Official Title: A Phase III, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab Compared With Chemotherapy in Patients With Treatment Naïve Advanced or Recurrent (Stage IIIb Not Amenable for Multimodality Treatment) or Metastatic (Stage IV) Non-Small Cell Lung Cancer Who Are Deemed Unsuitable for Platinum-Containing Therapy

NCT Number: NCT03191786

Document Date: Protocol Amendment Version 8: 09-May-2023

PROTOCOL

TITLE:	**A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB COMPARED WITH CHEMOTHERAPY IN PATIENTS WITH TREATMENT-NAÏVE ADVANCED OR RECURRENT (STAGE IIIB NOT AMENABLE FOR MULTIMODALITY TREATMENT) OR METASTATIC (STAGE IV) NON-SMALL CELL LUNG CANCER WHO ARE DEEMED UNSUITABLE FOR PLATINUM-CONTAINING THERAPY**
PROTOCOL NUMBER:	MO29872
VERSION NUMBER:	8
EUDRACT NUMBER:	2015-004105-16
IND NUMBER:	Not applicable
NCT NUMBER:	NCT03191786
TEST PRODUCT:	Atezolizumab (RO5541267)
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL:	See electronic signature and stamp date on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
8	See electronic date stamp on the final page of this document.
7	22 Dec 2021
6	03 Feb 2021
5	19 Dec 2019
4	14 Jan 2019
3	16 Jan 2018
2	29 Jun 2017
1	13 Feb 2017

PROTOCOL AMENDMENT, VERSION 8
RATIONALE

Protocol MO29872 has been amended to include updates following the Atezolizumab Investigator's Brochure, Version 19, release. Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- The medical term “Wegener granulomatosis” has been replaced by the term “granulomatosis with polyangiitis” to align with the updated preferred term in MedDRA (Section 4.1.2.2). In addition, this term has also been added to Appendix 11.
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Roche practices (Section 8.4).
- Benefit-risk assessment and guidance on concomitant administration of severe acute respiratory syndrome coronavirus 2 vaccines with atezolizumab has been added (Sections 1.8 and 4.4.1.1).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.11.6).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front matter and Section 5.4.1). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 9.5).
- The list of identified risks for atezolizumab has been revised to include myelitis and facial paresis (Section 5.1.1.1).
- Hemophagocytic lymphohistiocytosis (HLH) has been updated from a potential risk to an identified risk associated with atezolizumab and language has been revised accordingly (Section 5.1.1.1).
- The list of adverse events of special interest has been revised to include myelitis and facial paresis (Section 5.2.3).
- Appendix 11 has been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a pericardial disorder while receiving another immunostimulatory anti-cancer agent.
- Appendix 11 has been revised to include autoimmune myelitis.
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator’s Brochure, Version 19 and Addendum 1 and 2 to the Atezolizumab Investigator’s Brochure, Version 19 (Appendix 13).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB COMPARED WITH CHEMOTHERAPY IN PATIENTS WITH TREATMENT-NAÏVE ADVANCED OR RECURRENT (STAGE IIIB NOT AMENABLE FOR MULTIMODALITY TREATMENT) OR METASTATIC (STAGE IV) NON-SMALL CELL LUNG CANCER WHO ARE DEEMED UNSUITABLE FOR PLATINUM-CONTAINING THERAPY**
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SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB COMPARED WITH CHEMOTHERAPY IN PATIENTS WITH TREATMENT-NAÏVE ADVANCED OR RECURRENT (STAGE IIIB NOT AMENABLE FOR MULTIMODALITY TREATMENT) OR METASTATIC (STAGE IV) NON-SMALL CELL LUNG CANCER WHO ARE DEEMED UNSUITABLE FOR PLATINUM-CONTAINING THERAPY**
PROTOCOL NUMBER:	MO29872
VERSION NUMBER:	8
EUDRACT NUMBER:	2015-004105-16
IND NUMBER:	Not applicable
NCT NUMBER:	NCT03191786
TEST PRODUCT:	Atezolizumab (RO5541267)
PHASE:	Phase III
INDICATION:	Non-small cell lung cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of atezolizumab compared with single agent chemotherapy with respect to antitumor effects in patients with treatment-naïve locally advanced or metastatic non-small cell lung cancer (NSCLC) who are deemed unsuitable for any platinum-doublet chemotherapy. Specific objectives and corresponding endpoints for the study are outlined below.

EFFICACY OBJECTIVES

PRIMARY EFFICACY OBJECTIVE

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab compared with single agent chemotherapy in patients with treatment-naïve locally advanced or metastatic NSCLC who are deemed unsuitable for any platinum-doublet chemotherapy, as measured by overall survival (OS).

SECONDARY EFFICACY OBJECTIVES

The secondary efficacy objectives for this study are:

- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy as measured by OS rates at 6, 12, 18 and 24 months
- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator-assessed ORR using RECIST v1.1

- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator-assessed progression-free survival (PFS) using RECIST v1.1
- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator-assessed duration of response (DOR) using RECIST v1.1
- To evaluate the efficacy (OS and investigator-assessed PFS using RECIST v1.1) of atezolizumab compared with single agent chemotherapy in patients with PD-L1 expression defined by the PD-L1 SP263 immunohistochemistry (IHC) assay

SAFETY OBJECTIVE

The safety objective for this study is:

- To evaluate the safety and tolerability of atezolizumab compared with single agent chemotherapy

PATIENT-REPORTED OUTCOME OBJECTIVES

The patient-reported outcome (PRO) objective for this study is

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

EXPLORATORY OBJECTIVES

The exploratory objectives for this study are:

- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator-assessed ORR, PFS and DOR according to modified RECIST (immune-mediated response criteria; imRC)
- To evaluate and compare investigator-assessed disease control rates (DCR) between the two treatment arms using RECIST v1.1
- To evaluate the relationship between the main efficacy endpoints and tumor tissue programmed death-ligand 1 (PD-L1) expression
- To evaluate the relationship between the main efficacy endpoints and exploratory biomarkers in tumor tissue and plasma
- To evaluate the relationship between the main efficacy endpoints and the expression of immune markers in peripheral blood mononuclear cells (PBMCs)
- To generate utility scores for use in economic models for reimbursement by collecting patient's health status data using the EuroQoL-5 Dimensions 5-level (EQ-5D-5L) questionnaire

STUDY DESIGN

DESCRIPTION OF STUDY

This is a Phase III, global, multicenter, open-label, randomized, controlled study designed to evaluate the efficacy and safety of atezolizumab compared with a single agent chemotherapy regimen by investigator choice (vinorelbine or gemcitabine) in treatment-naïve patients with locally advanced or metastatic NSCLC who are deemed unsuitable for any platinum-doublet chemotherapy due to poor performance status (Eastern Cooperative Oncology Group performance status [ECOG PS] of 2-3).

However, patients ≥ 70 years of age who have an ECOG PS of 0 or 1 may be included if they are deemed unsuitable for platinum doublet chemotherapy by the investigator due to:

a) substantial comorbidities

b) contraindication(s) for platinum-doublet chemotherapy.

Eligible patients will be stratified by (a) histologic subtype (non-squamous vs squamous), (b) PD-L1 immunohistochemistry (IHC) status (positive/negative/unknown) and (c) brain metastases (yes/no) and then randomized at a 2:1 ratio to receive either atezolizumab or single agent chemotherapy.

Eligible patients must therefore provide a tumor tissue specimen for central assessment of PD-L1 expression by IHC at a central laboratory. The study will enroll all patients whose tissue is evaluable for PD-L1 analysis, regardless of PD-L1 expression status.

Given the unique toxicities associated with chemotherapy (i.e., alopecia, neutropenia, febrile neutropenia) and the pre-medications required (i.e., steroid, anti-emetics, and potentially growth factor support), this will be an open-label study.

No crossover will be allowed between treatment arms.

Atezolizumab at a fixed dose of 1200 mg will be administered intravenously on Day 1 of each 21-day cycle.

Patients randomized to receive single agent chemotherapy (vinorelbine [oral or intravenous] or gemcitabine [intravenous]), based on investigator's choice will receive chemotherapy per relevant local guidelines and summary of product characteristics (SmPC) management. Doses and dose modifications for the selected single agent chemotherapy should be made per relevant local guidelines and SmPC management.

At any time-point after RECIST v1.1 criteria for progressive disease are met, patients in the experimental arm who show evidence of clinical benefit, will be permitted to continue treatment with atezolizumab if they meet all of the following criteria:

- Evidence of clinical benefit (i.e., in the absence of symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], clinical status, and of laboratory values)
- Absence of unacceptable toxicity
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial progression.

Tumor assessments will be performed at baseline, every 6 weeks (± 5 days) following randomization for 48 weeks, and every 9 weeks (± 5 days) thereafter, with additional scans as clinically indicated. Assessments will continue until disease progression per RECIST v1.1. Patients randomized to atezolizumab who continue to receive atezolizumab following disease progression will undergo tumor assessments until treatment discontinuation. Tumor assessments should continue regardless of whether patients discontinue study treatment or start new anti-cancer therapy in the absence of disease progression unless they withdraw consent.

In all patients, response will be assessed by the investigator using RECIST v1 until disease progression. Patients randomized to receive atezolizumab will additionally be assessed by modified RECIST criteria until treatment discontinuation.

Follow-up data capture, including subsequent anticancer therapies, will continue for each patient until death, withdrawal of consent, loss to follow up, or study termination by Sponsor, whichever occurs first.

In addition to PD-L1 analysis, exploratory research will be performed on histological tumor tissue samples pre-treatment.

Patients will undergo blood sample collection for exploratory biomarker analyses using plasma and PBMCs as per schedule of assessments.

Tissue and plasma samples will be analyzed for example by methods like IHC, quantitative reverse transcriptase PCR (qRT-PCR), next-generation sequencing (NGS) and/or other methods to study tumor biomarkers and changes thereof on DNA, RNA and/or protein (or other analytes). These exploratory biomarker evaluations will not be used for any treatment-related decisions. Exploratory analyses aim to study tumor-associated alterations to further understand disease pathobiology (including but not limited to mechanisms of disease progression, pseudo-progression, acquired resistance), to evaluate surrogate biomarkers and to potentially allow for the development of blood-based and tissue-based diagnostic tests to help predict which patients may benefit from atezolizumab.

Primary imaging data used for tumor assessment may be collected by the Sponsor to enable centralized, independent review of response endpoints, if needed.

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 and assessed by immune-mediated adverse events (imAEs) and immune-mediated adverse reactions (imARs) methods. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. An external independent Data Monitoring Committee (iDMC) will be assembled and will be responsible for monitoring the safety of patients in the study in accordance with a pre specified iDMC charter.

During the study, assessments will be performed according to the Schedule of Assessments.

NUMBER OF PATIENTS

Approximately 120 sites globally will participate in the study, and 441 patients are expected to be randomized.

TARGET POPULATION

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Male or female, age ≥ 18 years
3. Able to comply with the study protocol, in the investigator's judgment
4. Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC as per the American Joint Committee on Cancer (AJCC) 7th edition
5. No sensitizing epidermal growth factor receptor (EGFR) mutation (L858R or exon 19 deletions) or anaplastic lymphoma kinase (ALK) fusion oncogene detected
6. No prior systemic treatment for advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC as per the AJCC 7th edition
7. Life expectancy ≥ 8 weeks
8. Deemed unsuitable for any platinum-doublet chemotherapy by the investigator due to poor performance status (ECOG PS of 2-3)

   However, patients ≥ 70 years of age who have an ECOG PS of 0 or 1 may be included due to:
   a) substantial comorbidities
   b) contraindication(s) for any platinum-doublet chemotherapy
9. Representative formalin-fixed paraffin-embedded (FPPE) tumor tissue block obtained during course of disease (archival tissue) or at screening (tumor blocks are highly preferred for central analysis of PD-L1 expression and exploratory biomarkers)
10. Patients with treated, asymptomatic central nervous system (CNS) metastases are eligible, provided they meet all of the following criteria:
    a) Measurable disease outside CNS
    b) Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)
    c) No ongoing requirement for corticosteroids as therapy for CNS disease; anticonvulsants at a stable dose allowed
    d) No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization
    e) No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to randomization, if all other criteria are met, including clinical confirmation of no evidence of interim disease progression.

11. Measurable disease (by RECIST v1.1)

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

12. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to randomization:

    a) Absolute neutrophil count (ANC) ≥ 1500 cells/μL without granulocyte colony-stimulating factor support
    b) White blood cell (WBC) counts > 2500/μL
    c) Lymphocyte count ≥ 500/μL
    d) Serum albumin ≥ 2.5 g/dL
    e) Platelet count ≥ 100,000/μL without transfusion (without transfusion within 2 weeks of laboratory test used to determine eligibility)
    f) Hemoglobin ≥ 9.0 g/dL, patients may be transfused or receive erythropoietic treatment to meet this criterion
    g) International normalized ratio (INR) or activated partial thromboplastin time (aPTT) ≤ 1.5 × upper limit of normal (ULN). This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation must have an INR or aPTT within therapeutic limits for at least 1 week prior to randomization
    h) Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase ≤ 2.5 × ULN with the following exceptions:
        - Patients with documented liver metastases: AST and/or ALT ≤ 5 × ULN
        - Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN
    i) Serum bilirubin ≤ 1.5 × ULN. Patients with known Gilbert's syndrome who have serum bilirubin level ≤ 3 × ULN may be enrolled
    j) Serum creatinine ≤ 1.5 × ULN

13. For female patients of childbearing potential randomized to the atezolizumab treatment arm: agreement (by patient and/or partner) to remain abstinent (refrain from heterosexual intercourse) or to use highly effective form(s) of contraceptive methods that result in a failure rate of < 1% per year when used consistently and correctly during the treatment period and for at least 5 months after the last dose of atezolizumab.

    - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and 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, and established, proper use of 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 adequate methods of contraception.

14. Female patients of childbearing potential and male patients with partners of childbearing potential treated in the comparative single agent chemotherapy arm should continue contraception use for at least 6 months after the last dose of study treatment. Such methods include: combined (estrogen and progestogen containing) hormonal contraception, progestogen-only hormonal contraception associated with inhibition of ovulation together with another additional barrier method always containing a spermicide, intrauterine device (IUD): intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner (on the understanding that this is the only one partner during the whole study duration), and sexual abstinence. Male patients should not donate sperm during this study and for at least 6 months after the last dose of comparative single agent chemotherapy treatment.
    - Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drug. The same rules are valid for male patients involved in this clinical study if they have a partner of childbirth potential. Male patients must always use a condom.
15. Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.

