, ascites requiring intervention, exposure, HPV infection and HPV subtypes, associated syndromes, *Helicobacter pylori* infection, relevant mutations, and reproductive status (women).
 - ^p Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. 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.
 - ^q Complete physical examination only has to be conducted at either the C2D1 visit or the pre-surgery visit, but not at both.
 - ^r Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Appendix 1

Schedule of Activities (cont.)

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- ^s Limited examination should be performed per SOC during adjuvant atezolizumab treatment.
 - ^t ECOG Performance Status must be of 0 or 1 at screening and before patients can start adjuvant treatment (see [Appendix 7](#)).
 - ^u In the Neoadjuvant Atezolizumab Therapy Phase, measure respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, temperature, and oxygen saturation by pulse oximetry. For both infusions of atezolizumab, measure the patient's vital signs within 60 minutes before the infusion; and during and after the infusion, if clinically indicated. For the Neoadjuvant Atezolizumab Therapy Phase, measure vital signs per SOC. Record abnormalities observed at screening on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
 - ^v For the Neoadjuvant Atezolizumab Therapy Phase, the patient's tumor will be staged at screening by contrast-enhanced helical CT scan of the chest, PET/CT, and brain MRI, preferably with gadolinium (for Stage II or III disease). If brain MRI is not feasible for technical or patient-related reasons (e.g., pacemaker, severe claustrophobia), brain CT scan with IV contrast should be obtained. All scans will be repeated prior to surgery to confirm surgical eligibility. Radiographic responses will be assessed by the investigator per RECIST v1.1 after the two cycles of atezolizumab. Scans will be repeated and collected at any time if progressive disease is suspected. For the Adjuvant Atezolizumab Therapy Phase, all tumor assessments will be per Surveillance schedule of activities (see [Appendix 2](#)). All imaging will be collected for further analyses. See imaging manual for specific instructions.
 - ^w Extended chest CT scan (including liver and adrenals). All other CT Scans will be performed as per SOC. For additional details on the timing of assessments, see [Appendix 2](#).
 - ^x Blood sample and extended chest CT scan from Post-surgery Visit will be a part of Baseline Surveillance assessments.
 - ^y For Group D only: Extended CT chest (including liver and adrenals) needs to be done after completion of SOC adjuvant Chemotherapy/Radiotherapy and before initiation of adjuvant atezolizumab to rule out disease progression/recurrence. If done as part of a surveillance visit, it does not need to be repeated. The other tumor assessments will sync with the surveillance visits (see [Appendix 2](#)).
 - ^z For the Neoadjuvant Atezolizumab Therapy Phase, pathologic responses will be scored by a pathologist based on the surgical resection as defined by (Hellmann et al. 2014).
 - ^{aa} Can be performed within 6 months of planned resection and repeated at screening.
 - ^{bb} Hematology includes CBC (WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells]).
 - ^{cc} Chemistry panel (serum) includes sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH.
 - ^{dd} All women of childbearing potential, including those who have had a tubal ligation, will have a serum pregnancy test at screening.
 - ^{ee} Includes specific gravity, pH, glucose, protein, ketones, and blood.
 - ^{ff} Perform thyroid function tests at baseline, the pre-surgery visit, at post-surgery visit and then approximately every 9 weeks (3 cycles) during adjuvant atezolizumab treatment in the Adjuvant Atezolizumab Therapy Phase.
 - ^{gg} Viral serology includes HIV, Hepatitis B (HBsAg, antibodies against HBsAg, hepatitis B core antigen; HBV DNA is required positive anti-HBc antibody test), and HCV antibody (anti-HCV).

Appendix 1

Schedule of Activities (cont.)

-
- hh See [Appendix 3](#) for detailed schedule.
- ii Tumor tissue may be archival; it does not need to be collected within 42 days of enrollment.
- jj Tissue biopsy (tumor and lymph node, if available); at disease progression/recurrence is optional and requires a separate ICF signature. Tissue collection by CNB is preferred, however collection by EBUS, or bronchoscopy are acceptable alternatives.
- kk The biomarker blood sample may be collected up to 7 days prior to the visit. Whole blood sample for biomarker assessments should preferably be collected on the day of surgery (prior to surgery and prior to antibiotic administration). It is acceptable to collect the sample up to 7 days prior to surgery (including the day of surgery, and prior to antibiotic administration). If sample needs to be collected outside of the recommended window, please contact the Medical Monitor for guidance and approval.
- ll Plasma, serum and, at selected timepoints, also PBMCs will be collected (see [Appendix 2](#)).
- mm Biomarker blood samples will be collected approximately at every 6 weeks to 3 months but can be adjusted to synchronize with Surveillance visits (See [Appendix 2](#)).
- nn Encouraged for patients undergoing EBUS and/or bronchoscopy. See lab manual for exact nomenclature and specific areas to be sampled during procedure.
- oo Should be performed after approximately 3–4 months of first adjuvant atezolizumab treatment.
- pp In the Neoadjuvant Atezolizumab Therapy Phase, neoadjuvant treatment with atezolizumab 1200 mg will be given q21d for a maximum of 2 cycles. In Adjuvant Atezolizumab Therapy Phase, adjuvant treatment with atezolizumab 1200 mg will be given q21d for maximum of 12 months (maximum 17 cycles). Patients may need to remain in the clinic post-infusion for monitoring if needed. See Section [4.3.2](#) for administration instructions.
- qq Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of atezolizumab treatment until the until the following visit: 1) For patients who will receive adjuvant atezolizumab treatment – until the Adjuvant Atezolizumab Completion/ Discontinuation Visit (whichever visit will occur last), or 2) For patients who will not receive adjuvant atezolizumab treatment – until the Post-surgery Visit.
- rr After informed consent has been obtained but prior to initiation of atezolizumab treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of atezolizumab treatment, adverse events will be reported until 30 days after the last dose of atezolizumab (neoadjuvant or adjuvant, whichever occurs last). Serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of atezolizumab (neoadjuvant or adjuvant, whichever occurs last; see Section [5.3.1](#)). All adverse events associated with CT scans, blood sample collection, and the optional biopsy (collected at the time of disease progression/recurrence) that occur after the 90-day reporting window, but during the Surveillance period, will also be collected and reported. After the designated reporting period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior atezolizumab treatment. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events and adverse events of special interest considered to be related to atezolizumab treatment or trial-related procedures until a final outcome can be reported.

Appendix 2

Timing of Surveillance Assessments

The overall Schema for Surveillance Assessments is provided in [Figure 1](#).