Exclusion Criteria

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

Cancer-Specific Exclusion Criteria

1. Patients younger than 70 years who have an ECOG PS of 0 or 1.
2. Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation of the brain during screening and prior radiographic assessments
    a) Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for > 2 weeks prior to randomization
    b) Leptomeningeal disease
    c) History of CNS metastases intracranial haemorrhage
3. Uncontrolled tumor-related pain
    a) Patients requiring pain medication must be on a stable regimen at study entry.
    b) Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment. Patients should have recovered from the effects of radiation. There is no required minimum recovery period.
    c) Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
4. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently). Patients with indwelling catheters (e.g., PleurX®) are allowed.
5. Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L or calcium > 12 mg/dL or corrected serum calcium > ULN)
6. History of other malignancy within 5 years prior to screening, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated with curative intent, breast ductal carcinoma in situ treated surgically with curative intent)

7. NCI CTCAE (v4.0) Grade 3 or higher toxicities due to any prior therapy (e.g., radiotherapy) (excluding alopecia), which have not shown improvement and are strictly considered to interfere with current study medication
8. Patients who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy, radiotherapy, or chemoradiotherapy

General Medical Exclusion Criteria

9. Women who are pregnant or lactating or intending to become pregnant during the study. Women of childbearing potential including women who have had a tubal ligation, must have a negative serum pregnancy test result within 14 days prior to initiation of study drug
10. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, granulomatosis with polyangiitis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis
    - Patients with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study
    - Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen are eligible for this study
11. Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
    a) Rash must cover less than 10% of body surface area (BSA)
    b) Disease is well controlled at baseline and only requiring low potency topical steroids
    c) No acute exacerbations of underlying condition within the last 12 months requiring treatment with either psoralen plus ultraviolet radiation (PUVA), methotrexate, retinoids, biologic agents, oral calcineurin inhibitors or high potency or oral steroids
12. History of idiopathic pulmonary fibrosis (IPF), organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted
13. Known positivity for human immunodeficiency virus (HIV)
    - Testing is not required in the absence of clinical symptoms and signs suggestive of HIV infection.
    - Patients with a past history of/or symptoms of HIV are eligible only if serological tests are negative.
14. Known active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or known active hepatitis C
    - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. HBV DNA test must be performed in these patients prior to randomization. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA
15. Active tuberculosis
16. Severe infections within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
17. Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina

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

18. Major surgical procedure other than for diagnosis within 4 weeks prior to randomization or anticipation of need for a major surgical procedure during the course of the study
19. Prior allogeneic bone marrow transplantation or solid organ transplant
20. Any serious medical condition (including metabolic dysfunction, physical examination finding) or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study or that may affect the interpretation of the results or render the patient at high risk for treatment complications
21. Patients with an illness or condition that may interfere with capacity or compliance with the study protocol, as per investigator's judgment
22. Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to randomization

Exclusion Criteria Related to Atezolizumab

23. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
24. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
25. Oral or IV antibiotic treatment. Patients will thus need to have recovered from any infection requiring antibiotics. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
26. Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine will be required during the study
    - Influenza vaccination is allowed but should be given during influenza season. However, patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to randomization, at any time during the study or within 5 months after the last atezolizumab dose
27. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-programmed death−1 (anti-PD-1), and anti-PD-L1 therapeutic antibodies. Patients who have had prior anti-cytotoxic T lymphocyte−associated antigen 4 (CTLA-4) treatment may be enrolled, provided the following requirements are met:
    a) Minimum of 6 weeks from the last dose of anti−CTLA-4
    b) No history of severe immune-mediated adverse effects from anti-CTLA-4 (NCI CTCAE Grade 3 and 4)
28. Treatment with systemic immunostimulatory agents (including but not limited to interferons, interleukin-2 [IL-2]) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to randomization
29. Treatment with systemic corticosteroids or other immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor [anti-TNF] agents)
    - Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.
    - The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.
    - Patients with history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumor assessments done by MRI.
30. Patients not willing to stop treatment with traditional herbal medicines

Exclusion Criteria Related to Chemotherapy

31. Known sensitivity and contraindications to the 2 comparative chemotherapy agents, i.e., vinorelbine (oral or intravenous) and gemcitabine (intravenous)

END OF STUDY AND LENGTH OF STUDY

This study is event-driven, with a recruitment period of approximately 24 months. The required number of 380 events for the final analysis of the primary endpoint of OS is expected to occur approximately 42 months after the first patient has been enrolled. A cut-off date for final analysis will be set at least 54 months after first patient in should 380 OS events not be reached.

For patients randomized to the atezolizumab treatment arm, treatment may continue beyond disease progression per RECIST v1.1 until loss of clinical benefit, unacceptable toxicity, patient or physician decision to discontinue, or death. For all patients, tumor response data collection will continue until disease progression, even if the patient stops study treatment prior to disease progression. Patients randomized to receive atezolizumab who continue study treatment after disease progression continue to undergo tumor assessments until treatment discontinuation. Follow-up data capture, including subsequent anticancer therapies, will continue for each patient until death, withdrawal of consent, loss to follow-up, or study termination by Sponsor, whichever occurs first.

The end of the study is when the required number of deaths has been observed. Additionally, the Sponsor may decide to terminate the study at any time.

INVESTIGATIONAL MEDICINAL PRODUCTS

TEST PRODUCT (INVESTIGATIONAL DRUG)

Atezolizumab, at a dose of 1200 mg, will be administered by IV infusion every 21 days.

COMPARATORS

Single agent chemotherapy (vinorelbine [oral or intravenous] or gemcitabine [intravenous]) based on investigator's choice will be administered per relevant local guidelines and SmPC management. Doses and dose modifications for the selected single agent chemotherapy should be made per relevant local guidelines and SmPC management.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary efficacy analysis is the comparison of OS between the two treatment arms (atezolizumab arm and single agent chemotherapy arm).

For OS, patients without a date of death will be censored on the date a patient was last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization plus 1 day.

The null and alternative hypotheses for OS analysis can be phrased in terms of comparison of survival function S(t) for the two treatment arms:

Ho: $S_{chemo}(t) = S_{Atezo}(t)$ vs

H1: $S_{chemo}(t) \neq S_{Atezo}(t)$.

The hazard ratio (HR) will be estimated using a stratified Cox regression model including 95% confidence intervals (CIs). The stratification factors will be: histologic subtype (non-squamous/squamous), PD-L1 IHC status (positive/negative/unknown) and brain metastases (yes/no).

An unstratified analysis will also be performed.

Kaplan-Meier methodology will be used to construct survival curves by treatment arms. The median OS and corresponding 95%CI will be provided for each treatment arm.

If non proportionality of HR is detected, then further analyses and tests will be run. Further details on this scenario will be provided in the statistical Analysis Plan (SAP).

DETERMINATION OF SAMPLE SIZE

Assuming a 10% withdrawal rate and accrual duration of 24 months, approximately 441 patients will be randomized in a 2:1 ratio to atezolizumab (294 patients) or chemotherapy (147 patients). A total of 380 OS events will provide 90% power to detect a significant improvement in the

primary endpoint (median OS) for treatment with atezolizumab versus chemotherapy from 7 months to 10 months (i.e., HR of 0.7) for a two-sided log-rank test at an alpha level of 5%. There is one planned interim analysis at 304 OS events. Operating characteristics (power and expected total number of events) for true underlying hazard ratio values of 0.7 are provided in the table below.

Sample Size Calculation Parameters	**Values**
Randomization ratio (Atezolizumab vs Chemotherapy)	2:1
Type 1 error (2-sided)	5%
Power	90%
Accrual duration	24 months
Duration until OS interim analysis	30 months
Duration until OS final analysis	42 months
Assumed drop-out rate	10%
Median control	7 months
Median atezolizumab	10 months
Hazard ratio	0.7
Number of events at interim analysis	304
Number of events at final analysis	380
Number of patients	441

Note: This is assuming validity of proportional Hazards assumption.

INTERIM ANALYSES

An interim analysis of OS will be performed when approximately 304 events in the ITT population have been reached. A group sequential design (Lan-DeMets with O'Brien-Fleming stopping boundaries) will be used to control the overall type I error rate (Lan and DeMets 1983).

The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter. The decision to conduct the planned interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP. The iDMC charter will document potential recommendations the iDMC can make to the Sponsor as a result of the analysis and the iDMC charter will also be made available to relevant health authorities, if applicable.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-TNF	anti-tumor necrosis factor
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATA	anti-therapeutic antibody
AUC	area under the curve
BSA	body surface area
BSC	best supportive care
BUN	blood urea nitrogen
CBC	complete blood count
CCOD	clinical cutoff date
CI	confidence interval
CL	clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CNS	central nervous system
CRC	colorectal carcinoma
CRO	clinical research organization
CRP	c-reactive protein
CRS	cytokine-release syndrome
CT	computed tomography
CTC	common toxicity criteria
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T lymphocyte−associated antigen 4
C_{trough}	trough concentration
DCR	disease control rate
DLT	dose limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Definition
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	electronic PRO
EQ-5D-5L	EuroQol 5 dimensions, 5-level questionnaire
ESMO	European Society of Medical Oncology
E.U.	European Union
FDA	Food and Drug Administration
FPPE	formalin-fixed paraffin embedded
5-FU	5-fluorouracil
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
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
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	health-related quality of life
HUS	hemolytic-uremic syndrome
IC	immune cell
ICH	International Conference on Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
IL-2	interleukin-2
imAE	immune mediated adverse event
imAR	immune mediated adverse reaction
IMP	investigational medicinal product
imRC	immune-mediated response criteria
IND	Investigational New Drug application
INR	international normalized ratio
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board

Abbreviation	Definition
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IxRS	interactive voice/web response system
K-ras	GTPase Kras
LDH	lactate dehydrogenase
LFT	liver function test
LOQ	lower limit of quantification
LV	leucovorin
LVEF	left ventricular ejection fraction
MAS	macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mUC	metastatic urothelial carcinoma
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
NGS	next-generation sequencing
NHL	Non-Hodgkin lymphoma
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	disease progression
PD-1	programmed death−1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PI	Prescribing Information
PK	pharmacokinetic
popPK	population pharmacokinetic

Abbreviation	Definition
PRO	patient-reported outcome
PS	performance status
PUVA	psoralen plus ultraviolet radiation
q3w	every 3 weeks
QLQ-C30	Quality-of-life Questionnaire Core 30
QLQ-LC13	Quality-of-Life Questionnaire Lung Cancer Module
QoL	quality of life
qRT-PCR	quantitative reverse transcriptase-polymerase chain reaction
RBC	red blood cell count
RBR	Research Biosample Repository
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RR	response rate
SADR	serious adverse drug reaction
SAP	statistical analysis plan
SCLC	squamous cell lung carcinoma
SmPC	Summary of Product Characteristics
SOC	system organ class
$t_{1/2}$	half live
T3	triiodothyronine
T4	thyroxine
TC	tumor cell
TKI	tyrosine kinase inhibitor
TNBC	triple-negative breast cancer
TNF-α	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
TTD	time to deterioration
TTF-1	thyroid transcription factor−1
TTP	time-to-progression
UBC	urothelial bladder cancer
UC	urothelial carcinoma
ULN	upper limit of normal
U.S.	United States
V_1	central compartment volume of distribution
V_{ss}	volume of distribution at steady state
WBC	white blood cell

Abbreviation	Definition
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON NON-SMALL CELL LUNG CANCER

Lung cancer remains the leading cause of cancer deaths worldwide; it is the most common cancer in both men and women and accounted for approximately 13% of all new cancers in 2008 (Jemal et al. 2011). In 2016, it was estimated that there would be 224,390 new cases of lung cancer and 158,080 lung cancer deaths in the United States (U.S.) alone (Siegel et al. 2016). Similar data from Europe estimate that there were 313,000 new cases of lung cancer and 268,000 deaths in 2012 (GLOBOCAN 2012).

Non−small cell lung cancer (NSCLC) is the predominant subtype of lung cancer, accounting for approximately 85% of all cases (Molina et al. 2008; Howlader et al. 2014). NSCLC can be divided into two major histologic types: adenocarcinoma and squamous cell carcinoma (Travis et al. 2011). Adenocarcinoma histology accounts for more than half of all NSCLC, while squamous cell histology accounts for approximately 25% of NSCLC (Langer et al. 2010). The remaining cases of NSCLC are represented by large cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and poorly differentiated histology.

Half of all newly diagnosed NSCLC patients present with advanced disease (stage IIIb and IV) (Davidoff et al. 2010) which directly contributes to poor survival prospects.

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

There are recognized differences in disease characteristics between adenocarcinoma and squamous NSCLC. First, squamous tumors commonly present in the central airways and typically remain localized in the bronchial epithelium (Hirsch et al. 2008), whereas non-squamous tumors are more commonly located in the lung parenchyma distal to the central airways. Evaluation of NSCLC tumor tissue will reveal cytological differences between the squamous cell type (keratinization, intracellular bridges, and central necrosis) and adenocarcinoma (glandular architecture). In cases where the tumor sample is poorly differentiated or there is limited tissue available, immunohistochemical (IHC) markers may support the histologic diagnosis. Thyroid transcription factor-1 (TTF-1) is infrequently expressed in squamous cells and strongly expressed in adenocarcinoma. In contrast, p63, CK5/6, and 34βE12 are strongly expressed in squamous cell carcinoma and less frequently in adenocarcinoma (Travis et al. 2011).

Genetic changes that have prognostic and/or predictive significance in NSCLC include mutations in the epidermal growth factor receptor (EGFR), the rearrangement in the

anaplastic lymphoma kinase (ALK) gene, and mutations in the GTPase Kras (K-ras) gene. The rates of these mutations differ between squamous cell carcinoma and adenocarcinoma. For example, EGFR kinase domain mutations have been reported in 10%–40% of patients with adenocarcinoma NSCLC but are infrequently observed in squamous NSCLC (Herbst et al. 2008). The ALK fusion oncogene, recognized as a driver of lung tumorigenesis, is very rare in the squamous histology but observed in approximately 7% of patients with adenocarcinoma (Herbst et al. 2008; Langer et al. 2010). In addition, K-ras mutations are very rare in squamous NSCLC, while they can be observed in up to 30% of cases of adenocarcinoma NSCLC (Travis et al. 2011).

1.2 FIRST-LINE TREATMENT FOR NSCLC

Patients with previously untreated NSCLC that does not harbor a driver mutation that confers sensitivity to a targeted agent are typically treated with chemotherapy. The first evidence that chemotherapy produced a significant survival benefit in patients with advanced NSCLC came in 1995; a meta-analysis showed that platinum-based doublet chemotherapy conferred a 2-month improvement in median survival over best supportive care (BSC) (NSCLC Collaborative Group 1995). More recently, the European Big Lung Trial demonstrated the potential benefits of chemotherapy. In this trial, 725 patients with advanced NSCLC were randomly assigned to BSC plus cisplatin-based chemotherapy or BSC alone (Spiro et al. 2004). Patients allocated to chemotherapy had a significantly longer median survival than did those managed with BSC (8 vs. 5.7 months; hazard ratio [HR] = 0.77, 95% confidence interval [CI]: 0.66, 0.89).

The benefit conferred by platinum-based chemotherapy regimens appears to have reached a plateau in overall response rate (approximately 15%−22%) and median survival (7−10 months). More recently, the addition of bevacizumab to carboplatin and paclitaxel resulted in an increase in response rate from 15% to 35% and an increase in median overall survival (OS) from 10 to 12 months (see Table 1).

Despite the limited survival benefit conferred by cytotoxic chemotherapy, platinum-based regimens remain the standard first-line option for most patients with locally advanced and metastatic NSCLC not harboring an activating EGFR mutation or ALK gene rearrangement. In particular, for newly diagnosed advanced stage non-squamous NSCLC, standard of care is a platinum doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. However, well-designed clinical trials conducted over the last decade have clearly demonstrated that bevacizumab and pemetrexed are not appropriate agents for the treatment of patients with squamous cell carcinoma of the lung (Johnson et al. 2004; Scagliotti et al. 2008; Sandler et al. 2006). The combination of gemcitabine and a platinum analog (either carboplatin or cisplatin) has demonstrated efficacy as first-line treatment for NSCLC and, as a result, is often a reference arm in clinical trials evaluating new therapeutics (Schiller et al. 2002; Treat et al. 2010). The median duration of progression-free survival (PFS) following treatment

with gemcitabine and a platinum analog in patients with treatment-naïve advanced NSCLC is approximately 4.2-4.7 months.

In patients with metastatic non-squamous NSCLC who lack an actionable mutation, guidelines of the National Comprehensive Cancer Network (NCCN) recommend platinum-doublet chemotherapy with or without bevacizumab is recommended (Table 1) (Ettinger et al. 2016)

Current guidelines for first, second and further treatment lines in advanced NSCLC have been published by the European Society for Medical Oncology (ESMO) (Novello et al. 2016) and National Comprehensive Cancer Network (NCCN NSCLC v.3.2017).

Table 1 Summary of Trials Assessing First- and Second-line Treatment of Metastatic Non-Squamous NSCLC Patients Lacking an Actionable Mutation

Treatment Regimen	Study Phase	Response Rate (%)	Median PFS (months)	Median OS (months)
First-line treatment				
Bevacizumab + paclitaxel/carboplatin (Sandler 2016, Patel 2013)	III	33–35	5.6–6.2	12.3–13.4
Bevacizumab + pemetrexed/carboplatin (Patel 2013)	III	34.1	6.0	12.6
Cetuximab [a] + cisplatin/vinorelbine, with cetuximab maintenance (Pirker 2009)	III	Not reported	Not reported	12.0 [b]
Carboplatin/paclitaxel (Sandler 2006)	III	15	4.5	10.3
Cisplatin/docetaxel (Fossella 2003)	III	31.6	5.1‖	11.3
Cisplatin/vinorelbine (Fossella 2003)	III	24.5	5.3‖	10.1
Cisplatin/paclitaxel (Smit 2003) [c]	III	31.8	4.2	8.1
Cisplatin/gemcitabine (Smit 2003, Scagliotti 2008) [c]	III	36.6	4.7	8.9–10.4
Cisplatin/pemetrexed (Scagliotti 2008)	III	Not reported	5.3	11.8
Second-line treatment				
Nivolumab (Borghaei 2015)	III	19	2.3	12.2
Pembrolizumab (Herbst 2016)	II/III	18.0 [d] / 18.5 [e]	3.9 [d] / 4.0 [e]	10.4 [d] / 12.7 [e]
Ramucirumab + docetaxel (Garon 2014)	III	23	4.5	10.5
Docetaxel (Borghaei 2015, Garon 2014, Hanna 2004)	III	8.8–14	2.9–4.2	7.9–9.4
Pemetrexed (Hanna 2004, Karampeazis 2013)	III	9.1–11	2.9	8.3–10.1
Erlotinib (Karampeazis 2013, Shepherd 2005, Ciuleanu 2012)	III	7.9–9	2.2–3.6	5.3–8.2
Gemcitabine (Cho 2006)	II	18.5	2.3 [f]	8.8 [f]

OS = overall survival; PFS = progression-free survival.

[a] Cetuximab is listed in NCCN guidelines but is not FDA or EMA approved for NSCLC;

[b] Patients with adenocarcinoma subtype;

[c] Patients with non-squamous and squamous histology;

[d] 2 mg/kg dose;

[e] 10 mg/kg dose;

[f] Estimated from original time in weeks.

In patients with metastatic squamous NSCLC who lack an actionable mutation, NCCN guidelines recommend chemotherapy and best standard of care are recommended (Ettinger et al. 2016).

Table 2 Summary of Trials Assessing First- and Second-line Treatment of Metastatic Squamous NSCLC Patients Lacking an Actionable Mutation

Treatment	Study Phase	ORR (%)	Median PFS (months)	Median OS (months)
First-line				
Gemcitabine/cisplatin (Scagliotti 2008)	III	Not reported	5.5	10.8
First-line continuation maintenance therapy (combined squamous and non-squamous NSCLC population)				
Gemcitabine (Perol 2012)	III	Not reported	3.8	15.2
First-line switch therapy (combined squamous and non-squamous NSCLC population)				
Docetaxel (Fidias 2009)	III	35.9	5.7	12.3
Second-line (combined squamous and non-squamous NSCLC population unless noted otherwise)				
Docetaxel (Hanna 2004, Fossella 2000, Shepherd 2000)	III	6.7–8.8	2.0[a]–2.9	5.7–7.9
Gemcitabine (van Putten 2015)	II	13	Not reported	6*
Nivolumab (Brahmer 2015, Reckamp 2015) [b]	III	20	3.5	7.2
Pembrolizumab (Soria 2015)	I	18.7	3.0	11.3
Ramucirumab + docetaxel (Garon 2014)	III	23	4.5	10.5

ORR = objective response rate; OS = overalls survival; PFS = progression-free survival

[a] Estimated from original time in weeks;

[b] Patients with squamous disease.

1.2.1 First-Line Therapy for NSCLC Patients with Poor Performance Status

The majority of patients with newly diagnosed NSCLC present with locally advanced or metastatic disease (Carnio et al. 2014). In addition, the average age at diagnosis of lung cancer in the U.S. is about 70 years (Avery et al. 2009, Gajra et al. 2014). As a result, a significant proportion of patients with lung cancer have intercurrent illnesses or comorbid conditions that can potentially affect their ability to receive standard therapy for lung cancer.

Patients with lung cancer with a poor PS, irrespective of age, have an increased incidence of adverse effects with standard chemotherapy and have a poorer OS (Sweeney et al. 2001, Ruckdeschel et al. 1986). An estimated 30% to 40% of patients diagnosed with NSCLC have a poor PS-defined as a score of 2 or higher on the Eastern Cooperative Oncology Group (ECOG) scale-because of their disease burden, comorbidities, or both (Govindan et al. 2004).

Performance status is the most powerful independent prognostic factor in advanced NSCLC since it is a reliable measure of functional independence, ability to perform daily activities and work, and a strong predictor of survival and adverse events (Gebbia et al. 2005).

Survival is shorter in patients with advanced NSCLC and a PS of 2 than in those with a better PS of 0-1, regardless of therapy (Azzoli et al., 2010). Patients with a PS of 2 do not tolerate chemotherapy as well, and treatment approaches should be different (Gridelli et al. 2006).

Available chemotherapy regimens are associated with substantial toxicities (such as febrile neutropenia, myelosuppression, nausea, alopecia, nephropathy, and neuropathy) and are generally poorly tolerated by the majority of the elderly and poor-performance status NSCLC patients. For this reason, fear of unacceptable toxicity is still one of the major concerns in treatment decisions for PS2 patients (Gridelli et al. 2004).

There is a dearth of literature clearly defining the management of patients with stage IV NSCLC and a PS of 2, including issues such as treatment with single agent versus combination and choice of specific agents, such as biologics (Gajra et al. 2014).

ESMO Guidelines 2016 (Novello et al. 2016) reference a recently published meta-analysis of randomised trials comparing the efficacy and safety of platinum-based doublets versus single-agent regimens in the first-line therapy of PS2 patients, which revealed platinum-based regimens to be superior in terms of RR and survival (74% higher probability of being alive after 1 year) despite an increase in toxicities (mainly haematological). In addition, the superiority of carboplatin-based combinations over monotherapy in PS2 patients has been identified in a subgroup analysis within large phase III trials, with an acceptable toxicity profile. Moreover, combination chemotherapy with carboplatin significantly improved survival compared with monotherapy alone in patients with PS2. Therefore, platinum-based (preferably carboplatin) doublets should be considered in eligible PS2 patients.

Single-agent chemotherapy with gemcitabine, vinorelbine and docetaxel represents an alternative treatment option (Novello et al. 2016). In this subgroup of patients, there are instances where poor PS is attributable to a high tumor burden, and improved PS may be expected in response to treatment. In other cases, poor PS may be related to co-morbidity, and a worsening PS may be expected during treatment. Therefore, clinicians

and patients should always discuss the risks and benefits of chemotherapy and should make a joint decision. Poor PS (3-4) patients should be offered BSC in the absence of documented activating (sensitizing) EGFR mutations or ALK rearrangements.

Recent studies that have examined single agents versus 2-drug combinations for patients with PS2 include 3 Phase III trials with planned subgroup analyses by PS, a phase II trial designed exclusively for patients with PS 2, a Phase II trial comparing traditional cytotoxic chemotherapy with erlotinib in patients with PS, and a recently published Phase III trial comparing carboplatin-based combination therapy to a single agent restricted to patients with PS2 (Novello et al. 2016).

Taken together, the median PFS and median OS with platinum-based combination chemotherapy are numerically and, in some studies, statistically superior to those measures in patients with PS2 treated with monotherapy. Notably, this improvement in survival comes with higher toxicity, including the risk of treatment-related death with combination therapy, ranging from 3.0% to 7.4% (Gajra et al. 2014).

There is currently a highly unmet medical need for novel safe treatment options that deliver an improved therapeutic index in newly diagnosed advanced, recurrent or metastatic NSCLC deemed unsuitable for any platinum-doublet chemotherapy due to poor performance status and/or comorbidities.

Targeted agents are widely believed to provide effective and less-toxic therapy while allowing patients to maintain their functional independence (Gonsalves and Ganti, 2011). As a result, great interest has been shown in using targeted agents in patients with poor PS. Data from 2 trials suggest that erlotinib and gefitinib do not have a role in patients with poor PS without activated EGFR mutations (Lilenbaum et al. 2008, Goss et al. 2009).

Clinical data in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer, such as atezolizumab, can result in a significant survival benefit in patients with Stage IV cancer (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

Immune checkpoint inhibition such as targeting the programmed death-ligand 1 (PD-L1) pathway with atezolizumab may provide a safe, less toxic and similarly efficacious treatment alternative to single agent chemotherapy for newly diagnosed patients with advanced or metastatic NSCLC who are considered unsuitable for platinum-containing chemotherapy due to low performance status, substantial comorbidities or contraindications to chemotherapy. Immune checkpoint inhibition treatment could increase the proportion of treatment naive advanced or metastatic NSCLC patients with low performance status who could be considered eligible for treatment (see also Section 1.5)

1.2.2 Platinum-Based Regimen for First-Line NSCLC

Currently, the standard-of-care for newly diagnosed advanced stage NSCLC is a platinum doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. In particular, the combination of platinum doublet with pemetrexed has been used more widely because of a better tolerability and safety profile (see also Section 1.2.3.1).

Pemetrexed disodium for injection was approved in 2008 by the U.S. Food and Drug Administration (FDA) for use in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic NSCLC. Pemetrexed is not indicated for treatment of patients with squamous cell lung carcinoma (SCLC).

Several meta-analyses have compared the use of cisplatin and carboplatin as treatments for NSCLC. In general, although the objective response rate (ORR) was higher in patients treated with cisplatin than in those treated with carboplatin, the 1-year and OS rates were comparable. When given in combination with a third-generation chemotherapy, cisplatin may result in longer survival than carboplatin (overall response of 30% vs. 24% respectively; Hotta et al. 2004; Ardizzoni et al. 2007), but with quite marginal overall benefit. Subgroup analyses including additional, more recent trials indicate that there may be no difference between the two agents (Azzoli et al. 2010; Jiang et al. 2007).

As to safety, cisplatin-based chemotherapy has been associated with more severe nausea and vomiting and nephrotoxicity, while severe thrombocytopenia has been more frequent during carboplatin-based chemotherapy (Hotta et al. 2004; Ardizzoni et al. 2007). The risk of treatment-related deaths was greater in the cisplatin arm, but this increase was not statistically significant (Jiang et al. 2007).

While randomized trials demonstrate that chemotherapy improves survival and quality of life in advanced NSCLC (Davidoff et al. 2010, Pfister et al. 2004) with two-drug platinum based regimens (platinum doublets) indicating a survival advantage compared with single agents (Sandler et al. 2000, Schiller at al. 2002, Kelly et al. 2001), the evidence of treatment efficacy for patients with diminished PS or with age older than 70 years is limited, as these patients are frequently excluded from clinical trials due to the potential for toxicity and an expectation of limited benefit (Gridelli et al. 2007). Patients with ECOG PS ≥ 2 have been shown to experience inferior outcomes when included in clinical trials (Davidoff et al. 2010).

Subset analyses of trials for patients with advanced NSCLC with eligibility ranging from PS 0 to 2 have historically shown that PS2 patients experience a much shorter survival, in the range of 3 to 4 months (Sweeney 2001, Soria et al. 2001, Quoix et al. 2011) highlighting the potential value of studying this population as a distinct clinical entity for which different treatment recommendations may be appropriate.

Current ESMO guidelines (Novello 2016) recommend to consider first-line chemotherapy with platinum doublets in all stage IV NSCLC patients with EGFR- and ALK-negative disease, without major comorbidities and PS 0-2.

1.2.3 Non-Platinum Based Chemotherapy for NSCLC PS2 Patients

After 1995, some advantage of chemotherapy versus supportive care alone has been shown not only with platinum-based combination chemotherapy (Cullen et al. 1999, Billingham et al. 2001, Stephens et al. 2002) but also with many other cytotoxic agents such as gemcitabine (Anderson et al. 2000), vinorelbine (ELVIS group. 1999), paclitaxel (Anderson et al. 2000) and docetaxel (Roszkowski et al. 2000), administered as single agents. These drugs are usually characterized by a good tolerability, with a low incidence of severe adverse events. Most of the studies show some advantage of chemotherapy in terms of overall survival also in the sub-group of PS2 patients, although formal statistical comparisons are precluded by the low absolute number of patients (Gridelli et al. 2006).

Fear of unacceptable toxicity is one of the major concerns in treatment decisions for PS2 patients and, from this point of view, platinum-free combination chemotherapy deserves attention as it is potentially less toxic than platinum-based treatment (Gridelli et al. 2006). Several trials comparing platinum free combinations containing new cytotoxic agents versus platinum-based treatment, enrolling patients with PS between 0 and 2, have been performed (Georgoulias et al. 2001, Kosmidis et al. 2002, Giaccone et al. 2002, Alberola et al. 2003, Gridelli et al. 2003). These trials are characterized by a remarkable heterogeneity among the drugs and schedules studied. As expected, platinum-based treatment is often associated with a higher occurrence of toxicity (Georgoulias et al. 2001, Gridelli et al. 2003).

Although a trend of slightly lower efficacy of combination chemotherapy without platinum is reported in some trials (Giaccone et al. 2002, Gridelli et al. 2003), none of the trials show a statistically significant advantage for platinum-containing schedules. No significant interaction between treatment and PS in terms of overall survival is described, and platinum-free combination chemotherapy could represent a reasonable, less toxic option for PS2 patients (Gridelli et al. 2006).

However, there is no consistent evidence that combination chemotherapy without platinum is better than third generation drugs given as single agents. An Italian randomised trial compared the combination of gemcitabine and vinorelbine to the two single drugs in patients > 70 years of age (Gridelli et al. 2003). PS2 patients represented 18-19% in each of the 3 arms of the study. The primary analysis of the study showed that the combination was more toxic, but it did not show advantage over monochemotherapy in terms of overall survival. Also, in the sub-group of PS2 patients (130 patients), there was no advantage for combination chemotherapy over single agents.

The results of a European Experts Panel on the topic, indicate that single-agent chemotherapy could be the preferred option in the treatment of PS2 patients, with carboplatin-based or low-dose cisplatin-based doublets representing alternative options (Gridelli et al. 2004).

Gemcitabine is one of the most widely used drugs for the treatment of NSCLC (Gridelli et al. 2006). The taxanes (paclitaxel and docetaxel) have demonstrated both activity and tolerability in the treatment of advanced NSCLC (Gridelli et al. 2006). Among the third-generation chemotherapy drugs, the vinca alkaloid vinorelbine showed better than supportive care controls on many quality of life (QoL) subscales in elderly NSCLC patients (Gridelli et al. 2006). Single-agent therapy with pemetrexed is an option for PS2 chemonaïve patients with excessive comorbidities and those who cannot tolerate combination therapy (Zinner et al. 2016).

A systematic database review, performed in 2014, on patients who are considered not suitable candidates for platinum treatment found low-quality evidence suggesting that non-platinum combination and single-agent therapy regimens have similar effects on survival (Santos et al. 2015).

A comparison of 4 studies assessing OS in PS2 patients treated with gemcitabine, docetaxel, pemetrexed and vinorelbine or gemcitabine respectively, is shown in Table 3.

Table 3 Overall Survival in PS2 Patients Treated with Gemcitabine, Docetaxel, Pemetrexed and Vinorelbine or Gemcitabine, respectively

Publication	Number of Patients	Performance Status	Chemo-therapy	Median OS estimate (months)	95% CI (months)
Morère 2010	42	PS2	Gemcitabine	2.4	(1.6-4.4)
Morère 2010	42	PS2	Docetaxel	3.5	(1.8-6.6)
Zukin 2013	102	PS2	Pemetrexed	5.3	(4.1-6.5)
Lilenbaum 2009	190	PS2	Vinorelbine or Gemcitabine	6.6	(5.8-7.3)

CI = confidence interval; OS = overall survival

1.2.3.1 Pemetrexed Monotherapy

Pemetrexed disodium (Alimta®) a third-generation multi-targeted antifolate (Shih et al. 1998), is currently approved in the U.S. and European Union (E.U.) for use in locally advanced or metastatic NSCLC in initial first-line treatment in combination with cisplatin, as a single agent in maintenance treatment for patients whose disease has not

progressed after 4 cycles of platinum-based first-line chemotherapy, and as second-line treatment after prior therapy (Zinner et al. 2016 and references therein).

The pemetrexed first-line and maintenance NSCLC registration trials enrolled patients with a PS of 0-1 (Zinner et al. 2016), whereas the second line registration trial enrolled patients with a PS of 0-2 (Hanna et al. 2004).

A multi-center, randomized, double-blind, placebo-controlled Phase III study (JMEN), compared the efficacy and safety of maintenance treatment with pemetrexed plus BSC (N = 441) with that of placebo plus BSC (N = 222) in patients with locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC who did not progress after 4 cycles of first-line doublet therapy containing cisplatin or carboplatin in combination with gemcitabine, paclitaxel, or docetaxel. First-line doublet therapy containing pemetrexed was not included. All patients included in this study had an ECOG PS of 0 or 1. Patients received maintenance treatment until disease progression. Efficacy and safety were measured from the time of randomization after completion of first-line (induction) therapy. Patients received a median of 5 cycles of maintenance treatment with pemetrexed and 3.5 cycles of placebo. A total of 213 patients (48.3%) completed ≥ 6 cycles and a total of 103 patients (23.4%) completed ≥ 10 cycles of treatment with pemetrexed.

The JMEN study met its primary endpoint and showed a statistically significant improvement in PFS in the pemetrexed arm over the placebo arm (N=581, independently reviewed population; median of 4.0 months and 2.0 months, respectively) (HR=0.60, 95% CI=0.49-0.73, p<0.00001). The independent review of patient scans confirmed the findings of the investigator assessment of PFS. The median OS for the overall population (N = 663) was 13.4 months for the pemetrexed arm and 10.6 months for the placebo arm, HR=0.79 (95% CI=0.65-0.95, p=0.01192). For details refer to Alimta® prescribing information.