Detailed timing of Surveillance assessments for each adjuvant treatment subgroup can be found in [Tables 1–4](#), as follows:

[Table 1](#) [Group A – No Adjuvant Treatment](#)

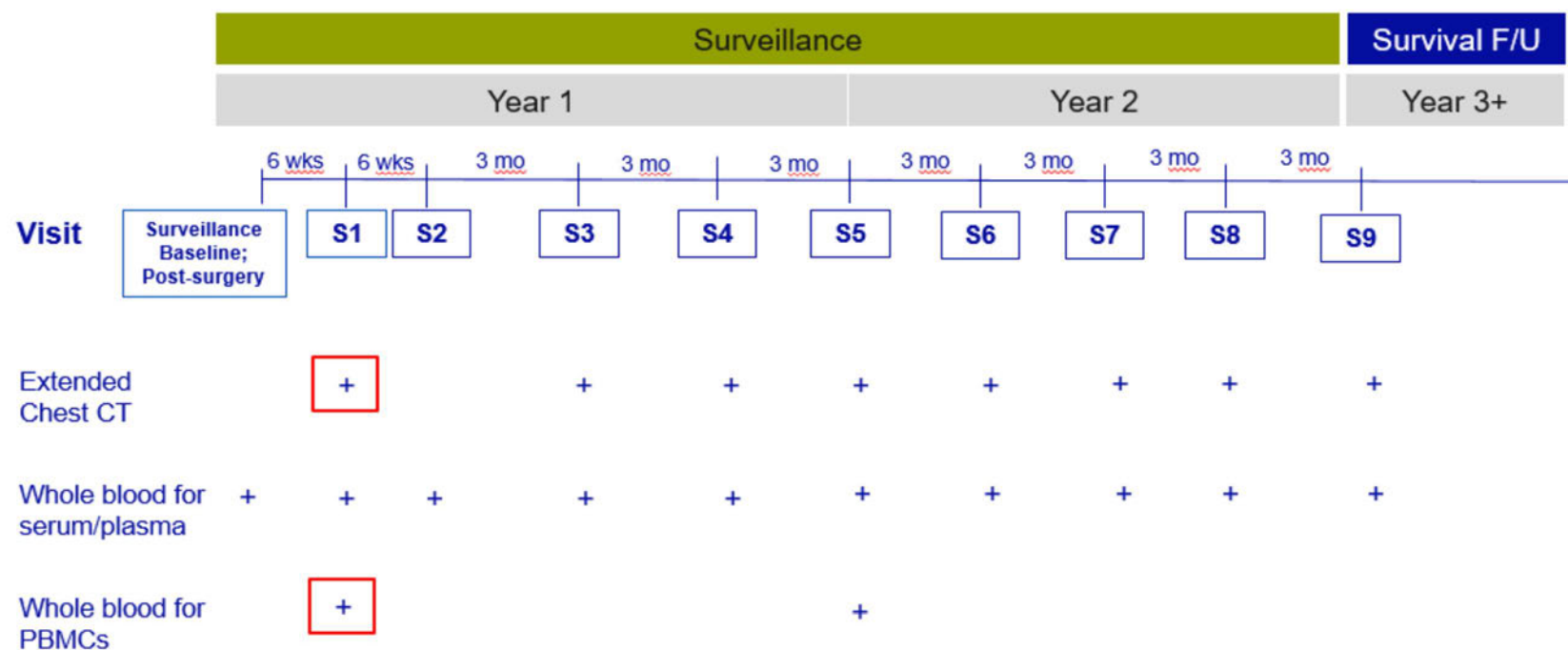
[Table 2](#) [Group B – Adjuvant Atezolizumab Treatment](#)

[Table 3](#) [Group C – SOC Chemotherapy \(\$\pm\$ Radiotherapy\) Only](#)

[Table 4](#) [Group D– SOC Chemotherapy \(\$\pm\$ Radiotherapy\) + Adjuvant Atezolizumab Treatment](#)

Appendix 2 Timing of Surveillance Assessments (cont.)

Figure 1: Surveillance Assessments Schema



S = Surveillance (Visit); PBMC = peripheral blood mononuclear cells.

Baseline Extended Chest CT scan and associated blood sample collection should ideally be obtained at the post-surgery visit/surveillance baseline (4–6 weeks after surgery). However, if it is not possible to perform the assessments at the post-surgery visit/surveillance baseline it is also acceptable to have them obtained at S1 (approximately 6 weeks after post-surgery visit/surveillance baseline). In this case:

- Baseline Chest CT Scan and blood sample collection for PBMC will be obtained at S1
- The next scans will be obtained at S3 and then approximately every 3 months up to S9 (if baseline scan is obtained at S1 then S2 scan does not need to be obtained)

* Whole blood sample for PBMC needs to be collected at S1 instead of S2 (on the same visit when the scans are performed).

Appendix 2

Timing of Surveillance Assessments (cont.)

Table 1 Group A – No Adjuvant Treatment

Post-Surgery Visit / Surveillance Baseline	S1 Visit	S2 Visit	Surveillance Assessments during SOC Chemotherapy	Surveillance Assessments during Adjuvant Atezolizumab	Assessments during Surveillance Only (S3 to S9)	Time in Survival Follow-Up ^a
(4-6 weeks after surgery)	6 weeks after Surveillance baseline (± 7days)	6 weeks after S1 Visit (± 7days)	N/A	N/A	See Below for Timing	–
Baseline extended chest CT scan and blood sample for biomarker analysis	Blood sample for biomarker analysis	Extended chest CT scan and blood sample for biomarker analysis	N/A	N/A	Extended chest CT scan and blood sample collection for biomarker analysis At approximately every 3 months after S2 for 2 years (S3 to S9).	1 year

EBUS = Endobronchial ultrasound; SOC = standard of care; S = Surveillance (visit).

Notes: If visit is outside of the recommended window, please contact Medical Monitor for guidance and approval; if visit is outside of window, all indicated procedures should still be performed. Patients whose disease progresses or recurs during Surveillance will discontinue from Surveillance and enter Survival Follow-up.

^a If patient discontinues surveillance for any reason, patient will still be followed up for 3 years after last dose of atezolizumab treatment.

Appendix 2

Timing of Surveillance Assessments (cont.)

Table 2 Group B – Adjuvant Atezolizumab Treatment

Post-Surgery Visit / Surveillance Baseline	Surveillance 1 (S1) Visit	S2 Visit	Surveillance Assessments during SOC Chemotherapy	Surveillance Assessments during Adjuvant Atezolizumab	Assessments during Surveillance Only	Time in Survival Follow-Up ^a
(4–6 weeks after surgery)	6 weeks after Surveillance baseline (± 7days)	6 weeks after S1 Visit (± 7days)	N/A	See footnote ^b	See footnote ^d	–
Baseline Extended chest CT scan and blood sample for biomarker analysis	Blood sample for biomarker analysis	Extended chest CT scan and blood sample for biomarker analysis	N/A	Extended chest CT scan and blood sample collection for biomarker analysis; Optional bronchial brushings ^c	Extended chest CT scan and blood sample collection for biomarker analysis	Upon completion of surveillance, 2 years in Survival follow-up (until patients completes 3 years after last dose of adjuvant atezolizumab)

C=cycle; D=day; EBUS=Endobronchial ultrasound; SOC=standard of care; S= Surveillance (visit).

Notes: If visit is outside of the recommended window, please contact Medical Monitor for guidance and approval; if visit is outside of window, all indicated procedures should still be performed. Patients whose disease progresses or recurs during Surveillance will discontinue from Surveillance and enter Survival Follow-up.

^a If patients discontinues surveillance for any reason, patient will still be followed up for 3 years after last dose of atezolizumab treatment.

^b Below is guidance on how to synchronize the Surveillance and adjuvant atezolizumab treatment visits, however adjustments can be done as needed:

- If C1D1 performed within 6 weeks after Post-Surgery Visit/Surveillance Baseline, assessments can be synchronized with S1. Subsequent visits will follow the Surveillance schedule, with S2 approximately 6 weeks after S1 and subsequent visits (S3 to S9) at approximately every 3 months. Please note subsequent adjuvant cycles can also be adjusted to synchronize with Surveillance visits.

Appendix 2

Timing of Surveillance Assessments (cont.)

- If C1D1 is performed between 6 to 12 weeks after Post-Surgery Visit/Surveillance Baseline, C1D1 can be synchronized with S2. Subsequent assessments (S3 to S9) should be done approximately at every 3 months and can also be adjusted to synchronize with adjuvant atezolizumab cycles.
- If first adjuvant atezolizumab cycle is performed > 12 weeks after Post-Surgery Visit/Surveillance Baseline, C1D1 can be synchronized with S3. Subsequent assessments (S4 to S9) should be done approximately at every 3 months and can also be adjusted to synchronize with adjuvant atezolizumab cycles.
- ° Optional Bronchial Brushings: will optionally be performed after approximately 3 to 4 months from the initiation of adjuvant atezolizumab (can be adjusted to synchronize with atezolizumab cycle). Bronchial brushings are highly encouraged for patients undergoing EBUS or bronchoscopy. See the laboratory manual for exact nomenclature and specific areas to be sampled during procedure
- ° Upon completion/discontinuation of adjuvant atezolizumab treatment, patients will enter a Surveillance only period.
 - Treatment discontinuation visit will be performed 30 (\pm 5) days after last dose of adjuvant atezolizumab and a blood sample for biomarker assessment will be collected (see [Appendix 1](#)).
 - Surveillance Only assessments: First assessment (Extended chest CT scan and blood sample for biomarker analysis) will be done approximately 3 months after last dose of adjuvant atezolizumab and subsequent assessments approximately at every 3 months until the patient completes a total of 2 years in Surveillance (Adjuvant Atezolizumab + Surveillance = 2 years).

Appendix 2

Timing of Surveillance Assessments (cont.)

Table 3 Group C – SOC Chemotherapy (± Radiotherapy) Only

Post-Surgery Visit / Surveillance Baseline	Surveillance 1 (S1) Visit	S2 Visit	Surveillance Assessments during SOC Chemotherapy	Surveillance Assessments during Adjuvant Atezolizumab	Assessments during Surveillance Only	Time in Survival Follow-Up ^a
(4–6 weeks after surgery)	6 weeks after Surveillance baseline (± 7 days)	6 weeks after S1 Visit (± 7 days)	See footnote ^b	N/A	See footnote ^c	–
Baseline extended chest CT scan and blood sample for biomarker analysis	Blood sample for biomarker analysis	Extended chest CT scan and blood sample for biomarker analysis	Extended Chest CT scan and blood sample collection for biomarker analysis ^c	N/A	Extended chest CT scan and blood sample collection for biomarker analysis ^d	Upon completion of surveillance, until patient completes 3 years after last dose of neo adjuvant atezolizumab

C=cycle; D=day; SOC=standard of care; S=Surveillance (visit).

Notes: If visit is outside of the recommended window, please contact Medical Monitor for guidance and approval; all indicated procedures should still be performed. Patients whose disease progresses or recurs during Surveillance will discontinue from Surveillance and enter Survival Follow-up.

^a If patient discontinues surveillance for any reason, patient will still be followed up for 3 years after last dose of atezolizumab treatment.

^b SOC Adjuvant Chemotherapy/Radiotherapy cycles can be adjusted to synchronize with the Surveillance visits. Below is guidance on how to synchronize the visits, but adjustments can be done as needed.

- If C1D1 (chemotherapy) is performed within 6 weeks after Post-Surgery Visit/Surveillance Baseline, it can be synchronized with S1. Subsequent visits will follow the Surveillance schedule, with S2 approximately 6 weeks after S1, and subsequent visits (S3 to S9) at approximately every 3 months. Please note subsequent adjuvant cycles can also be adjusted to synchronize with Surveillance visits.

Appendix 2

Timing of Surveillance Assessments (cont.)

- If C1D1 (chemotherapy) is performed between 6 to 12 weeks after Post-Surgery Visit/Surveillance Baseline, C1D1 can be synchronized with S2. Subsequent assessments (S3 to S9) should be done approximately at every 3 months and can also be adjusted to synchronize with adjuvant atezolizumab cycles.
- If C1D1 (chemotherapy) cycle is performed > 12 weeks after Post-Surgery Visit/Surveillance Baseline, C1D1 can be synchronized with S3. Subsequent assessments (S4 to S9) should be done approximately at every 3 months and can also be adjusted to synchronize with adjuvant atezolizumab cycles.
- ° Upon completion/discontinuation of SOC Chemotherapy/Radiotherapy, patients will move to Surveillance only period. The first assessment (Extended chest CT scan and blood sample for biomarker analysis) will be done approximately 3 months after last dose of SOC Chemotherapy/Radiotherapy and subsequent assessments approximately at every 3 months until the patient completes a total of 2 years in Surveillance (SOC Chemotherapy/Radiotherapy + Surveillance = 2 years).

Appendix 2

Timing of Surveillance Assessments (cont.)

Table 4 Group D– SOC Chemotherapy (± Radiotherapy) + Adjuvant Atezolizumab Treatment

Post-Surgery Visit / Surveillance Baseline	Surveillance 1 (S1) Visit	S2 Visit	Surveillance Assessments during SOC Chemotherapy	Surveillance Assessments during Adjuvant Atezolizumab	Assessments during Surveillance Only	Time in Survival Follow-Up ^a
(4–6 weeks after surgery)	6 weeks after Surveillance baseline (± 7days)	6 weeks after S1 Visit (± 7days)	See footnote ^b	See footnote ^c	See footnote ^d	–
Surveillance baseline chest CT scan and blood sample	Blood sample for biomarker analysis	Extended chest CT scan and blood sample for biomarker analysis	Chest CT scan and blood sample collection for biomarker analysis	Extended chest CT scan and blood sample collection for biomarker analysis	Extended chest CT scan and blood sample collection for biomarker analysis	Upon completion of surveillance, until patient completes 3 years after last dose of neoadjuvant atezolizumab

C=cycle; D=day; SOC=standard of care; S=Surveillance (visit).

Notes: If a visit is outside of the recommended window, please contact Medical Monitor for guidance and approval; all indicated procedures should still be performed. Patients whose disease progresses or recurs during Surveillance will discontinue from Surveillance and enter Survival Follow-up.

^a If patients discontinues surveillance for any reason, patient will still be followed up for 3 years after last dose of atezolizumab treatment.

^b SOC Adjuvant Chemotherapy/Radiotherapy cycles can be adjusted to synchronize with the Surveillance visits.

Below is guidance on how to synchronize the visits but adjustments can be done as needed.

- If C1D1 (chemotherapy) performed within 6 weeks after Post-Surgery Visit/Surveillance Baseline, it can be synchronized with S1. Subsequent visits will follow the Surveillance schedule, with S2 approximately 6 weeks after S1 and subsequent visits (S3 to S9) at approximately every 3 months. Please note subsequent adjuvant cycles can also be adjusted to synchronize with surveillance visits
- If C1D1 (chemotherapy) is performed between 6 to 12 weeks after Post-Surgery Visit/Surveillance Baseline, C1D1 can be synchronized with S2. Subsequent assessments (S3 to S9) should be done approximately at every 3 months and can also be adjusted to synchronize with adjuvant atezolizumab cycles.

Appendix 2

Timing of Surveillance Assessments (cont.)