A review of the literature on studies involving the use of pemetrexed in patients with advanced NSCLC and a PS of 2 concluded that single-agent therapy remains an option for PS2 chemonaïve patients with excessive comorbidities and those who cannot tolerate combination therapy (Zinner et al. 2016). The authors concluded that supportive care with a focus on palliation of symptoms is important for all patients; and that quality of life should be a key determinant in selecting treatment.

1.2.3.2 Docetaxel Monotherapy

Docetaxel (Taxotere®) is a member of the taxane family of antineoplastic agents and mediates its cytotoxic activity by inhibiting microtubule depolymerization. Docetaxel is administered intravenously (IV).

Docetaxel monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy. Docetaxel is also indicated in

combination with cisplatin for the treatment of unresectable, locally advanced or metastatic NSCLC in patients who have not previously received chemotherapy. The recommended dosage is 75 mg/m² IV over 1 hour every three weeks (q3w).

In NSCLC, docetaxel phase-III trials confirmed its effectiveness in pretreated and chemotherapy-naive patients. Single agent docetaxel showed significant improvement in both survival and quality of life when compared to either best supportive care or standard chemotherapy in previously treated patients. Therefore, it is considered standard for NSCLC second-line chemotherapy.

1.2.3.3 Gemcitabine Monotherapy

Gemcitabine (Gemzar®) is a nucleoside metabolic inhibitor and is given in the management of solid tumors. Gemcitabine is indicated as first-line treatment of patients with locally advanced or metastatic NSCLC, in combination with cisplatin. Gemcitabine monotherapy can also be considered in elderly patients or those with PS2.

Gemcitabine at 1250 mg/m^2 is given intravenously on days 1 and 8 of each q3w cycle.

In a randomised phase III study of 522 patients with inoperable, locally advanced or metastatic NSCLC, gemcitabine in combination with cisplatin showed a statistically significant higher response rate than cisplatin alone (31.0% and 12.0%, respectively, p<0.0001). A statistically significant prolongation of the time to progression, from 3.7 to 5.6 months (log-rank p<0.0012) and a statistically significant prolongation of median survival from 7.6 months to 9.1 months (log-rank p<0.004) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with cisplatin. In another randomised phase III study of 135 patients with stage IIIB or IV NSCLC, a combination of gemcitabine and cisplatin showed a statistically significant higher response rate than a combination of cisplatin and etoposide (40.6% and 21.2%, respectively, p=0.025). A statistically significant prolongation of the time to progression, from 4.3 to 6.9 months (p=0.014) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with etoposide/cisplatin. In both studies it was found that tolerability was similar in the two treatment arms (see gemcitabine SmPC).

ESMO Guidelines (Novello 2016) recommend gemcitabine single-agent chemotherapy as an alternative treatment option in patients with metastatic NSCLC and a PS of 2 and beyond. The NCCN Guidelines Version 3.2017 recommend gemcitabine as monotherapy after progression on doublet chemotherapy or bevacizumab plus chemotherapy in patients with PS 0-2, and as maintenance therapy in PS2 patients following response to chemotherapy or stable disease.

1.2.3.4 Vinorelbine Monotherapy (Intravenous and Oral)

Vinorelbine tartrate (Navelbine®) is a semi-synthetic vinca alkaloid with antitumor activity. Vinorelbine is indicated as a single agent or in combination for first-line treatment of stage III or IV NSCLC.

Vinorelbine is available as concentrate for solution for infusion and as soft capsule for oral administration.

Single-agent vinorelbine was studied in a North American, randomized clinical trial in which patients with Stage IV NSCLC, no prior chemotherapy, and Karnofsky PS ≥ 70 were treated with vinorelbine (30 mg/m^2) weekly or 5-fluorouracil (5-FU) (425 mg/m^2 IV bolus) plus leucovorin (LV) (20 mg/m^2 IV bolus) daily for 5 days every 4 weeks. A total of 211 patients were randomized at a 2:1 ratio to vinorelbine (143) or 5-FU/LV (68). Vinorelbine showed improved survival time compared to 5-FU/LV. In an intent-to-treat analysis, the median survival time was 30 weeks versus 22 weeks for patients receiving vinorelbine versus 5-FU/LV, respectively (p=0.06). The 1-year survival rates were 24% (±4% SE) for vinorelbine and 16% (±5% SE) for the 5-FU/LV group, using the Kaplan-Meier product-limit estimates. The median survival time with 5-FU/LV was similar to or slightly better than that usually observed in untreated patients with advanced NSCLC, suggesting that the difference was not related to some unknown detrimental effect of 5-FU/LV therapy. The response rates (all partial responses) for vinorelbine and 5-FU/LV were 12% and 3%, respectively.

ESMO Guidelines 2016 (Novello 2016) recommend vinorelbine single-agent chemotherapy as an alternative treatment option in patients with metastatic NSCLC and a PS of 2 and beyond. The NCCN guidelines v. 3.2017 recommend vinorelbine single agent chemotherapy as second line treatment in patients who have experienced disease progression either during or after first-line therapy.

1.3 TARGETED THERAPY FOR NSCLC

Genotype-directed therapy has the potential to dramatically improve the balance of benefit and toxicity for selected patients with NSCLC (mainly non-squamous histology) characterized by alterations of driver oncogenes, including sensitizing EGFR mutations and ALK rearrangements. However, these mutations are more prevalent in adenocarcinoma NSCLC and are very rare in squamous NSCLC.

Randomized Phase III trials of gefitinib (IPASS), erlotinib (EURTAC), and afatinib (Lux-Lung 3) showed significant improvement of PFS and ORR compared with platinum doublet chemotherapy (Fukuoka et al. 2011; Rosell et al. 2012; Yang et al. 2012; respectively). Similarly, the ALK inhibitor crizotinib has demonstrated efficacy in patients with NSCLC positive for ALK rearrangement as defined by fluorescence in situ hybridization (Crino et al. 2011; Camidge et al. 2012; Shaw et al. 2012; Shaw and Engelman 2014; Xalkori® U.S. Package Insert).

A randomized open-label Phase III trial demonstrated superior PFS of alectinib to crizotinib in NSCLC patients positive for ALK rearrangement without prior ALK inhibitor treatment. Treatment on both arms was continued until disease progression (PD) or unacceptable toxicity. The PFS HR of the alectinib arm to crizotinib arm was 0.34 (99.6826% CI: 0.17-0.70, stratified log-rank p<0.0001). Grade 3-4 adverse events (AEs)

occurred with greater frequency in the crizotinib arm (51%) compared to the alectinib arm (27%). There were no treatment related deaths in either arm (Nokihara et al. 2016).

Crizotinib (Xalkori) and ceritinib (Zykadia) are approved by the FDA for treatment of NSCLC. Alectinib (Alecensa) was approved by the U.S. FDA in December 2015 to treat patients with advanced ALK-positive NSCLC whose disease worsened after, or who could not tolerate, treatment with crizotinib. These drugs have demonstrated robust clinical activity in patients who developed resistance to crizotinib, and they are now being investigated in the first-line setting (Katayama et al. 2015). Current ESMO guidelines recommend crizotinib as the preferred first-line treatment of patients with ALK-rearranged NSCLC (Novello et al 2016).

Gainor et al. (2016) found that second-generation inhibitors are generally effective even in the absence of crizotinib-resistant ALK mutations, likely reflecting incomplete inhibition of ALK by crizotinib in many cases. The authors found that each ALK inhibitor is associated with a distinct spectrum of ALK resistance mutations and that the frequency of one mutation, ALKG1202R, increases significantly after treatment with second-generation agents. The presence of ALK resistance mutations is highly predictive for sensitivity to the third-generation ALK inhibitor lorlatinib, whereas those cell lines without ALK mutations are resistant.

Despite current progress in treatment of patients with EGFR mutations and ALK rearrangements, survival rates for advanced disease remain low and acquired resistance to targeted agents is a major clinical problem. Therefore, alternative treatment options that yield durable responses and enhance OS remain an important focus of research. Against this background, immunotherapeutic agents, such as cancer vaccines and antibodies that modulate immune cell activity, offer an alternative treatment approach that could potentially improve the prognosis of patients with this disease.

1.4 SECOND-LINE TREATMENT FOR NSCLC

The large majority of NSCLC patients ultimately progress after first-line treatment (Bluthgen and Blesse 2015). Many factors are taken into account when choosing further therapy, including performance status, previous treatment, histology and the presence of a driver mutation (Bluthgen and Blesse 2015). However, only 50–70% of patients with advanced NSCLC patients will have second line treatment, while a substantial proportion of patients do not get further therapy due to side effects or low performance status (Chen et al. 2013).

Several guidelines recommend erlotinib, pemetrexed, or docetaxel for second-line chemotherapy in patients with advanced NSCLC (Nishiyama et al. 2015, Carnio et al. 2014). There is growing evidence that cytotoxics are better than EGFR-tyrosine kinase inhibitors (TKIs) in EGFR wild-type patients.

Patients with a good performance status in second-line trials have a median survival duration of approximately 8 to 9 months and may receive two salvage therapies during the course of their treatment (Stinchcombe et al. 2008).

A retrospective study performed in the U.S. (Pan et al. 2013) assessed actual second-line treatment patterns and outcomes in NSCLC patients with stage IIIB/IV at diagnosis and an ECOG PS < 3. The most frequently used second-line therapies were pemetrexed (54.4%), erlotinib-containing regimens (17.6%), and docetaxel (10.0%). Median OS and PFS were 7.5 (95% CI: 6.6–8.4) and 4.1 (95% CI: 3.7-4.5) months, respectively. Compared with other second-line treatment, erlotinib-containing regimens prolonged adjusted time-to-progression (TTP) (HR = 0.69; p=0.015).

In NSCLC patients with ECOG PS ≥ 2, chemotherapy prolongs survival and possibly improves QoL (Gridelli et al. 2004), when compared with BSC. Single-agent chemotherapy with gemcitabine, vinorelbine, and taxanes represents an option (Gridelli et al., 1999).

A recent study (Maneechawakajorn et al. 2016) compared QoL achieved by carboplatin plus etoposide as third-line chemotherapy (27 cases) compared with BSC (20 cases) in NSCLC Stage IIIB/IV patients. No statistically significant differences were found in baseline characteristics and QoL in the two groups. The median PFS after two months was significantly higher (88.9% vs. 75.0%, p<0.001) in the chemotherapy group than in the best supportive care group, but there were no statistically significant differences between QoL of patients in the two groups.

1.5 IMMUNOTHERAPY IN METASTATIC NSCLC

Immunotherapeutic targeting of PD-L1 or programmed cell death protein 1 (PD-1) is revolutionizing the treatment of metastatic NSCLC (see next section for mechanism). Currently, two anti-PD-1 therapeutic antibodies (pembrolizumab and nivolumab) (Keytruda PI, Opdivo PI) and one anti-PD-L1 antibody (atezolizumab) (Tecentriq PI) have been approved for treatment of NSCLC. All three of these agents are recommended as second-line agents in advanced NSCLC after prior progression on platinum-containing chemotherapy.

As the current clinical study focuses exclusively on atezolizumab, a detailed summary of the efficacy and safety profiles of atezolizumab is provided in subsequent sections.

A brief summary of the activities of the two approved anti-PD-1 agents is provided in Table 4.

Table 4 Nivolumab and Pembrolizumab Immunotherapy in Advanced NSCLC

Trial	**Checkmate 017** (Brahmer 2015, Reckamp 2015)	**Checkmate 057** (Borghaei 2015)	**Keynote 010** (Herbst 2016)
Therapy	2L nivo vs. doc	2/3L nivo vs. doc	≥2L pembro vs. doc
n	272	582	1033
Histology	Squamous	Non-squamous	All comers
PD-L1 selected	No	No	Yes (TPS ≥ 1) [a]
Median OS (months)	9.2 vs. 6.0	12.2 vs. 9.4	12.7 [b] vs. 8.5
Median PFS (months)	3.5 vs. 2.8	2.3 vs. 4.2	4.0 [b] vs. 4.0
ORR (%)	20% vs. 9%	19% vs. 12%	18% [b] vs. 9%

Doc = docetaxel; L = line; nivo = nivolumab; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; pembro = pembrolizumab; PFS = progression-free survival; TPS = tumor proportion score.

[a] Tumor proportion score (TPS) is the proportion of viable tumor cells showing partial or complete membrane PD-L1 expression.

[b] 10 mg/kg q3w dose.

Current ESMO Guidelines (Novello et al. 2016) state that PD-L1-positive tumor patients benefitted from the use of nivolumab (Opdivo), compared with docetaxel. In PD-L1-negative tumors, nivolumab and docetaxel showed similar results, with a more favorable toxicity profile for nivolumab. Ramucirumab (Cyramza) combined with docetaxel is described as a treatment option in patients with NSCLC progressing after first-line chemotherapy with PS 0-2. In patients unfit for chemotherapy, erlotinib (Tarceva) is described as a potential option in patients with unknown EGFR status, wild-type EGFR and unfit for chemotherapy (Novello et al. 2016).

The NCCN Panel recommends immune checkpoint inhibitors nivolumab, pembrolizumab, and atezolizumab as preferred options for subsequent therapy for all histologic subtypes based on improved survival rates, longer duration of response, and fewer adverse events when compared with cytotoxic chemotherapy see NCCN Guidelines v.3 2017 NSCLC, page MS-55).

1.6 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (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.

Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans.

On 18 Oct 2016, U.S. FDA approved atezolizumab for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab.

This approval was based on two international, randomized, open-label clinical trials (OAK and POPLAR) that demonstrated consistent results in efficacy and safety in a total of 1137 patients with NSCLC. Compared with docetaxel, treatment with atezolizumab in the intended patient population in the two trials resulted in a 4.2 and a 2.9 month improvement in OS, respectively.

The median OS in OAK was 13.8 months (95% CI 11.8,15.7) in the atezolizumab arm compared to 9.6 months (95% CI 8.6,11.2) in the docetaxel arm (HR=0.74 [95% CI 0.63,0.87]; p=0.0004). The median OS in POPLAR was 12.6 months (95% CI 9.7, 16.0) and 9.7 months (95% CI 8.6, 12.0) (HR=0.69 [95% CI 0.52, 0.92]) for the atezolizumab and docetaxel arms, respectively.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

1.6.1 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, PK, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support 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 trials in patients.

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

1.7 CLINICAL EXPERIENCE WITH ATEZOLIZUMAB

Refer to the Atezolizumab Investigator's Brochure for details on all clinical studies conducted to date.

1.7.1 Clinical Studies in NSCLC

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 studies that include patients with NSCLC include:

- **Study PCD4989g** is multicenter, first-in-human, open-label Phase Ia, 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 q3w to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.

- **Study GO28625 (FIR)** is an open-label, non-controlled, single-arm Phase II study of atezolizumab in PD-L1−positive patients with locally advanced or metastatic NSCLC, with the evaluation of ORR (modified Response Evaluation Criteria in Solid Tumors [modified RECIST] criteria) as the primary endpoint. This study seeks to better understand whether the assessment of PD-L1 by IHC in fresh biopsy versus archival specimens is more predictive of response to atezolizumab.

- **Study GO28753 (POPLAR)** is an open-label, randomized, Phase II study of atezolizumab compared with docetaxel in patients with locally advanced or metastatic NSCLC following progression on a platinum-containing regimen. Eligible patients were enrolled regardless of PD-L1 status and stratified by PD-L1 expression. The primary endpoint is OS.

- **Study GO28915 (OAK)** is an open-label, randomized, Phase III study of atezolizumab compared with docetaxel in patients with locally advanced or metastatic NSCLC after failure with platinum-containing chemotherapy.

- **Study GO28754 (BIRCH)** is an open-label, non-controlled, single-arm Phase II study of atezolizumab in PD-L1−positive patients with locally advanced or metastatic NSCLC.

- **Study GO29527 (IMpower010)** is a randomized, open-label Phase III study of atezolizumab compared with best supportive care following adjuvant cisplatin-based chemotherapy in patients with completely resected Stage IB to IIIA NSCLC.

- **Study GO29431 (IMpower110)** is a randomized, open-label Phase III study of atezolizumab compared with cisplatin/carboplatin + pemetrexed or cisplatin/carboplatin + gemcitabine in PD-L1−selected chemotherapy-naïve patients with Stage IV non-squamous NSCLC.

- **Study GO29436 (IMpower150)** is an open-label Phase III study of atezolizumab + carboplatin + paclitaxel with or without bevacizumab compared with carboplatin + paclitaxel + bevacizumab in chemotherapy-naïve patients with Stage IV non-squamous NSCLC.