- If C1D1 (chemotherapy) cycle is performed > 12 weeks after Post-Surgery Visit/Surveillance Baseline, C1D1 can be synchronized with S3. Subsequent assessments (S4 to S9) should be done approximately at every 3 months and can also be adjusted to synchronize with adjuvant atezolizumab cycles.
- ^c Upon completion of SOC Chemotherapy/Radiotherapy patients will move to adjuvant atezolizumab treatment for up to 12 months (maximum of 17 cycles). Extended CT scan needs to be done after completion of SOC adjuvant Chemotherapy/Radiotherapy and before initiation of adjuvant atezolizumab to rule out disease progression/recurrence. C1D1 (adjuvant atezolizumab) can be initiated within 60 days of last SOC Chemotherapy/Radiotherapy. If adjuvant treatment is planned to start outside of the recommended window, *Investigators may discuss it with the Medical Monitor*). All atezolizumab adjuvant cycles can be adjusted to synchronize with the surveillance visits.
- ^d Upon completion/discontinuation of adjuvant atezolizumab treatment, patients will move to Surveillance only period. Treatment discontinuation visit will be performed 30 (\pm 5) days after last dose of adjuvant atezolizumab and blood sample for biomarker assessment will be collected (see [Appendix 1](#)).
 - Surveillance Only assessments: First assessment (Extended chest CT scan and blood sample for biomarker analysis) will be done approximately 3 months after last dose of adjuvant atezolizumab and subsequent assessments approximately at every 3 months until the patient completes a total of 2 years in Surveillance (Adjuvant Atezolizumab + Surveillance = 2 years).

Appendix 3 Schedule of Biomarker Samples

Visit/Phase	Timepoint/Visit	Sample Type
Screening, Day –42 to –1	At visit	FFPE tumor tissue ^a
		Fresh frozen tumor tissue ^a
		Fresh lymph node (if available, highly encouraged)
		Bronchial Brushing (optional) ^b
		FFPE lymph node (optional, highly encouraged)
Atezolizumab Neoadjuvant Cycle 1, Day 1	Prior to infusion	Whole blood PBMC
		Whole blood flow cytometry
		Whole blood for serum and plasma biomarkers
		Whole blood for DNA
Surgery	Day of surgery (–7 to 1 day[s]) ^e	Whole blood PBMC
		Whole blood flow cytometry
		Whole blood for serum and plasma biomarkers
	At time of surgery	Fresh frozen tumor tissue surgical resection
		FFPE tumor tissue surgical resection
		Fresh lymph nodes (for IMMUNOME: only if also collected at Screening; for dissociation: only if collected together with a fresh tumor tissue sample at surgery); tumor involved and/or not involved, as available
		FFPE normal lung tissue (if available)
		FFPE lymph node (tumor involved and/or not involved)
		Fresh tumor tissue surgical resection (optional)
		Fresh normal lung tissue (optional and only if collected together with a fresh tumor tissue sample)
	Post-surgery follow-up (30 [± 7] days after surgery)	Whole blood for serum and plasma biomarkers
Surveillance	Every 6 weeks to 3 months (see Appendix 2)	Whole blood PBMC (at S2 and S5 only)
		Whole blood for serum and plasma biomarkers

Appendix 3 Schedule of Biomarker Samples (cont.)

Visit/Phase	Timepoint/Visit	Sample Type
Atezolizumab Adjuvant	Cycle 1 Day 1 ^c (prior to infusion)	Whole blood PBMC (if not within ± 2 weeks of S2)
		Whole blood for serum and plasma biomarkers (if not within ± 2 weeks of any S visit)
	Unscheduled (Tumor Evaluation and Response)	Whole blood for serum and plasma biomarkers
	3–4 months after initiation of adjuvant atezolizumab therapy	Bronchial Brushings (optional)
Disease Progression or Recurrence ^d	At visit	FFPE tumor biopsy (optional) ^d
		FFPE lymph node (if available) ^d
		Whole blood for serum and plasma biomarkers
Atezolizumab completion/discontinuation visit	At visit	Whole blood for serum and plasma biomarkers

EBUS = endobronchial ultrasound; FFPE = formalin-fixed, paraffin-embedded; PMBC = peripheral blood mononuclear cells; S = Surveillance (Visit).

^a Archival tissue >42 days is acceptable.

^b Encouraged for patients undergoing EBUS or bronchoscopy. See lab manual for exact nomenclature and specific areas to be sampled during procedure

^c Biomarker blood samples will be collected at Cycle 1 of Day 1 and at every tumor and response evaluation.

^d Patient must sign consent form for optional biopsy at disease progression/recurrence.

^e Whole blood sample for biomarker assessments should preferably be collected on the day of surgery (prior to surgery and pre-medication for surgery). However, if it is not possible it is also acceptable to collect the sample up to 7 days prior to surgery (including the day of surgery, prior to the procedure). If a sample needs to be collected outside of the recommended window, please contact the Medical Monitor for guidance and approval.

Appendix 4

American Joint Committee on Cancer Non-Small Cell Lung Cancer Staging, 8th Edition

T: Primary tumor	
Tx	Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus) ^a
T1a(mi)	Minimally invasive adenocarcinoma ^b
T1a	Tumor ≤ 1 cm in greatest dimension ^a
T1b	Tumor >1 cm but ≤ 2 cm in greatest dimension ^a
T1c	Tumor >2 cm but ≤ 3 cm in greatest dimension ^a
T2	Tumor >3 cm but ≤ 5 cm or tumor with any of the following features ^c : - Involves main bronchus regardless of distance from the carina but without involvement of the carina - Invades visceral pleura - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
T2a	Tumor >3 cm but ≤ 4 cm in greatest dimension
T2b	Tumor >4 cm but ≤ 5 cm in greatest dimension
T3	Tumor >5 cm but ≤ 7 cm in greatest dimension or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
T4	Tumor >7 cm in greatest dimension or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina
N: Regional lymph node involvement	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion ^d
M1b	Single extrathoracic metastasis ^e
M1c	Multiple extrathoracic metastases in one or more organs

Note: Changes to the seventh edition are in bold.

^aThe uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.

^bSolitary adenocarcinoma, ≤ 3 cm with a predominately lepidic pattern and ≤ 5 mm invasion in any one focus.

^cT2 tumors with these features are classified as T2a if ≤ 4 cm in greatest dimension or if size cannot be determined, and T2b if >4 cm but ≤ 5 cm in greatest dimension.

^dMost pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor and the fluid is nonbloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.

^eThis includes involvement of a single distant (nonregional) lymph node.

Appendix 4

American Joint Committee on Cancer Non-Small Cell Lung Cancer Staging, 8th Edition (cont.)

Descriptor in 7th edition	Proposed T/M	N categories			
		Overall stage			
		N0	N1	N2	N3
T1 ≤ 1 cm	T1a	IA1 (IA)	IB (IIA)	IIIA	IIIB
T1 > 1-2 cm	T1b	IA2 (IA)	IB (IIA)	IIIA	IIIB
T1 > 2-3 cm	T1c	IA3 (IA)	IB (IIA)	IIIA	IIIB
T2 > 3-4 cm	T2a	IB	IB (IIA)	IIIA	IIIB
T2 > 4-5 cm	T2b	IIA (IB)	IB (IIA)	IIIA	IIIB
T2 > 5-7 cm	T3	IIIB (IIA)	IIA (IIB)	IIIB (IIIA)	IIIC (IIIB)
T3 structures	T3	IIIB	IIIA	IIIB (IIIA)	IIIC (IIIB)
T3 > 7 cm	T4	IIIA (IIB)	IIIA	IIIB (IIIA)	IIIC (IIIB)
T3 diaphragm	T4	IIIA (IIB)	IIIA	IIIB (IIIA)	IIIC (IIIB)
T3 endobronchial: location/atelectasis 3-4 cm	T2a	IB (IIB)	IB (IIIA)	IIIA	IIIB
T3 endobronchial: location/atelectasis 4-5 cm	T2b	IIA (IIB)	IB (IIIA)	IIIA	IIIB
T4	T4	IIIA	IIIA	IIIB	IIIC (IIIB)
M1a	M1a	IVA (IV)	IVA (IV)	IVA (IV)	IVA (IV)
M1b single lesion	M1b	IVA (IV)	IVA (IV)	IVA (IV)	IVA (IV)
M1c multiple lesions	M1c	IVB (IV)	IVB (IV)	IVB (IV)	IVB (IV)

^aWhere there is a change, the resultant stage groupings proposed for the eighth edition are in bold, and the stage in the seventh edition is given in parenthesis.
T, tumor; M, metastasis.

Appendix 5

Pathological Response

A detailed pathological evaluation will be performed on the surgically resected samples to obtain data described below.

Detailed pathological analysis will be performed for the post-treatment biopsies to determine the following:

1. Tumor size (3 measurements)
2. Tumor diagnosis using the 2015 World Health Organization (WHO) classification
3. Predominant differentiation of the tumor (well, moderately, or poorly differentiated), and for adenocarcinoma histology, the histology subtypes present
4. Lowest degree of tumor differentiation
5. Angiolymphatic invasion
6. Neural invasion
7. Margin status in mm
8. Degree of response International Union Against Cancer (UICC) pathological T and N stage
9. Total percentage of areas of necrosis
10. Total percentage of areas of fibrosis
11. Total percentage of viable tumor tissue
12. Total percentage of viable malignant cells
13. Evidence of field effect.

The pathology review will determine if the percentage of malignant cells after treatment is $\leq 10\%$, which is considered a major pathologic response (Hellmann et al. 2014).

Appendix 6

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

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

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows.

a. Measurable Tumor Lesions

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

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

b. Non-Measurable Tumor Lesions

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

c. Special Considerations Regarding Lesion Measurability

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

Bone lesions:

- *Techne-99m* bone scans, positron emission tomography (PET) scans, and plain films are not considered adequate imaging techniques *for measuring* bone lesions.

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

Appendix 6

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

- However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

a. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and *not usually* more than 4 weeks *prior to* the beginning of the treatment.

b. Method of Assessment

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

Clinical Lesions. Clinical lesions will be considered measurable when they are superficial and ≥ 10 mm in diameter assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, *because* CT is more sensitive than X-ray, particularly in identifying

Appendix 6

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

new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

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

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

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, and Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two

Appendix 6

Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) **(cont.)**

organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is > 10 mm by CT scan).

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

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

Lesions irradiated within 3 weeks prior to Cycle 1 Day 1 may not be counted as target lesions.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression.”

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

Appendix 6
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
(cont.)

RESPONSE CRITERIA

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): disappearance of all target lesions
 - Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline
 - In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
 - The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met, *given that* a normal lymph node is defined as having a short axis < 10 mm.

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

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

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

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

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. Although some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level)
- All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions
 - The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the

Appendix 6

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

increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease; that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. Although it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. New Lesions

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

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

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

EVALUATION OF RESPONSE

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. [Table 1](#) provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

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

Appendix 6
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
(cont.)

**Table 1: Timepoint Response: Patients with Target Lesions
(with or without Non-Target Lesions)**

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

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

Table 2: Timepoint Response: Patients with Non-Target Lesions Only

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

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

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

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm; the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Appendix 6

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

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess” if either the target response or the non-target response is “unable to assess,” except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

c. **Best Overall Response: All Timepoints**

The best overall response is determined once all data for the patient is known, and is interpreted as in [Table 3](#). Complete or partial responses may be claimed if the criteria for each are met at a subsequent time point ≥ 4 weeks later.

Table 3: Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR ^a
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

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

^a If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Appendix 6
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
(cont.)

d. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to “normal” size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of “zero” on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in [Tables 1–3](#).

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

If a patient undergoes an excisional biopsy or other appropriate approach (e.g., multiple passes with large core needle) of a new lesion or an existing solitary progressive lesion that following serial sectioning and pathological examination reveals no evidence of malignancy (e.g., inflammatory cells, fibrosis, etc.), then the new lesion or solitary progressive lesion will not constitute disease progression.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 7

Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 8

Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

1. Stop the study drug 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 as required by patient status and directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 9

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

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology, when clinically indicated.

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

The investigator should consider the benefit–risk balance for a given patient prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-*mediated* event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise, as needed.*

MANAGEMENT GUIDELINES

PULMONARY EVENTS

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

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in [Table 1](#).

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	<ul style="list-style-type: none"> Continue atezolizumab and monitor closely. Re-evaluate on serial imaging. Consider patient referral to pulmonary specialist. <i>For Grade 1 pneumonitis, consider withholding atezolizumab.</i>
Pulmonary event, Grade 2	<ul style="list-style-type: none"> Withhold atezolizumab for up to 12 weeks after event onset.^a Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. Initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day oral prednisone</i>. If event resolves to Grade 1 or better, resume atezolizumab.^b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c For recurrent events, or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	<ul style="list-style-type: none"> Permanently discontinue atezolizumab and contact Medical Monitor.^c Bronchoscopy or BAL is recommended. Initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone</i>. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise, as needed.

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

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.

HEPATIC EVENTS

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

monitored throughout *study* treatment. Management guidelines for hepatic events are provided in [Table 2](#).

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	<ul style="list-style-type: none"> Continue atezolizumab. Monitor LFTs until values resolve to within normal limits or to baseline values
Hepatic event, Grade 2	<p>All events:</p> <ul style="list-style-type: none"> Monitor LFTs more frequently until return to baseline values. <p>Events of > 5 days' duration:</p> <ul style="list-style-type: none"> Withhold atezolizumab for up to 12 weeks after event onset.^a Initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day oral prednisone</i>. If event resolves to Grade 1 or better, resume atezolizumab.^b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c

LFT = liver function test.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of ≤ 10 mg/day oral prednisone*. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator*. The Medical Monitor *is available to advise, as needed*.

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

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated event*. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate)*. The Medical Monitor *is available to advise, as needed*.

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^c • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day oral prednisone</i> • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT=liver function test.

- ^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of ≤ 10 mg/day oral prednisone*. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator*. The Medical Monitor *is available to advise, as needed*.
- ^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to *the equivalent of ≤ 10 mg/day oral prednisone* before atezolizumab can be resumed.
- ^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate)*. The Medical Monitor *is available to advise, as needed*.

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in [Table 3](#).

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of
Adverse Events Associated with Atezolizumab (cont.)