- **Study GO29537 (IMpower130)** is a randomized, open-label Phase III study of atezolizumab + carboplatin + nab-paclitaxel compared with carboplatin + nab-paclitaxel in chemotherapy-naïve patients with Stage IV non-squamous NSCLC.

- **Study GO29437 (IMpower131)** is a Phase III, open-label, multicenter, randomized study evaluating the efficacy and safety of atezolizumab in combination with Carboplatin+ Paclitaxel or atezolizumab in combination with carboplatin+nab-paclitaxel versus carboplatin+nab-paclitaxel in chemotherapy-naive patients with stage IV NSCLC.

- **GO29438 (IMpower132)** is a phase III, open-label, randomized study of atezolizumab in combination with carboplatin or cisplatin + pemetrexed compared with carboplatin or cisplatin + pemetrexed in patients who are chemotherapy-naive and have stage IV NSCLC.

1.7.2 Clinical Safety

1.7.2.1 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. It 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 carcinoma (UC), 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 ≥ 10% of all patients) included fatigue, nausea, decreased appetite, diarrhea, constipation, dyspnea, pyrexia, and cough (see Table 5).

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 5 Adverse Events Reported in ≥ 10% of Patients in Study PCD4989g

Preferred Term	
Any AE ≥ 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%)

1.7.2.2 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 every 3 weeks and 135 patients were treated with docetaxel 75 mg/m2 IV q21d 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 6.

Table 6 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%)

1.7.2.3 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 q21d. In Study GO28754, 93.8% of patients experienced at least one adverse event, 65% of patients experienced one treatment-related adverse event, and 12% of patients experienced a Grade ≥ 3 treatment-related adverse event.

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

1.7.2.4 Atezolizumab as a Combination Agent

To date, there are no additional SADRs considered "expected" for regulatory reporting purposes specific to the combination of atezolizumab when given with another therapeutic agent beyond those presented in Section 1.7.2.1. The SADRs of other therapeutic agents used in combination with atezolizumab can be found in their respective Investigators' Brochure or Prescribing Information.

1.7.3 Clinical Activity

Both the preliminary and more mature efficacy data available suggest that treatment with atezolizumab as a single agent or in combination with other therapeutic agents results in anti-tumor activity across a range of tumor types and hematologic malignancies (urothelial carcinoma [UC], NSCLC, RCC, triple-negative breast cancer [TNBC], melanoma, colorectal carcinoma [CRC], and Non-Hodgkin lymphoma [NHL]) and across lines of therapy.

As of July 2016, the Phase Ia Study PCD4989g (NSCLC Cohort) and the Phase II FIR, POPLAR, and BIRCH had enrolled approximately 1170 efficacy-evaluable patients with locally advanced or metastatic NSCLC across all lines of therapy and PD-L1 expression subgroups who received atezolizumab monotherapy. Overall, the results of these studies demonstrated that 1) higher PD-L1 expression on tumor cells (TCs) or immune cells (ICs) was associated with higher ORRs, 2) responses were durable, and 3) single-agent treatment with atezolizumab resulted in clinically meaningful OS improvement compared to docetaxel in the intent-to-treat (ITT) population, as well as in a positive risk-benefit across all PD-L1 expression subgroups.

An IHC assay has been used that measures specific PD-L1 signals in tumor-infiltrating ICs and TCs. PD-L1 staining categories in ICs are defined as IC0, IC1, IC2, and IC3 and are defined in TCs as TC0, TC1, TC2, and TC3 (see Appendix 12).

Refer to the Atezolizumab Investigator's Brochure for criteria for PD-L1 expression assessment in atezolizumab studies and for updated details on clinical activity in patients with NSCLC treated to date.

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

Patients with multiple tumor types are included in Study PCD4989g, with the largest cohorts consisting of patients with NSCLC, RCC, and urothelial bladder cancer (UBC).

As of the clinical cut-off date of 02 Dec 2014, there were 88 efficacy-evaluable patients with locally advanced or metastatic NSCLC from all lines of therapy in the single-arm Phase Ia Study PCD4989g. The 88 patients received the following atezolizumab dosing: 1 mg/kg q3w = 1, 10 mg/kg q3w = 11, 15 mg/kg q3w = 26, and 20 mg/kg q3w = 50. The primary efficacy endpoint for the NSCLC Cohort in Study PCD4989g was investigator-assessed ORR per RECIST v1.1. Table 7 demonstrates that higher PD-L1 expression

levels on TCs or ICs were associated with higher ORRs (50.0% in TC3 or IC3 vs. 33.3% in TC2/3 or IC2/3 vs. 22.7% in all patients).

Table 7 Study PCD4989g: Investigator-Assessed ORR and DOR per RECIST v1.1 in Efficacy-Evaluable Patients with NSCLC by PD-L1 Expression Subgroup and All Patients

Efficacy Endpoint	TC3 or IC3	TC2/3 or IC2/3	All Patients [a]
ORR	n = 22	n = 48	n = 88
Responders (%)	11 (50.0)	16 (33.3)	20 (22.7)
95% CI	(28.2, 71.8)	(20.4, 48.4)	(14.5, 32.9)
Complete response	0	0	0
Partial response	11	16	20
DOR	n = 11	n = 16	n = 20
Median DOR (months)	14.6	17.3	17.3
95% CI	(8.7, 25.3)	(14.2, NE)	(14.2, 24.7)
Patients with event (%)	6 (66.7)	8 (50.0)	12 (60.0)

CCOD = clinical cutoff date; CI = confidence interval, DOR = duration of response; IC = tumor-infiltrating immune cell; NE = not estimable; NSCLC = non−small cell lung cancer; ORR = objective response rate; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, v1.1; TC = tumor cell.

Notes: The CCOD for these data was 2 December 2014. These responses were confirmed responses.

The primary efficacy analyses in NSCLC were performed using a combination of PD-L1 scores generated at the time of enrollment and available scores generated after enrollment (retrospectively) by pathologist consensus read.

[a] The study population may be reflective of an enriched population, and may not reflect a natural distribution of IC scores.

The median duration of survival follow-up at the time of the clinical cutoff date (CCOD) was 22.5 months. At that timepoint, the median duration of all responders was 17.3 months, with 40% (8 of 20) of responders having an ongoing response.

1.7.3.2 Single-Agent Clinical Activity in Patients with NSCLC in Study GO28753 (POPLAR)

For this Phase II study in advanced or metastatic NSCLC patients who failed prior platinum therapy, preliminary results at the cut-off date of 07 January 2015 (efficacy data available for 137 efficacy evaluable patients with locally advanced or metastatic NSCLC who had a minimum follow-up of 6 months) showed agreement between ORR per modified RECIST and RECIST v1.1. Patients who were responders per modified RECIST but not RECIST v1.1 included a patient in Cohort 1 (first line treatment) who developed a new cerebellar metastasis that was irradiated; the patient went on to experience a complete remission of extra-cranial disease. A patient in Cohort 2 (≥ 2 lines of previous treatment, no brain metastases) who experienced an initial 25% increase in the size of an adrenal lesion (progressive disease) and later achieved a durable response. The majority of responding patients (per modified RECIST and

RECIST v1.1) continued to respond. 13 of 15 RECIST v1.1 responders in Cohort 2 continued to respond, including 8 of 9 patients with TC3 or IC3 tumors. TC3 and IC3 were independently predictive for response in Cohort 2. For patients with TC3 (any IC) tumors (n = 22) the ORR (95% CI) was 23% (8%-45%), and for patients with IC3 (any TC) tumors (n = 21), the ORR was 29% (11%-52%) (Spigel et al. 2015).

At the time of primary analysis of OS (data cutoff: 08 May 2015), data was available for 287 patients in the ITT population (144 and 143 patients in the atezolizumab and docetaxel treatment arms, respectively) with a minimum follow-up duration of 13 months. At this time, 173 deaths had occurred (60.3% event-patient rate; approximately 13 months after the last patient was enrolled). The ITT population analysis showed a clinically meaningful and statistically significant improvement in OS for atezolizumab-treated patients compared with docetaxel with a stratified HR of 0.73 (95% CI: 0.53, 0.99; p=0.04). The median OS was 12.6 months in the atezolizumab arm versus 9.7 months in the docetaxel arm. Improvement in OS in the atezolizumab arm relative to docetaxel increased with increasing PD-L1 expression. TC3 or IC3 with unstratified HR of 0.49 (p = 0.068), TC2/3 or IC2/3 with unstratified HR of 0.54 (p=0.015), and TC1/2/3 or IC1/2/3 with unstratified HR of 0.59 (p=0.0050). In the TC0 or IC0 subgroup, median OS was 9.7 months in both, the atezolizumab and docetaxel arms, suggesting that atezolizumab-treated patients in this subgroup also derived clinical benefit.

Relative to the primary analysis, an updated analysis of efficacy and safety with longer follow-up conducted with 200 events (70% event/patient ratio) and a minimum follow-up of 20 months (data cutoff: 01 Dec 2015) showed improvement in OS benefit in ITT (HR, 0.69 vs 0.73) and PD-L1 subgroups, most notably, the TC0 and IC0 subgroup (HR, 0.88 vs 1.04) (Smith et al. 2016).

At the time of 173 OS events (data cutoff: 08 May 2015), in the ITT population, investigator-assessed ORR (confirmed responses) per RECIST v1.1 was similar in both treatment groups (14.6% in atezolizumab and 14.7% in docetaxel), with the atezolizumab arm having 1 confirmed response. Objective response benefit was most pronounced in the atezolizumab arm relative to the docetaxel arm in the TC3 or IC3 (37.5% vs. 13.0%) and TC2/3 or IC2/3 subgroups (22.0% vs. 14.5%). The overall results suggested that higher PD-L1 expression levels on TCs or ICs correlated with higher ORRs.

Among responders at the primary analysis on 8 May 2015, the median duration of response (DOR) in the atezolizumab arm of the ITT population was doubled that of the docetaxel arm: 14.3 months versus 7.2 months (unstratified HR of 0.41, 95% CI: 0.18, 0.96). Further, 12 of the 21 (57.1%) atezolizumab responders had ongoing responses compared with 5 of 21 (23.8%) docetaxel responders. Across the PD-L1 expression subgroups, the atezolizumab arm generally had more patients with ongoing responses (range of 33% to 100% of patients without disease progression or death) than the docetaxel arm (range of 24% to 33% of patients without disease progression or death).

1.7.3.3 First Phase III Study of Atezolizumab in Previously-treated NSCLC in Study GO28915 (OAK)

OAK is a phase III study of atezolizumab monotherapy versus docetaxel in 1225 patients with locally-advanced or metastatic NSCLC. Eligible patients had relapsed disease that was progressing after 1–2 prior lines of chemotherapy (including at least 1 platinum-based regimen) and were allowed to have any PD-L1 expression status. OAK has two co-primary endpoints: OS in the ITT population; and OS in the TC1/2/3 or IC1/2/3 subgroup (≥ 1% PD-L1 expression). A pre-specified analysis of the first 850 patients, which provided sufficient power to test both co-primary endpoints, was presented at the 2016 meeting of the European Society for Medical Oncology (Barlesi 2016).

At baseline, the atezolizumab (n=425) and the docetaxel (n=425) treatment groups had similar histology distributions, performance statuses, prior therapy rate, tobacco use, central nervous system (CNS) metastasis rates, and EGFR statuses.

In all patients (ITT population), the median OS was 13.8 months (95% CI, 11.8–15.7 months) in the atezolizumab group versus 9.6 months (95% CI, 8.6–11.2 months) in the docetaxel group, indicating a significant treatment effect in favor of atezolizumab (HR, 0.73; p=0.0003). One-year survival rates were 55% and 41% in the atezolizumab and docetaxel groups of the ITT population, respectively, whereas the 18-month survival rates were 40% and 27% in the two treatment groups.

In the TC1/2/3 or IC1/2/3 subgroup (≥ 1% PD-L1 expression), which comprised 55% of enrolled patients, the median OS was 15.7 months (95% CI, 12.6–18.0 months) in the atezolizumab group versus 10.3 months (95% CI, 8.8–12.0 months) in the docetaxel group, again indicating a significant treatment effect in favor of atezolizumab (HR, 0.74; p=0.0102). Median OS positively correlated with PD-L1 expression status. Thus, 16% of patients were classified as TC3 or IC3; 31% were classified as TC2/3 or IC2/3; 55% were classified as TC1/2/3 or IC1/2/3; and 45% were classified as TC0 and IC0. Median OS in these subgroups were 20.5 months, 16.3 months, 15.7 months, and 12.6 months, respectively.

In other analyses, patients with nonsquamous histology, squamous histology, CNS metastases, and no CNS metastases all had significantly longer median survival rates in the atezolizumab group, while patients in the TC3 or IC3 subgroup and in the TC2/3 or IC2/3 subgroup had also longer PFS times in the atezolizumab group. The ORR rates in the ITT population in the atezolizumab and docetaxel groups were 16.3% and 6.2%, respectively.

1.7.3.4 Single-Agent Clinical Activity in Patients with NSCLC in Study GO28625 (FIR)

The single-arm Phase II FIR evaluated atezolizumab monotherapy (1200 mg IV q3w) in patients with PD-L1−selected (defined as TC2/3 or IC2/3) NSCLC. Patients were enrolled in the following cohorts: Cohort 1 (1L), Cohort 2 (2L +) and Cohort 3 (2L + with

previously treated brain metastases). At the primary analysis on 7 January 2015, there were 137 efficacy-evaluable patients with at least 6 months of follow-up across all 3 cohorts.

The primary efficacy endpoint was investigator-assessed ORR (confirmed responses) per modified RECIST. For each cohort, the confirmed ORR for each PD-L1 expression subgroup was similar using either modified RECIST or RECIST v1.1 criteria. At the time of the CCOD, median DOR per RECIST v1.1 was not reached in any cohort or PD-L1 expression subgroup (see Table 8).

Table 8 Study GO28625 (FIR): Investigator-Assessed ORR per RECIST v1.1 and Immune-Modified RECIST

	Immune-Modified RECIST			RECIST v1.1		
	Cohort 1 (1L)	**Cohort 2 (2L +)**	**Cohort 3 (2L + with brain mets)**	**Cohort 1 (1L)**	**Cohort 2 (2L +)**	**Cohort 3 (2L + with brain mets)**
ORR						
TC3 or IC3	n = 7	n = 38	n = 8	n = 7	n = 38	n = 8
ORR n (%)	2 (28.6)	10 (26.3)	2 (25.0)	2 (28.6)	9 (23.7)	2 (25.0)
(95% CI)	3.7, 71.0	13.4, 43.1	3.2, 65.1	3.7, 71.0	11.4, 40.2)	3.2, 65.1)
CR	0	1	0	0	1	0
PR	2	9	2	2	8	2
TC2/3 or IC2/3	n = 31	n = 93	n = 13	n = 31	n = 93	n = 13
ORR n (%)	9 (29.0)	16 (17.2)	3 (23.1)	8 (25.8)	15 (16.1)	3 (23.1)
(95% CI)	14.2, 48.0	10.2, 26.4	5.0, 53.8	11.9, 44.6	9.3, 25.2	5.0, 53.8
CR	1	2	0	0	2	0
PR	8	14	3	8	13	3
DOR						
TC3 or IC3	n = 2	n = 10	n = 2	n = 2	n = 9	n = 2
Median DOR (months)	NE	NE	NE	NE	NE	NE
(95% CI)	(2.9, NE)	(10.4, NE)	(NE)	(2.9, NE)	(10.4, NE)	(NE)
Pts w. event (%)	1 (50.0)	1 (10.0)	0	1 (50.0)	1 (11.1)	0
TC2/3 or IC2/3	n = 9	n = 16	n = 3	n = 8	n = 15	n = 3
Median DOR (months)	9.0	NE	NE	NE	NE	NE
(95% CI)	(NE)	(10.4, NE)	(NE)	(2.9, NE)	(10.4, NE)	(4.2, NE)
Pts w. event (%)	3 (33.3)	2 (12.5)	0	2 (25.0%)	2 (13.3)	1 (33.3)

1L = first line; 2L + = second line and beyond; CCOD = clinical cutoff date; CI = confidence interval; CR = complete response; DOR = duration of response; IC = tumor-infiltrating immune cell; L = line; mets = metastases; NE = not estimable; ORR = objective response rate; PR = partial response; PTs = patients; RECIST = Response Evaluation Criteria in Solid Tumors; TC = tumor cell.

Notes: The CCOD for these data was 7 January 2015. These responses were confirmed responses.