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

Event	Management
Diarrhea or colitis, Grade 1	<ul style="list-style-type: none"> Continue atezolizumab. Initiate symptomatic treatment. Endoscopy is recommended if symptoms persist for > 7 days. Monitor closely.
Diarrhea or colitis, Grade 2	<ul style="list-style-type: none"> Withhold atezolizumab for up to 12 weeks after event onset. ^a Initiate symptomatic treatment. Patient referral to GI specialist is recommended. For recurrent events or events that persist > 5 days, initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day oral prednisone</i>. If event resolves to Grade 1 or better, resume atezolizumab. ^b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. ^c
Diarrhea or colitis, Grade 3	<ul style="list-style-type: none"> Withhold atezolizumab for up to 12 weeks after event onset. ^a Refer patient to GI specialist for evaluation and confirmatory biopsy. Initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</i> If event resolves to Grade 1 or better, resume atezolizumab. ^b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. ^c

GI = gastrointestinal.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise, as needed.

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

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

Event	Management
Diarrhea or colitis, Grade 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor.^c • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</i> • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

- ^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise, as needed.
- ^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to *the equivalent of* ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.
- ^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.*

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in [Table 4](#).

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. Patients should be referred to an endocrinologist if an endocrinopathy is suspected. TSH and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotrophic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	<ul style="list-style-type: none"> Continue atezolizumab. Initiate treatment with thyroid replacement hormone. Monitor TSH <i>closely</i>.
Symptomatic hypothyroidism	<ul style="list-style-type: none"> Withhold atezolizumab. Initiate treatment with thyroid replacement hormone. Monitor TSH <i>closely</i>. Consider patient referral to endocrinologist. Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	<p>TSH ≥ 0.1 mU/L and < 0.5 mU/L:</p> <ul style="list-style-type: none"> Continue atezolizumab. Monitor TSH every 4 weeks. <i>Consider patient referral to endocrinologist.</i> <p>TSH < 0.1 mU/L:</p> <ul style="list-style-type: none"> Follow guidelines for symptomatic hyperthyroidism. <i>Consider patient referral to endocrinologist.</i>
Symptomatic hyperthyroidism	<ul style="list-style-type: none"> Withhold atezolizumab. Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. Consider patient referral to endocrinologist. Resume atezolizumab when symptoms are controlled and thyroid function is improving. Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism.^c

MRI=magnetic resonance imaging; TSH=thyroid-stimulating hormone.

- ^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event ^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise, as needed.
- ^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to *the equivalent of* ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.
- ^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.*

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grades 2–4	<ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset.^a • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone upon improvement.</i> • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab.^b • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c
Hyperglycemia, Grade 1 or 2	<ul style="list-style-type: none"> • Continue atezolizumab. • <i>Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines.</i> • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	<ul style="list-style-type: none"> • Withhold atezolizumab. • Initiate treatment with insulin. • <i>Evaluate for diabetic ketoacidosis and manage as per institutional guidelines.</i> • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI=magnetic resonance imaging.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise, as needed.

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

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.*

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	<ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset. ^a • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</i> • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. ^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. ^c • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^c • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</i> • Initiate hormone replacement if clinically indicated.

MRI=magnetic resonance imaging.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise, as needed.

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

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in [Table 5](#).

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	<ul style="list-style-type: none"> Continue atezolizumab. Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	<ul style="list-style-type: none"> Withhold atezolizumab for up to 12 weeks after event onset.^a Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If event resolves to Grade 1 or better, resume atezolizumab.^b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c
Ocular event, Grade 3 or 4	<ul style="list-style-type: none"> Permanently discontinue atezolizumab and contact Medical Monitor.^c Refer patient to ophthalmologist. Initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day oral prednisone</i>. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise, as needed.

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

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to,

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. *Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly.* Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 6](#).

Table 6 Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 2–4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor.^a • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider anti-arrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</i> • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO=extracorporeal membrane oxygenation; VAD=ventricular assist device.

^a Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.*

INFUSION-RELATED REACTIONS AND CYTOKINE RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine release syndrome (CRS) with atezolizumab may receive medication with antihistamines, anti-pyretics, and/or analgesics (e.g., acetaminophen) *for subsequent infusions.*

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in [Table 7](#).

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

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of
Adverse Events Associated with Atezolizumab (cont.)

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

Event	Management
Grade 1^a Fever ^b with or without constitutional symptoms	<ul style="list-style-type: none"> • Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment,^c including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2^a Fever ^b with hypotension not requiring vasopressors and/or Hypoxia requiring low-flow oxygen ^d by nasal cannula or blow-by	<ul style="list-style-type: none"> • Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment.^c • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor.^e • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

Event	Management
<p>Grade 3^a Fever^b with hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen^d by nasal cannula, face mask, non-rebreather mask, or Venturi mask</p>	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor.^e • Administer symptomatic treatment.^c • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
<p>Grade 4^a Fever^b with hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)</p>	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor.^e • Administer symptomatic treatment.^c • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments^f may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: These management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

- ^a Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
- ^b Fever is defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
- ^c Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
- ^d Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.
- ^e Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.* For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after *assessing* the benefit-risk ratio.
- ^f Refer to Riegler et al. (2019).

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in [Table 8](#).

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of
Adverse Events Associated with Atezolizumab (cont.)

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	<p><i>Amylase and/or lipase > 1.5–2.0 × ULN:</i></p> <ul style="list-style-type: none"> Continue atezolizumab. Monitor amylase and lipase weekly. For prolonged elevation (e.g., > 3 weeks), consider treatment with <i>corticosteroids equivalent to 10 mg/day oral prednisone.</i> <p><i>Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:</i></p> <ul style="list-style-type: none"> <i>Treat as a Grade 3 event.</i>
Amylase and/or lipase elevation, Grade 3 or 4	<ul style="list-style-type: none"> Withhold atezolizumab for up to 12 weeks after event onset.^a Refer patient to GI specialist. Monitor amylase and lipase every other day. If no improvement, consider treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.</i> If event resolves to Grade 1 or better, resume atezolizumab.^b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.^c

GI = gastrointestinal.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of ≤ 10 mg/day oral prednisone*. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator*. The Medical Monitor *is available to advise, as needed*.

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

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.*

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	<ul style="list-style-type: none"> Withhold atezolizumab for up to 12 weeks after event onset. ^a Refer patient to GI specialist. Initiate treatment with <i>corticosteroids equivalent to</i> 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to Grade 1 or better, resume atezolizumab. ^b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. ^c For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. ^c
Immune-mediated pancreatitis, Grade 4	<ul style="list-style-type: none"> Permanently discontinue atezolizumab and contact Medical Monitor. ^c Refer patient to GI specialist. Initiate treatment with <i>corticosteroids equivalent to</i> 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise, as needed.

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

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in [Table 9](#).

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	<ul style="list-style-type: none"> Continue atezolizumab. Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	<ul style="list-style-type: none"> Continue atezolizumab. Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. Initiate treatment with topical corticosteroids. Consider treatment with higher-potency topical corticosteroids if event does not improve. <i>If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day</i>
Dermatologic event, Grade 3	<ul style="list-style-type: none"> Withhold atezolizumab for up to 12 weeks after event onset. ^a Refer patient to dermatologist for evaluation and, if indicated, biopsy. Initiate treatment with <i>corticosteroids equivalent to 10 mg/day oral prednisone</i>, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. If event resolves to Grade 1 or better, resume atezolizumab. ^b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. ^c
Dermatologic event, Grade 4	<ul style="list-style-type: none"> Permanently discontinue atezolizumab and contact Medical Monitor. ^c
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	<p>Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:</p> <ul style="list-style-type: none"> Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. Follow the applicable treatment and management guidelines above. If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator*. The Medical Monitor is *available to advise, as needed*.

- ^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to *the equivalent of ≤ 10 mg/day oral prednisone* before atezolizumab can be resumed.
- ^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate)*. The Medical Monitor is *available to advise, as needed*.

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in [Table 10](#).

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	<ul style="list-style-type: none"> Continue atezolizumab. Investigate etiology.
Immune-mediated neuropathy, Grade 2	<ul style="list-style-type: none"> Withhold atezolizumab for up to 12 weeks after event onset.^a Investigate etiology <i>and refer patient to neurologist</i>. Initiate treatment as per institutional guidelines. If event resolves to Grade 1 or better, resume atezolizumab.^b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c
Immune-mediated neuropathy, Grade 3 or 4	<ul style="list-style-type: none"> Permanently discontinue atezolizumab and contact Medical Monitor.^c <i>Refer patient to neurologist</i>. Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	<ul style="list-style-type: none"> Permanently discontinue atezolizumab and contact Medical Monitor.^c Refer patient to neurologist. Initiate treatment as per institutional guidelines. Consider initiation of <i>corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone</i>.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of ≤ 10 mg/day oral prednisone*. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator*. The Medical Monitor is *available to advise, as needed*.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to *the equivalent*

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

- Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.*

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 11](#).

Table 11 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor.^a • Refer patient to neurologist. • Initiate treatment with <i>corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.</i> • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

^a Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.*

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

RENAL EVENTS

Immune-*mediated* nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout *study* treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 12](#).

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	<ul style="list-style-type: none"> Continue atezolizumab. Monitor kidney function, including creatinine <i>and urine protein</i>, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	<ul style="list-style-type: none"> Withhold atezolizumab for up to 12 weeks after event onset. ^a Refer patient to renal specialist. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. If event resolves to Grade 1 or better, resume atezolizumab. ^b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. ^c
Renal event, Grade 3 or 4	<ul style="list-style-type: none"> Permanently discontinue atezolizumab and contact Medical Monitor. Refer patient to renal specialist and consider renal biopsy. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

- ^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise, as needed.
- ^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.
- ^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 13](#).

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 13 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	<ul style="list-style-type: none"> • Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	<ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset ^a and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. ^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. ^c

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise, as needed.*

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

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.*

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 13 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 3	<ul style="list-style-type: none"> Withhold atezolizumab for up to 12 weeks after event onset ^a and contact Medical Monitor. Refer patient to rheumatologist or neurologist. Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, resume atezolizumab. ^b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. ^c For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	<ul style="list-style-type: none"> Permanently discontinue atezolizumab and contact Medical Monitor. ^c Refer patient to rheumatologist or neurologist. Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

^a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise, as needed.*

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

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise, as needed.*

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of
Adverse Events Associated with Atezolizumab (cont.)

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE
ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab.

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

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever $\geq 38.5^{\circ}\text{C}$
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
 - Hemoglobin $< 90 \text{ g/L}$ (9 g/dL) ($< 100 \text{ g/L}$ [10 g/dL] for infants < 4 weeks old)
 - Platelet count $< 100 \times 10^9/\text{L}$ ($100,000/\mu\text{L}$)
 - ANC $< 1.0 \times 10^9/\text{L}$ ($1000/\mu\text{L}$)
- Fasting triglycerides $> 2.992 \text{ mmol/L}$ (265 mg/dL) and/or fibrinogen $< 1.5 \text{ g/L}$ (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin $> 500 \text{ mg/L}$ (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin $> 684 \text{ mg/L}$ (684 ng/mL)
- At least two of the following:
 - Platelet count $\leq 181 \times 10^9/\text{L}$ ($181,000/\mu\text{L}$)
 - AST $\geq 48 \text{ U/L}$
 - Triglycerides $> 1.761 \text{ mmol/L}$ (156 mg/dL)
 - Fibrinogen $\leq 3.6 \text{ g/L}$ (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in [Table 14](#).

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

Event	Management
Suspected HLH or MAS	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, <i>and/or anti-cytokine therapy</i>. • If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH=hemophagocytic lymphohistiocytosis; MAS=macrophage activation syndrome.

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Risks Associated with Atezolizumab and Guidelines for Management of
Adverse Events Associated with Atezolizumab (cont.)

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Appendix 10

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

Adverse events of special interest (regardless of causality) 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 include the following:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, hyperthyroidism, adrenal insufficiency, and hypophysitis
- Hepatitis, including AST or ALT > 10 × ULN
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré Syndrome, myasthenic syndrome or myasthenia gravis, and meningioencephalitis
- Nephritis
- Events suggestive of hypersensitivity, cytokine-release syndrome, influenza-like illness, HLH, and MAS
- Infusion-related reactions
- Cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome (SIRS), systemic immune activation (SIA)
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below
 - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

Appendix 11

Protocol Version 3 Schedule of Activities

Assessment	Screening ^a		Part 1 – Atezolizumab Neoadjuvant Treatment		Surgery			Part 2 – Atezolizumab Adjuvant Treatment (Medical Oncologist) ^c	Study Completion/ D/C ^d	Disease Progression or Recurrence ^{cc}	Follow- up ^e
					Pre- surgery ^b	Surgery	Post- Surgery				
(Window [Days])	Day –42 to –1	Day –14 to –1	C1D1 (Day 1 ±3)	C2D1 (Day 22 ±3) ^f	Day 36 (±3)	Day 40 (±10) ^g	30 (±7) days after surgery	Adjuvant Cycle Day 1 (±3) days	30 (±5) days after last dose	30 days after progression/ recurrence (±5) days ^{dd}	Up to 3 years
Informed consent (prescreening biopsy ICF and main ICF) ^h	x										
Prescreening biopsy	See footnote ^j										
Medical history and demographic data ⁱ	x										
Weight	x							x			
Height	x										
Complete physical examination ^k	x				x ^l						
Limited physical examination ^l						x		x ^a	x		
ECOG Performance Status ^m	x							x ^m	x		
Vital signs ⁿ	x		x ⁿ	x		x		x ^{a, n}	x		
Tumor and response evaluations ^o	x				x			x ^a			
Pathologic response assessment ^p							x				
Pulmonary function tests	x ^{ff}				x						
Hematology ^q		x		x	x			x ^a			

Appendix 11

Protocol Version 3 Schedule of Activities (cont.)

Assessment (Window [Days])	Screening ^a		Part 1 – Atezolizumab Neoadjuvant Treatment		Surgery			Part 2 – Atezolizumab Adjuvant Treatment (Medical Oncologist) ^c	Study Completion/ D/C ^d	Disease Progression or Recurrence ^{cc}	Follow- up ^e
					Pre- surgery ^b	Surgery	Post- Surgery				
	Day –42 to –1	Day –14 to –1	C1D1 (Day 1 ± 3)	C2D1 (Day 22 ± 3) ^f	Day 36 (± 3)	Day 40 (± 10) ^g	30 (± 7) days after surgery	Adjuvant Cycle Day 1 (± 3) days	30 (± 5) days after last dose	30 days after progression/ recurrence (± 5) days ^{dd}	Up to 3 years
Chemistry ^r		x		x	x			x ^a			
Coagulation (aPTT and INR)		x									
Pregnancy test ^s		x									
Urinalysis ^t		x									
Thyroid function test (TSH, free T3, and free T4) ^u		x			x		x	x (q3 cycles)			
C-reactive protein		x									
Viral serology ^v		x									
Biomarker samples (tissue) ^w	x					x				x ^{ee}	
Biomarker samples (blood-based) ^{w, x}			x			x	x	x ^y	x	x ^{ee}	
Optional bronchial brushing ^{gg}	x							x ^{hh}			
Study treatment administration ^z			x	x				x			
Concomitant medications ^{aa}	x	x	x	x	x	x	x	x	x	x	
Adverse events ^{bb}	x	x	x	x	x	x	x	x	x	x	
Survival and recurrence follow-up ^e											x

C1D1=Cycle 1, Day 1; C2D1=Cycle 2, Day 1; D/C=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; q=every; SOC=standard of care.