1.7.3.5 Clinical Pharmacokinetics

Atezolizumab PK and other data have been analyzed from the following atezolizumab monotherapy studies: PCD4989g, JO28944, IMvigor 210, BIRCH, POPLAR, and FIR. The key PK findings from the above-listed atezolizumab monotherapy clinical studies are summarized below:

- The PK of atezolizumab monotherapy has been characterized in patients in Study PCD4989g at doses 0.01 mg/kg to 20 mg/kg q3w, including the fixed dose 1200 mg (equivalent to 15 mg/kg). Exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg. While a subset of ATA-positive patients in Study PCD4989g receiving 0.3 to 3 mg/kg atezolizumab q3w experienced a reduction of atezolizumab minimum observed plasma concentration (C_{min}) to below the PK assay lower limit of quantification (LOQ), patients receiving 10 to 20 mg/ kg atezolizumab, including the fixed 1200 mg dose, maintained geometric mean C_{min} that was in excess of both the LOQ and the target serum concentration of 6 µg/mL.

- A Phase I population pharmacokinetic (popPK) analysis that included 472 patients from Studies PCD4989g and JO28944 described atezolizumab pharmacokinetics for the dose range 1−20 mg/kg with a linear two-compartment disposition model with first-order elimination. The popPK analysis indicated that central compartment volume of distribution (V_1) was 3.28 L and the volume of distribution at steady state (V_{ss}) was 6.91 L in the typical patient. Further, the clearance (CL) of atezolizumab was 0.20 L/day and the half live ($t_{1/2}$) was 27 days. Steady state was obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in area under the curve (AUC), maximum observed plasma concentration (C_{max}) and C_{min} was 1.91, 1.46, and 2.75-fold, respectively.

- Based on an analysis of exposure, safety, and efficacy data, the following factors had no clinically relevant effect: age (21−89 years), body weight, gender, positive ATA status, albumin levels, tumor burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status.

- The effect of moderate or severe hepatic impairment (bilirubin > upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or bilirubin ≥ 1.0 to 1.5 × ULN and any AST) on the pharmacokinetics of atezolizumab is unknown.

- No formal PK drug-drug interaction studies have been conducted with atezolizumab. The drug interaction potential of atezolizumab is unknown.

Refer to the Atezolizumab Investigator's Brochure for details regarding atezolizumab pharmacokinetics.

1.7.3.6 Immunogenicity

Immunogenicity data are available for the following single-agent atezolizumab studies: PCD4989g, IMvigor 210, POPLAR, BIRCH, and FIR. ATAs to atezolizumab have been observed at all dosing levels. ATA positivity had no major effect on atezolizumab concentrations and pharmacokinetics although there was a trend for lower C_{min} values in the ATA−positive subgroup. For doses ≥ 10 mg/kg, average C_{min} remained well in excess of the target serum concentration of 6 µg/mL in the ATA−positive patients.

The presence of ATAs did not appear to have a clinically significant impact on pharmacokinetics, safety, or efficacy. Samples that could be evaluated for neutralizing antibodies in these studies were too few in number (approximately 6%) to draw any conclusions.

Refer to the Atezolizumab Investigator's Brochure for updated details regarding atezolizumab immunogenicity.

1.8 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

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

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). Ligation 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 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 reinvigorate tumor-specific T-cell immunity.

PD-L1 expression is prevalent in many human tumors, and elevated PD-L1 expression is associated with a poor prognosis in patients with NSCLC (Mu et al. 2011). Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies and who have failed standard-of-care therapies. In Study PCD4989g, a Phase I dose-escalation and expansion study, objective responses with

atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, UBC, CRC, head and neck cancer, gastric cancer, breast cancer, and sarcoma.

Patients newly diagnosed with advanced or metastatic NSCLC and a poor PS, irrespective of age, have an increased incidence of adverse effects with standard chemotherapy and have a poorer OS (Gajra et al. 2014, Sweeney et al. 2001). Therefore, novel treatments are needed that provide comparable efficacy to the existing treatment options but ensure a higher tolerability of treatment.

OS benefit with atezolizumab vs docetaxel has been seen in both unselected patients (ITT population) and PD-L1-expression subgroups in study GO28753 (POPLAR) (Vansteenkiste et al. 2015, Fehrenbacher et al. 2016, also Section 1.7.3.2) and OAK (see Section 1.7.3.3).

In study GO28625 (FIR), which enrolled PD-L1-selected first-line or greater NSCLC patients, at the primary analysis on 137 efficacy-evaluable patients, confirmed ORR (RECIST v1.1) after the first-line treatment with atezolizumab was 28.6% (95% CI: 3.7-71.0) in IHC TC3 or IC3 patients and 25.8% (95% CI: 11.9-44.6) in IHC TC2/3 or IC2/3 patients (see Section 1.7.3.4).

Study GO28754 (BIRCH) enrolled PD-L1-selected first-line or greater NSCLC patients with locally advanced or metastatic NSCLC. At the time of the primary analysis on 28 May 2015, 659 efficacy-evaluable patients had completed at least 6 months of follow-up. The highest level of PD-L1 IHC expression (TC3 or IC3) showed the highest ORRs across all lines of therapy: 27.0% in third line and beyond, 25.3% in second line and beyond, 23.8% in second line, and 26.2% in first line. The median OS was not reached for all subgroups with the exception of TC2/3 or IC2/3 in Cohort 1 (first line), where the median was 14.0 months (95% CI: 14.0, NE). Overall, however, the OS data across all subgroups were not mature, with ≥ 60.5% of patient still alive (range of 60.5% to 74.1%). The landmark 12-month event-free OS rate in the 2L + TC2/3 or IC2/3 subgroup was 55.3%.

Atezolizumab has been generally well tolerated (see Section 1.7). Across all studies and tumor types, the most commonly reported adverse events with single-agent atezolizumab include fatigue, nausea, decreased appetite, diarrhea, constipation, and cough. To date, these events have been manageable with treatment. The tolerability profile of atezolizumab encourages atezolizumab treatment beyond disease progression (RECIST v.1.1) and until loss of clinical benefit in newly diagnosed NSCLC patients with advanced or metastatic disease who present with a poor performance status (≥ PS2).

On the basis of these observations, Study MO29872 is designed to evaluate whether the anti-tumor effect seen in atezolizumab-treated patients would translate into prolonged OS compared with single agent chemotherapy in patients with in patients with

treatment-naïve locally advanced or metastatic NSCLC who are deemed unsuitable for any platinum-doublet chemotherapy due to an ECOG performance status of ≥ 2 or substantial comorbidities and/or contraindication(s) for platinum-based antineoplastic drugs.

Given the unique toxicities (i.e., alopecia, neutropenia, febrile neutropenia) associated with the single agent chemotherapy agents used to treat patients with Stage IV NSCLC who are deemed unsuitable for any platinum-doublet chemotherapy, this study assumes about equal efficacy of atezolizumab treatment in prolonging OS compared to single agent chemotherapy while providing a significantly better tolerability profile.

This study will enroll patients with NSCLC. Given the relatively poor prognosis and limited treatment options for these patients, this population is considered appropriate for trials of novel therapeutic candidates. The benefit–risk ratio for atezolizumab is expected to be acceptable in this setting.

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

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

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

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for *SARS-CoV-2 infection*–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 of 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 4.4.1.1).

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab compared with single agent chemotherapy in patients with treatment-naïve locally advanced or metastatic NSCLC who are deemed unsuitable for any platinum-doublet chemotherapy, as measured by OS.

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives for this study are:

- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy as measured by OS rates at 6, 12, 18 and 24 months
- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator-assessed ORR using RECIST v1.1 (Appendix 3)
- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator-assessed PFS using RECIST v1.1
- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator-assessed DOR using RECIST v1.1.
- To evaluate the efficacy (OS and investigator-assessed PFS using RECIST v1.1) of atezolizumab compared with single agent chemotherapy in patients with PD-L1 expression defined by the PD-L1 SP263 IHC assay

2.2 SAFETY OBJECTIVES

The safety objective of this study is:

- To evaluate the safety and tolerability of atezolizumab compared with single agent chemotherapy

2.3 PATIENT-REPORTED OUTCOME OBJECTIVE

The patient-reported outcome (PRO) objective for this study is:

- To evaluate and compare PROs of lung cancer symptoms, patient functioning, and health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and treatment of Cancer (EORTC) Quality-of-life Questionnaire Core 30 (QLQ-C30) (Appendix 6) and its Lung Cancer Module (QLQ-LC13) (Appendix 7)

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are:

- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator-assessed ORR, PFS and DOR according to modified RECIST (immune-mediated response criteria; imRC) (Appendix 4)
- To evaluate and compare investigator-assessed disease control rates (DCR) between the two treatment arms using RECIST v1.1
- To evaluate the relationship between the main efficacy endpoints and tumor tissue PD-L1 expression
- To evaluate the relationship between the main efficacy endpoints and exploratory biomarkers in tumor tissue and plasma
- To evaluate the relationship between the main efficacy endpoints and the expression of immune markers in peripheral blood mononuclear cells (PBMCs)
- To generate utility scores for use in economic models for reimbursement by collecting patient's health status data using the EuroQoL-5 Dimensions 5-level (EQ-5D-5L) questionnaire (Appendix 8)

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, global, multicenter, open-label, randomized, controlled study designed to evaluate the efficacy and safety of atezolizumab compared with a single agent chemotherapy regimen by investigator choice (vinorelbine or gemcitabine) in treatment-naïve patients with locally advanced or metastatic NSCLC who are deemed unsuitable for any platinum doublet chemotherapy due to poor performance status (ECOG PS of 2-3).

However, patients ≥ 70 years of age who have an ECOG PS of 0 or 1 may be included if they are deemed unsuitable for any platinum-doublet chemotherapy by the investigator due to:

a) substantial comorbidities

b) contraindication(s) for platinum-doublet chemotherapy.

Eligible patients will be stratified by (a) histologic subtype (non-squamous/squamous), (b) PD-L1 IHC status (positive/negative/unknown) and (c) brain metastases (yes/no) and then randomized at a 2:1 ratio to receive either atezolizumab or single agent chemotherapy.

Eligible patients must therefore provide a tumor tissue specimen for central assessment of PD-L1 expression by IHC at a central laboratory. The study will enroll all patients whose tissue is evaluable for PD-L1 analysis, regardless of PD-L1 expression status.

Given the unique toxicities associated with chemotherapy (i.e., alopecia, neutropenia, febrile neutropenia) and the pre-medications required (i.e., steroid, anti-emetics, and potentially growth factor support), this will be an open-label study.

No crossover will be allowed between treatment arms.

Atezolizumab at a fixed dose of 1200 mg will be administered intravenously on Day 1 of each 21-day cycle.

Patients randomized to receive single agent chemotherapy approved in their country (vinorelbine [oral or intravenous] or gemcitabine [intravenous]), based on investigator's choice will receive chemotherapy per relevant local guidelines and SmPC management. Doses and dose modifications for the selected single agent chemotherapy should be made per relevant local guidelines and SmPC management.

At any time-point after RECIST v1.1 criteria for progressive disease are met, patients in the experimental arm with atezolizumab who show evidence of clinical benefit, will be permitted to continue treatment with atezolizumab until loss of clinical benefit, unacceptable toxicity, patient or physician decision to discontinue, or death, if they meet all of the following criteria:

- Evidence of clinical benefit (i.e., in the absence of symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], clinical status, and of laboratory values)
- Absence of unacceptable toxicity
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial progression.

Tumor assessments will be performed at baseline, every 6 weeks (± 5 days) following randomization for 48 weeks, and every 9 weeks (± 5 days) thereafter, with additional scans as clinically indicated. Assessments will continue until disease progression per RECIST v1.1. Patients randomized to atezolizumab who continue to receive atezolizumab following disease progression will undergo tumor assessments until treatment discontinuation. Tumor assessments should continue regardless of whether patients discontinue study treatment or start new anti-cancer therapy in the absence of disease progression unless they withdraw consent.

In all patients, response will be assessed by the investigator using RECIST v1.1 (see Appendix 3) until disease progression. Patients randomized to receive atezolizumab will additionally be assessed by modified RECIST criteria (see Appendix 4) until treatment discontinuation.

Follow-up data capture, including subsequent anticancer therapies, will continue for each patient until death, withdrawal of consent, loss to follow-up, or study termination by Sponsor, whichever occurs first.

In addition to PD-L1 analysis, exploratory research will be performed on histological tumor tissue samples pre-treatment.

Patients will undergo blood sample collection for exploratory biomarker analyses using plasma and PBMCs as per schedule of assessments.

Tissue and plasma samples will be analyzed for example by methods like IHC, quantitative reverse transcriptase PCR (qRT-PCR), next-generation sequencing (NGS) and/or other methods to study tumor biomarkers and changes thereof on DNA, RNA and/or protein (or other analytes).

These exploratory biomarker evaluations will not be used for any treatment-related decisions. Exploratory analyses aim to study tumor-associated alterations to further understand disease pathobiology (including but not limited to mechanisms of disease progression, pseudo-progression, acquired resistance), to evaluate surrogate biomarkers and to potentially allow for the development of blood-based and tissue-based diagnostic tests to help predict which patients may benefit from atezolizumab.

Primary imaging data used for tumor assessment may be collected by the Sponsor to enable centralized, independent review of response endpoints, if needed.

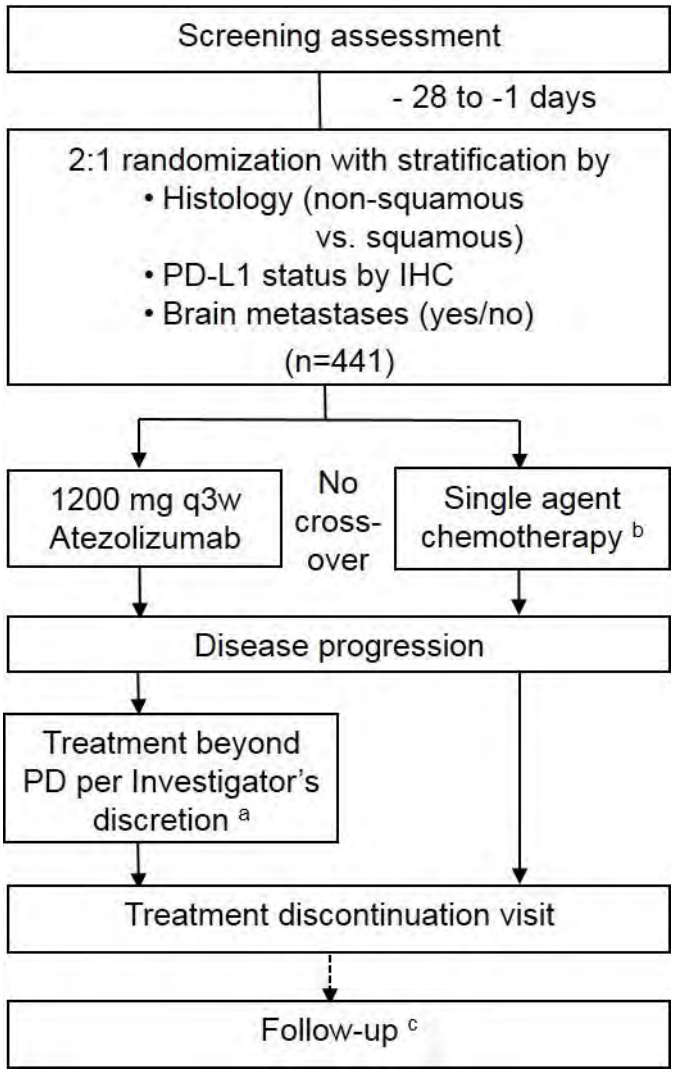
Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 and assessed by immune-mediated adverse event (imAE) and immune-mediated adverse reaction (imAR) methods. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. An external independent Data Monitoring Committee (iDMC) will be assembled and will be responsible for monitoring the safety of patients in the study in accordance with a pre-specified iDMC charter.

During the study, assessments will be performed according to the Schedule of Assessments (Appendix 1).

3.1.1 Overview of Study Design

An overview of the study design is provided in Figure 1.

Figure 1 Study Schema



IHC = immunohistochemistry; NSCLC = non-small cell lung cancer; PD = disease progression; PD-L1 = programmed cell death-ligand 1; q3w = every 3 weeks.

[a] Patients in the experimental arm with atezolizumab who show evidence of clinical benefit, may continue atezolizumab treatment after disease progression (RECIST v 1.1) if they meet criteria specified in Section 3.1.

[b] Single agent chemotherapy (vinorelbine, oral or intravenous, or gemcitabine, intravenous) based on investigator's choice will be administered per relevant local guidelines and SmPC management. Chemotherapy cycles may be 3-weekly or 4-weekly.

[c] Follow-up information, including subsequent anticancer therapies and any treatment related adverse events, will be collected via telephone calls and/or clinic visits every 2 months (± 5 days) until death, withdrawal of consent, loss to follow-up, study termination by the Sponsor, or protocol-defined end of study, whichever comes first.

3.1.2 Independent Data Monitoring Committee

An iDMC will be used to evaluate safety data during the study on a periodic basis, approximately every 6 months from the time when the first patient is enrolled. Members of the iDMC will be external to the Sponsor and will follow a predefined Charter that outlines their roles and responsibilities.

All summaries and analyses by treatment arm for the iDMC review will be prepared by an unblinded independent statistician (independent Data Coordinating Center [iDCC]) external to the Sponsor. The safety data will include demographic data, adverse events, serious adverse events, and relevant laboratory data.

Following the data review, the iDMC will provide a recommendation to the Sponsor as to whether the study may continue, whether amendment(s) to the protocol should be implemented, or whether the study should be stopped. The final decision will rest with the Sponsor.

The iDMC will also be responsible for evaluating efficacy data at the pre-specified OS interim analysis. The interim analysis of efficacy data will be conducted in accordance with the methods that are specified in the Statistical Analysis Plan (SAP). The iDMC recommendations to stop the study because of substantial evidence of efficacy of the study drug or to continue to the final analysis shall be based on the specified interim analysis stopping guidelines as specified in the iDMC charter and SAP.

Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the Institutional Review Boards/Ethics Committees (IRBs/ECs) and to the study sites.

3.2 END OF STUDY AND LENGTH OF STUDY

This study is event-driven, with a recruitment period of approximately 24 months. The required number of 380 events for the final analysis of the primary endpoint of OS is expected to occur approximately 42 months after the first patient has been enrolled. A cut-off date for final analysis will be set at least 54 months after first patient in should 380 OS events not be reached.

For patients randomized to the atezolizumab treatment arm, treatment may continue beyond disease progression per RECIST v1.1 until loss of clinical benefit, unacceptable toxicity, patient or physician decision to discontinue, or death. For all patients, tumor response data collection will continue until disease progression, even if the patient stops study treatment prior to disease progression. Patients randomized to receive atezolizumab who continue study treatment after disease progression continue to undergo tumor assessments until atezolizumab discontinuation.

Follow-up data capture, including subsequent anticancer therapies, will continue for each patient until death, withdrawal of consent, loss to follow-up, or study termination by Sponsor, whichever occurs first.

The end of the study is when the required number of deaths have been observed. Additionally, the Sponsor may decide to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

This Phase III study design is based on the assumption that in patients with treatment-naïve advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC, who are deemed unsuitable for any platinum-doublet chemotherapy, treatment with atezolizumab has the potential to demonstrate superior efficacy by prolonging OS with possibly favorable safety profile compared to single agent chemotherapy.

This first Phase III trial of a PD-L1-directed drug in NSCLC, study GO28915 (OAK), demonstrated that atezolizumab treatment results in a statistically significant and clinically relevant improvement in OS versus docetaxel in second line/third line NSCLC, regardless of PD-L1 expression and histology. Atezolizumab was well tolerated with a favorable safety profile versus docetaxel (Barlesi, Park et al. 2016).

3.3.1 Rationale for Patient Population

Most of patients with newly diagnosed NSCLC present with locally advanced or metastatic disease (Carnio et al. 2014). In addition, it is estimated that 30% to 40% of patients with NSCLC have a poor PS, defined as a score of 2 or higher on the ECOG scale, because of their disease burden, comorbidities, or both. Survival is shorter in these patients than in those with a better PS, and they do not tolerate chemotherapy as well (Govindan, 2004).

Efficient therapies for patients unsuitable for chemotherapy who have poor ECOG PS2 are not available to date, which shows the need for a safe and tolerable treatment option in this patient population. The safety profile of atezolizumab as well as the benefit seen in good performing patients across PD-L1 strata give rationale to include all patients irrespective of PD-L1 status into the study.

Responses to atezolizumab have been observed in patients with high PD-L1 expression (TC2/3 or IC2/3) as well as patients in the TC0 or IC0 subgroups, suggesting that PD-L1 negative patients also derive clinical benefit (see Section 1.7.3.2 and Section 1.7.3.3). The inclusion of patients irrespective of PD-L1 expression level will allow (a) a robust assessment of the hypothesis that PD-L1-positive status is predictive of increased efficacy with atezolizumab treatment relative to PD-L1-negative status, but also (b) allow for the evaluation of OS benefit in the overall population relative to single agent chemotherapy treatment irrespective of PD-L1 status. In addition, because of the

assumed higher tolerability of atezolizumab compared to chemotherapy and also assumed higher efficacy, this immunotherapeutic agent should not be withheld from patients who have a low, negative or unknown PD-L1 status, given there is a chance of treatment benefit.

The OAK phase III randomized trial assessed atezolizumab versus docetaxel alone in patients with metastatic NSCLC who had progressed during or after systemic therapy survival was improved with atezolizumab regardless of PD-L1 expression levels, including in patients with no PD-L1 expression (TC0 and IC0; HR=0.75) (Barlesi, Park et al. 2016).

This study includes NSCLC patients with squamous and non-squamous histology, as OS benefit to atezolizumab has been observed in both groups (see OAK study, Section 1.7.3.3).

3.3.2 Rationale for Control Arm

This study aims to compare response to atezolizumab treatment with standard of care treatment in patients with locally advanced or metastatic NSCLC who are deemed unsuitable for any platinum-doublet chemotherapy.

The two chemotherapeutic agents permitted in this study, vinorelbine (oral capsules and for intravenous infusion) or gemcitabine (for intravenous infusion), are internationally recognized and recommended treatment options in locally advanced stage III and metastatic non-small-cell lung cancer) (Eberhardt et al. 2015, Reck et al. 2014).

Current ESMO guidelines recommend single-agent chemotherapy with gemcitabine, vinorelbine (oral and intravenous) and docetaxel as an alternative treatment option for NSCLC patients with a PS of 2 and beyond who do not tolerated platinum-based chemotherapy (Novello 2016).

However, docetaxel is not included in this trial because of the assumption that docetaxel has a markedly worse safety profile compared to vinorelbine (oral and intravenous) and gemcitabine in the study population of patients with a PS of 2-3. Immunotherapy is generally better tolerated than chemotherapy. Considering further the lower safety profile of docetaxel compared with atezolizumab observed in the POPLAR study (Table 9), the use of docetaxel as a comparator in this study seems unjustified.

Table 9 Safety Profile of Atezolizumab versus Docetaxel in Study GO28753 (POPLAR)

Parameter	Docetaxel (n=135)	Atezolizumab (n=142)
Any AE	130 (96.3%)	136 (95.8%)
Related AE	119 (88.1%)	95 (66.9%)
Grade 3-4	71 (52.6%)	58 (40.8%)
Related Grade 3-4	52 (38.5%)	17 (12.0%)
Grade 5	5 (3.7%)	7 (4.9%)
Related Grade 5	3 (2.2%)	1 (0.7%)
SAE	46 (34.1%)	51 (35.9%)
Any AE leading to withdrawal of study drug	30 (22.2%)	12 (8.5%)

AE = adverse event; SAE = serious adverse event.

[a] The CCOD for POPLAR was 1 December 2015, corresponding to an updated safety analysis.

3.3.3 Rationale for Atezolizumab Dosing

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 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. The MTD of atezolizumab was not reached. Currently, no maximum tolerated dose, no dose-limiting toxicities, and no clear dose-related trends in the incidence of adverse events have been determined, and no DLTs have been observed. 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 pharmacokinetics evaluation.

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

3.3.4 Rationale for Open-Label Study

An open-label study design was chosen for this study for the following reasons: Given the known toxicities associated with single agent chemotherapy and due to different dosing schedules, patients assigned to chemotherapy, as well as physicians, may be capable of identifying treatment assignment in a blinded study. In addition, a blinded study would require prolonged administration of placebo, which would pose a significant burden to patients.

Adequate steps have been taken to ensure the validity of data in an open-label study design. This includes performing efficacy assessments at the same frequency in both arms, adhering to protocol-defined schedules, and determining the strategy for the final analysis of the primary endpoint prior to study start, including predefined methods for handling missing data and censoring rules. Efficacy analyses will only be performed at the prespecified analysis timepoints in the protocol (primary analysis once the number of OS events presented in Section 6.1 have occurred in the ITT population).

3.3.5 Rationale for Primary and Secondary Endpoints

Improvement in OS is generally accepted as the best measure of clinical benefit for patients with advanced/unresectable or metastatic NSCLC. The assumption that treatment with atezolizumab will prolong OS compared with treatment with single-agent chemotherapy is based on the durable response rates observed in Phase I trials with atezolizumab, as well as other PD-L1/PD-1 blocking agents. Given the poor prognosis with an assumed median duration of OS in the control arm in this study population of 7 months, a surrogate primary endpoint (e.g., PFS, response rate [RR]) would be unjustifiable.

In Study GO28915 (OAK), OS was improved regardless of PD-L1 expression levels, including in pts with no PD-L1 expression (TC0 and IC0). OS was 59% greater among patients in the highest tertile of PD-L1 expression (TC3 or IC3) ($p<0.0001$). However even in patients with no PD-L1 expression, there was still a significant 25% improvement in OS with atezolizumab compared to those treated with docetaxel. The improvements in overall survival were similar in patients with squamous and non-squamous histology.

The secondary efficacy endpoints of OS rates at 6, 12, 18 and 24 months, ORR, PFS and DOR will allow the evaluation of differences in response and progression patterns

between the two treatment groups. The secondary efficacy endpoint of OS and PFS in patients with PD-L1 expression defined by the PD-L1 SP263 IHC assay will help to identify subsets of patients who benefit most from atezolizumab monotherapy when tested with the Ventana PD-L1 SP263 IHC assay. Patients will be evaluated for disease progression at predefined, standard intervals to minimize evaluation-time biases and will be followed off-treatment for continued safety monitoring and date of death. Safety and tolerability of study treatments will be assessed. The evaluation of efficacy data across the PD-L1 IHC category strata will be defined by IHC-subpopulations and analyzed by subgroups defined by the different PD-L1 IHC categories used for patient stratification. PRO data will allow further evaluation of the relative tolerability of treatment and the impact of therapy on disease symptoms between the two treatment groups.

3.3.6 Rationale for Allowing Patients to Continue Atezolizumab Treatment until Loss of Clinical Benefit

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Because of the potential for pseudoprogression/tumor-immune infiltration, this study will allow patients randomized to the atezolizumab treatment arms to remain on atezolizumab after apparent radiographic progression, provided the benefit-risk ratio is judged to be favorable. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status (see also Section 3.1).

In addition, while the secondary endpoint measures of efficacy (OS rates, ORR, PFS, DOR) comparing the atezolizumab and single agent chemotherapy arms will be using RECIST v1.1 criteria, noncomparative analyses of these measures using modified RECIST criteria (see Appendix 3) will only be performed for patients randomized to receive atezolizumab. Modified RECIST criteria allow the incorporation of new lesions into the calculation of total tumor burden after baseline. Similar to the imRC (Wolchok et al. 2009), it is recommended that radiological progression be confirmed at a subsequent tumor assessment to take into account the potential for pseudoprogression/tumor immune infiltration. Additionally, it is highly recommended that evidence of progressive disease in responding patients be confirmed by a biopsy of the growing or new lesion when feasible.

3.3.7 Rationale for Patient-Reported Outcome Assessments

In the treatment of lung cancer, it is important to both increase survival and palliate symptoms because disease symptoms have negative impacts on HRQoL (Hyde and Hyde 1974; Hopwood and Stephens 1995; Sarna et al. 2004). This is especially true for studies in patients with a low performance status, where it is important to better understand in what regard the delay in disease progression is meaningful to patients.

Chest pain, dyspnea, and cough have been regarded as the most frequent and clinically relevant disease-related symptoms experienced by patients with NSCLC. The BR.21 study (erlotinib vs. best supportive care in second- or third-line NSCLC) demonstrated that longer time to deterioration (TTD) in the pain, dyspnea, and cough scales of the EORTC QLQ-C30 and QLQ-LC13 was consistent with superior PFS, OS, and quality-of-life benefits in the erlotinib arm compared with the placebo arm (Aaronson et al. 1993; Bergman et al. 1994; Bezjak et al. 2006). Patients in the afatinib LUX-Lung first-line study also reported significant delay of TTD in lung cancer symptoms (chest pain, dyspnea, and cough) as measured by the EORTC QLQ-C30 and EORTC QLQ-LC13. (Yang et al. 2013). In this study, the validated EORTC QLQ-C30 and EORTC QLQ-LC13 will be used to assess HRQoL and symptom severity.

The EQ-5D-5L instrument is included in the study to generate utility scores for potential use in economic models for reimbursement.

3.3.8 Rationale for Assessment of Response using Modified (Immune-Mediated) RECIST Criteria

Immunotherapeutic agents produce antitumor effects by inducing cancer-specific immune responses or by modifying native immune processes. Resulting clinical response patterns extend beyond those of cytotoxic agents and can manifest after an initial increase in tumor burden or the appearance of new lesions (progressive disease). RECIST or WHO criteria, designed to detect early effects of cytotoxic agents, may not provide a complete assessment of immunotherapeutic agents. Novel criteria for the evaluation of antitumor responses with immunotherapeutic agents use designated imRC, which can better capture the response patterns observed with some immunotherapeutic agents. Use of the imRC may allow more comprehensive evaluation of immunotherapeutic agents in clinical trials and, potentially, may offer guidance in clinical care (Wolchok et al. 2009).

In the phase II GO28625 (FIR) study, which assessed atezolizumab in patients with PD-L1 positive locally advanced or metastatic NSCLC, efficacy data by investigator-assessed modified RECIST and RECIST v1.1, showed an overall agreement between ORR per modified RECIST and RECIST v1.1, however 2 patients were responders per modified RECIST but not RECIST v1.1.

While the primary endpoint in this study measures efficacy (OS) by using RECIST v1.1 criteria, exploratory analyses of ORR, PFS, DCR and DOR will be using modified RECIST criteria (see Section 2.4) for patients randomized to receive atezolizumab. Modified RECIST criteria (Appendix 4) allow for the incorporation of new lesions into the calculation of total tumor burden after baseline.

3.3.9 Rationale for Biomarker Assessments

3.3.9.1 Tumor Tissue Specimens for Patient Stratification According to PD-L1 IHC Status and Exploratory Biomarker Analyses

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti-PD-1 therapy (Topalian et al. 2012). This correlation is also observed with atezolizumab in preliminary data from Study PCD4989g.

In this study, tumor specimens obtained pre-therapy (archival or during screening) from patients will be prospectively tested for PD-L1 expression by a central laboratory during the screening period. PD-L1 positivity will be assessed for tumor and immune cells and patients will be stratified according to the percentage of positive cells within the tumor. In order to stratify based on PD-L1 IHC status, formalin-fixed paraffin-embedded (FPPE) tissue (block or slides) are mandated. Refer to Section 4.2 for definition of PD-L1 status for stratification.

Exploratory markers will be assessed with the objective to further study prognostic or predictive biomarkers related to the response to atezolizumab, tumor immunobiology or mechanisms of resistance. Biomarker assessments include the analysis of e.g., protein, DNA or RNA (or other analytes) to study gene expression signatures related to response to atezolizumab and tumor mutational burden.

3.3.9.2 Blood Sample

An exploratory objective of this study is to evaluate surrogate biomarkers (that may include circulating tumor DNA [ctDNA]) in blood samples. Evaluation of blood biomarkers may provide evidence for biologic activity of atezolizumab in patients with NSCLC and may allow for the development of blood-based biomarkers to help predict which patients may benefit from atezolizumab.

In addition, potential correlations of these biomarkers with the safety and activity of atezolizumab will be explored.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

3.4.1.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure for this study is the following:

- OS defined as the time from randomization to death from any cause.