Notes: All assessments should be performed within the time windows specified for the scheduled visit. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

^a Limited examination should be performed per SOC during adjuvant atezolizumab treatment. Results of SOC tests or examinations performed prior to obtaining informed consent and within 42 days prior to Day 1 (or within 14 days prior to Day 1 for laboratory tests) may be

Appendix 11

Protocol Version 3 Schedule of Activities (cont.)

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- used; such tests do not need to be repeated for screening.
- b Assessments at this visit may be performed by either the Medical Oncologist or the surgeon.
 - c For Part 2, all vital sign measurements, routine laboratory tests, and tumor and response assessments will be performed per SOC.
 - d Patients who discontinue study treatment or complete the study will return to the clinic 30 (+ 5) days after the last dose of study treatment, and then followed for survival. The visit at which progressive disease occurs may be used as the treatment discontinuation visit.
 - e Documentation of disease recurrence, off-protocol cancer-related treatment, and survival will occur every 6 months for up to 3 years after the patient receives the last dose of atezolizumab treatment (neoadjuvant or adjuvant, whichever occurs last), or until loss to follow-up, withdrawal of consent, or study termination by the Sponsor. After study treatment discontinuation, patients will be followed per SOC but information on recurrence, off-protocol cancer-related treatment, and survival will be collected every 6 months for up to 3 years after the patient receives the last dose of atezolizumab neoadjuvant or adjuvant, whichever occurs last. This information may be obtained at clinic visits or by telephone, mail, or email. The last Survival Follow-up Visit will serve as the Study Completion/Discontinuation Visit.
 - f If C2D1 visit is delayed, all subsequent visits will be delayed accordingly.
 - g Delay in surgery due to an adverse event is permitted.
 - h Informed consent must be documented before any prescreening or screening procedure is performed.
 - i Includes clinically significant diseases, surgeries, cancer history (including histology, stage, prior cancer therapies and procedures), smoking history, asbestos, pleural or pericardial effusion, ascites requiring intervention, exposure, HPV infection and HPV subtypes, associated syndromes, *Helicobacter pylori* infection, relevant mutations, and reproductive status (women).
 - j A prescreening biopsy will be conducted for patients who do not have an adequate archival tumor specimen. This biopsy will not need to be repeated at study screening. If a patient has an adequate archival tumor specimen, no additional biopsy will be needed.
 - k Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. 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.
 - l Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Complete physical examination only has to be conducted at either the C2D1 visit or the pre-surgery visit, but not at both. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
 - m ECOG Performance Status must be of 0 or 1 at screening and before patients can start adjuvant treatment (see [Appendix 7](#)).
 - n In Part 1, measure respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, temperature, and oxygen saturation by pulse oximetry. For both infusions of study treatment, measure the patient's vital signs within 60 minutes before the infusion; and during and after the infusion, if clinically indicated. For Part 2, measure vital signs per SOC. Record abnormalities observed at screening on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
 - o For Part 1, the patient's tumor will be staged at screening by contrast-enhanced (if patient is not contrast-allergic) helical CT scan of the chest, PET/CT, and brain MRI, preferably with gadolinium (for Stage II or III disease). If brain MRI is not feasible for technical or patient-related reasons (e.g., pacemaker, severe claustrophobia), brain CT scan with IV contrast should be obtained. All scans will be repeated prior to surgery to confirm surgical eligibility. Radiographic responses will be assessed by the investigator per RECIST v1.1 after the two cycles of atezolizumab. At the investigator's discretion, scans may be repeated at any time if progressive disease is suspected. For Part 2, all tumor assessments will be per SOC.
 - p For Part 1, pathologic responses will also be scored by a pathologist based on the surgical resection as defined by prior studies (Hellmann et al. 2014). For Part 2, all tumor and laboratory assessments will be per SOC.

Appendix 11

Protocol Version 3 Schedule of Activities (cont.)

- ^q Hematology includes CBC (WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells]).
- ^r Chemistry panel (serum) includes sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH.
- ^s All women of childbearing potential, including those who have had a tubal ligation, will have a serum pregnancy test at screening.
- ^t Includes specific gravity, pH, glucose, protein, ketones, and blood.
- ^u Perform thyroid function tests at baseline, the pre-surgery visit, at post-surgery visit and then every 9 weeks (3 cycles) during adjuvant atezolizumab treatment in Part 2.
- ^v Viral serology includes HIV, Hepatitis B (HBsAg, antibodies against HBsAg, hepatitis B core antigen; HBV DNA is required positive anti-HBc antibody test), and HCV antibody (anti-HCV).
- ^w See [Appendix 3](#) for detailed schedule.
- ^x The biomarker blood sample may be collected up to 7 days prior to the visit.
- ^y Biomarker blood samples will be collected at Cycle 1 of Day 1 and at every tumor and response evaluation. Plasma, serum and, at selected timepoints, also PBMCs will be collected (see [Appendix 2](#)).
- ^z In Part 1, neoadjuvant treatment with atezolizumab 1200 mg will be given q21d for a maximum of 2 cycles. In Part 2, adjuvant treatment with atezolizumab 1200 mg will be given q21d for maximum of 12 months. Patients may need to remain in the clinic post-infusion for monitoring if needed. See [Section 4.3.2](#) for administration instructions.
- ^{aa} Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study treatment until the following visit: 1) For patients who will receive adjuvant atezolizumab treatment – until the Adjuvant Atezolizumab Completion/ Discontinuation Visit, or 2) For patients who will not receive adjuvant atezolizumab treatment – until the Post-surgery 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 atezolizumab, adverse events will be reported until 30 days after the last dose of atezolizumab (neoadjuvant or adjuvant, whichever occurs last). Serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of atezolizumab (neoadjuvant or adjuvant, whichever occurs last). After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study treatment. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events and adverse events of special interest considered to be related to study treatment or trial-related procedures until a final outcome can be reported.
- ^{cc} Disease progression/recurrence must be confirmed by tumor imaging.
- ^{dd} Exceptions may be made with Medical Monitor approval.
- ^{ee} Tissue biopsy (tumor and lymph node, if available) and blood sample at disease progression/recurrence are optional and require a separate ICF signature. Tissue collection by core needle biopsy is preferred, however collection by endobronchial ultrasound or bronchoscopy are acceptable alternatives.
- ^{ff} PFT Can be performed within 6 months of planned resection and repeated at screening.
- ^{gg} Encouraged for patients undergoing EBUS and/or bronchoscopy. See lab manual for exact nomenclature and specific areas to be sampled during procedure
- ^{hh} Optional bronchial brushing should be performed after approximately 3–4 months of first adjuvant atezolizumab treatment.