3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are the following:

- OS rates at 6, 12, 18 and 24 months
- ORR, defined as overall response (partial response plus complete response), as determined by the investigator using RECIST v1.1

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first
- DOR, defined as the time from the first occurrence of a documented objective response to the time of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are the following:

- Incidence, nature, and severity of adverse events graded according to the NCI CTCAE v4.0
- Changes in vital signs, physical findings, and clinical laboratory results during and following study drug administration

3.4.3 Patient-Reported Outcome Measures

The patient-reported outcome measures for this study are the following:

- Change from baseline in PROs of lung cancer symptoms, patient functioning, HRQoL as assessed by EORTC QLQ-C30 and its supplementary Lung Cancer module (LC13)
- TTD in patient-reported lung cancer symptoms of cough, dyspnea (single-item and multi-item subscales), chest pain, arm/shoulder pain, or fatigue using EORTC QLQ-C30 and QLQ-LC13

3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are the following:

- ORR, PFS and DOR as determined according to modified RECIST v1.1 (Appendix 4)
- DCR defined as the rate of patients with complete response or partial response as best response or stable disease as determined by the investigator per RECIST v1.1
- Tumor tissue PD-L1 expression
- Exploratory biomarkers in tumor tissue and plasma
- Expression of immune markers in PBMCs
- Utility scores of the EQ-5D-5L questionnaire

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 120 sites globally will participate in the study, and approximately 441 treatment-naïve patients with locally advanced or metastatic NSCLC who are deemed unsuitable for any platinum-doublet chemotherapy will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Male or female, age ≥18 years
3. Able to comply with the study protocol, in the investigator's judgment
4. Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC as per the American Joint Committee on Cancer (AJCC) 7th edition (see Appendix 2)
5. No sensitizing EGFR mutation (L858R or exon 19 deletions) or ALK fusion oncogene detected
6. No prior systemic treatment for advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC as per the AJCC 7th edition (see Appendix 2)
7. Life expectancy ≥ 8 weeks
8. Deemed unsuitable by the investigator for any platinum-doublet chemotherapy due to poor performance status (ECOG PS of 2-3)

   However, patients ≥ 70 years of age who have an ECOG PS of 0 or 1 may be included due to:

   a) substantial comorbidities

   b) contraindication(s) for any platinum-doublet chemotherapy.
9. Representative FPPE tumor tissue block obtained during course of disease (archival tissue) or at screening (tumor blocks are highly preferred for central analysis of PD-L1 expression and exploratory biomarkers [see Section 4.5.7 for details on tissue requirements])
10. Patients with treated, asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:

    a) Measurable disease outside CNS

    b) Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)

    c) No ongoing requirement for corticosteroids as therapy for CNS disease; anticonvulsants at a stable dose allowed

    d) No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization

    e) No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

    Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional

brain scan prior to randomization, if all other criteria are met, including clinical confirmation of no evidence of interim disease progression

11. Measurable disease (by RECIST v1.1)
    - Previously irradiated lesions can only be considered as measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of disease.
12. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to randomization:
    a) Absolute neutrophil count (ANC) ≥ 1500 cells/μL without granulocyte colony-stimulating factor support
    b) White blood cell (WBC) counts > 2500/μL
    c) Lymphocyte count ≥ 500/μL
    d) Serum albumin ≥ 2.5 g/dL
    e) Platelet count ≥ 100,000/μL without transfusion (without transfusion within 2 weeks of laboratory test used to determine eligibility)
    f) Hemoglobin ≥ 9.0 g/dL, patients may be transfused or receive erythropoietic treatment to meet this criterion
    g) International normalized ratio (INR) or activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN. This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation must have an INR or aPTT within therapeutic limits for at least 1 week prior to randomization.
    h) AST, alanine aminotransferase (ALT), and alkaline phosphatase ≤ 2.5 × ULN with the following exceptions:
        - Patients with documented liver metastases: AST and/or ALT ≤ 5 × ULN
        - Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN
    i) Serum bilirubin ≤ 1.5 × ULN. Patients with known Gilbert's syndrome who have serum bilirubin level ≤ 3 × ULN may be enrolled
    j) Serum creatinine ≤ 1.5 × ULN.
13. For female patients of childbearing potential randomized to the atezolizumab treatment arm: agreement (by patient and/or partner) to remain abstinent (refrain from heterosexual intercourse) or to use highly effective form(s) of contraceptive methods that result in a failure rate of < 1% per year when used consistently and correctly during the treatment period and for at least 5 months after the last dose of atezolizumab.
        - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state

(≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and 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, and established, proper use of 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 adequate methods of contraception.

14. Female patients of childbearing potential and male patients with partners of childbearing potential treated in the comparative single agent chemotherapy arm should continue contraception use for at least 6 months after the last dose of study treatment. Such methods include: combined (estrogen and progestogen containing) hormonal contraception, progestogen-only hormonal contraception associated with inhibition of ovulation together with another additional barrier method always containing a spermicide, intrauterine device (IUD): intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner (on the understanding that this is the only one partner during the whole study duration), and sexual abstinence. Male patients should not donate sperm during this study and for at least 6 months after the last dose of comparative single agent chemotherapy treatment.
    - Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drug. The same rules are valid for male patients involved in this clinical study if they have a partner of childbirth potential. Male patients must always use a condom.
15. Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.

4.1.2 Exclusion Criteria

4.1.2.1 Cancer-Specific Exclusion Criteria

1. Patients younger than 70 years who have an ECOG PS of 0 or 1.
2. Active or untreated CNS metastases as determined by CT or magnetic resonance imaging (MRI) evaluation of the brain during screening and prior radiographic assessments (see Section 4.1.1 for definition of treated and asymptomatic CNS metastases)
    a) Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for > 2 weeks prior to randomization
    b) Leptomeningeal disease

c) History of CNS metastases intracranial haemorrhage

3. Uncontrolled tumor-related pain
    a) Patients requiring pain medication must be on a stable regimen at study entry.
    b) Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment. Patients should have recovered from the effects of radiation. There is no required minimum recovery period.
    c) Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
4. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently). Patients with indwelling catheters (e.g., PleurX®) are allowed.
5. Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L or calcium > 12 mg/dL or corrected serum calcium > ULN)
6. History of other malignancy within 5 years prior to screening, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated with curative intent, breast ductal carcinoma in situ treated surgically with curative intent)
7. NCI CTCAE (v4.0) Grade 3 or higher toxicities due to any prior therapy (e.g., radiotherapy) (excluding alopecia), which have not shown improvement and are strictly considered to interfere with current study medication.
8. Patients who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy, radiotherapy, or chemoradiotherapy.

4.1.2.2 General Medical Exclusion Criteria

1. Women who are pregnant or lactating or intending to become pregnant during the study. Women of childbearing potential including women who have had a tubal ligation, must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
2. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, *granulomatosis with polyangiitis*, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 11 for a more comprehensive list of autoimmune diseases)

- Patients with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study
- Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen are eligible for this study

3. Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
    a) Rash must cover less than 10% of body surface area (BSA)
    b) Disease is well controlled at baseline and only requiring low potency topical steroids
    c) No acute exacerbations of underlying condition within the last 12 months requiring treatment with either psoralen plus ultraviolet radiation (PUVA), methotrexate, retinoids, biologic agents, oral calcineurin inhibitors or high potency or oral steroids
4. History of idiopathic pulmonary fibrosis (IPF), organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
5. Known positivity for human immunodeficiency virus (HIV)
    - Testing is not required in the absence of clinical symptoms and signs suggestive of HIV infection.
    - Patients with a past history of/or symptoms of HIV are eligible only if serological tests are negative.
6. Known active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or known active hepatitis C
    - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. HBV DNA test must be performed in these patients prior to randomization. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
7. Active tuberculosis
8. Severe infections within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
9. Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina.
    - Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction (LVEF) < 50% must be on a stable medical regimen that is optimized

in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

10. Major surgical procedure other than for diagnosis within 4 weeks prior to randomization or anticipation of need for a major surgical procedure during the course of the study
11. Prior allogeneic bone marrow transplantation or solid organ transplant
12. Any serious medical condition (including metabolic dysfunction, physical examination finding) or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study or that may affect the interpretation of the results or render the patient at high risk for treatment complications
13. Patients with an illness or condition that may interfere with capacity or compliance with the study protocol, as per investigator's judgment
14. Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to randomization

4.1.2.3 Exclusion Criteria Related to Atezolizumab

1. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
2. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
3. Oral or IV antibiotic treatment. Patients will thus need to have recovered from any infection requiring antibiotics. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
4. Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine will be required during the study
    - Influenza vaccination is allowed but should be given during influenza season. However, patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to randomization, at any time during the study or within 5 months after the last atezolizumab dose.
5. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti−PD-1, and anti−PD-L1 therapeutic antibodies. Patients who have had prior anti−cytotoxic T lymphocyte−associated antigen 4 (CTLA-4) treatment may be enrolled, provided the following requirements are met:
    a) Minimum of 6 weeks from the last dose of anti-CTLA-4
    b) No history of severe immune-mediated adverse effects from anti-CTLA-4 (NCI CTCAE Grade 3 and 4)
6. Treatment with systemic immunostimulatory agents (including but not limited to interferons, interleukin-2 [IL-2]) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to randomization

7. Treatment with systemic corticosteroids or other immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor [anti-TNF] agents)
    - Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.
    - The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.
    - Patients with history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumor assessments done by MRI.
8. Patients not willing to stop treatment with traditional herbal medicines

4.1.2.4 Exclusion Criteria Related to Chemotherapy

1. Known sensitivity and contraindications to the 2 comparative chemotherapy agents (i.e., vinorelbine, oral or intravenous, and gemcitabine, intravenous)

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study.

After written informed consent has been obtained and eligibility has been established, the study site will enter demographic and baseline characteristics in the interactive voice/web response system (IxRS). For patients who are eligible for enrollment, the study site will obtain the patient's randomization number and treatment assignment from the IxRS.

Randomization to one of the two treatment arms will occur at a 2:1 ratio.

Permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm. Randomization will be stratified by the following criteria:

- Histologic subtype (non-squamous/squamous)
- PDL-1 IHC status (positive/negative/unknown)
- Brain metastases (yes/no)

Patients should receive their first dose of study drug on the day of randomization if possible. If this is not possible, the first dose should occur within 5 days after randomization.

PD-L1 IHC status for treatment assignment is assessed by IHC and defined as:

PD-L1 IHC Positive:	Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma (IC3) OR Presence of discernible PD-L1 staining of any intensity in ≥ 50% tumor cells (TC3)
PD-L1 IHC Negative:	Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering <10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma AND Presence of discernible PD-L1 staining of any intensity in <50% tumor cells
PD-L1 IHC Status unknown:	PD-L1 IHC status could not be determined (e.g. not enough tumor)

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are atezolizumab, vinorelbine (oral or intravenous) and gemcitabine (intravenous), and will be provided by the Sponsor (see Section 4.3.3).

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab

The atezolizumab Drug Product is provided by Roche or its designee in a single-use, 20-mL 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 or the diluent; therefore, each vial is intended for single use only. Discard any unused portion of drug remaining in a vial. Vial contents should not be frozen or shaken and should be protected from light.

For further details on the storage and preparation of atezolizumab, see the Pharmacy Manual and Atezolizumab Investigator's Brochure.

Atezolizumab will be supplied by the Sponsor.

4.3.1.2 Vinorelbine, Gemcitabine

Vinorelbine, oral and intravenous, and gemcitabine, intravenous will be provided as study medication by Roche or its designee in compliance with local drug management regulations.

For information on the formulation, packaging, and handling of, vinorelbine (oral and intravenous) and gemcitabine (intravenous), see the local Prescribing Information for each drug and formulation (vinorelbine).

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Atezolizumab

Patients randomized to atezolizumab will receive 1200 mg of atezolizumab administered by IV infusion every 21 days in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions.

Atezolizumab infusions will be administered per the instructions outlined in Table 10.

Table 10 Administration of First and Subsequent Infusions of Atezolizumab

First Atezolizumab Infusion	Subsequent Infusions
• No premedication administered for atezolizumab specifically is permitted • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 min before starting infusion. • Infuse atezolizumab (1200 mg in a 250 mL 0.9% NaCl IV infusion bag) over 60 min (± 15 min). • If clinically indicated: record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion at 15 min, 30 min, 45 min, and 60 min (± 5 min windows are allowed for all timepoints). • If clinically indicated: record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) at 30 min (± 10 min) after the infusion. • Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If patient experienced infusion-related reaction during any previous infusion, premedication with antihistamines may be administered for Cycles ≥ 2 at the discretion of the treating physician. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 min before starting infusion. • If the patient tolerated the first infusion well without infusion-associated adverse events, the second infusion may be delivered over 30 min (± 10 min). • If no reaction occurs, subsequent infusions may be delivered over 30 min (± 10 min) minutes. Continue to record vital signs within 60 minutes before starting infusion and during and after the infusion, if clinically indicated. • If the patient had an infusion-related reaction during the previous infusion, the subsequent infusion must be delivered over 60 min (± 15 min).

First Atezolizumab Infusion	Subsequent Infusions
	• Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) every 15 min (± 5 min) during the infusion if clinically indicated or patient experienced symptoms during the previous infusion. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) 30 min (± 10 min) after the infusion if clinically indicated or patient experienced symptoms during previous infusion.

Dose modifications to atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided in Sections 5.1.3.2 and 5.1.3.3.

Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. Section 5.3.5.12 summarizes available safety data related to overdosing of atezolizumab.

4.3.2.2 Vinorelbine

Vinorelbine is indicated as a single agent or in combination for the first line treatment of stage III or IV NSCLC. Vinorelbine will be administered (orally or intravenously) per relevant local guidelines and SmPC management. Reliable dose correspondence has been confirmed between vinorelbine 80 mg/m^2 oral and 30 mg/m^2 IV (Bourgeois et al. 2007).

Vinorelbine for infusion may be administered at 25-30 mg/m^2 d1/8 q21d or d1/8/15 q28d.

Vinorelbine for oral administration may be administered at 60-80 mg/m^2 d1/8 q21d or d1/8/15 q28d, with weekly dosing recommended in some labels.

All patients receiving vinorelbine should be monitored for myelosuppression both during and after therapy. Granulocytopenia is dose-limiting, with granulocyte nadirs occurring between 7 and 10 days after dosing and granulocyte count recovery usually within the following 7 to 14 days. Vinorelbine should not be administered to patients with granulocyte counts < 1,000 cells/mm^3.

Risks and adverse reactions following vinorelbine administration are summarized in Section 5.1.1.2. Dose modifications should be performed according to Section 5.1.3.4. For further details, see the local Prescribing Information for vinorelbine.

4.3.2.3 Gemcitabine

Gemcitabine, in combination with cisplatin, is indicated as first-line treatment of patients with locally advanced or metastatic NSCLC. Gemcitabine monotherapy can be considered in elderly patients or those with PS2.

Gemcitabine will be administered per relevant local guidelines and SmPC management.

Gemcitabine may be administered intravenously at 1000-1250 mg/m^2 d1/8 q21d or d1/8/15 q28d.

Myelosuppression is the principal dose-limiting toxicity with gemcitabine. Risks and adverse reactions following gemcitabine administration are summarized in Section 5.1.1.3. Dose modifications should be performed according to Section 5.1.3.5. For further details, see the local Prescribing information for gemcitabine.

4.3.3 Additional Required Medication

Any premedication doses administered should be in compliance with the respective Summary of Product Characteristics (SmPC).

For further details, see the respective local Prescribing Information for chemotherapy agents.

4.3.3.1 Atezolizumab

No premedication is indicated for the administration of atezolizumab in Cycle 1. Patients who experience an infusion-related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions (see Section 4.4.1.1).

4.3.3.1.1 Infusion Related Reactions

Guidelines for medical management of infusion-related reactions during Cycle 1 are provided in Table 11. For subsequent cycles, infusion-related reactions should be managed according to institutional guidelines.

Table 11 Management Guidelines for Infusion-related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate
IRR, Grade 2	• Interrupt atezolizumab infusion.

Event	Management
	• Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, administer oral premedication with antihistamine and anti-pyretic and monitor closely for IRRs.
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue atezolizumab and contact *the* Medical Monitor.[a]

IRR = infusion-related reaction; IV = intravenous.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

4.3.3.2 Vinorelbine

No pre- and additional medications are required for vinorelbine.

For further details, see the local Prescribing Information for vinorelbine.

4.3.3.3 Gemcitabine

No pre- and additional medications are required for gemcitabine.

For further details, see the local Prescribing Information for gemcitabine.

4.3.4 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (atezolizumab, vinorelbine and gemcitabine) will be provided by the Sponsor where required by local health authority regulations. The study site is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

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

controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

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

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or 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.

Refer to the pharmacy manual and/or the atezolizumab Investigator's Brochure or vinorelbine and gemcitabine local prescribing information for information on IMP handling, including preparation and storage, and accountability.

4.3.5 Continued Access to Atezolizumab

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

A patient will be eligible to receive Roche IMP (atezolizumab) after completing the study if all of the following conditions are met:

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

A patient will not be eligible to receive Roche IMP (atezolizumab) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for NSCLC
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for NSCLC
- Provision of the Roche IMP for is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is 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, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening until death, withdrawal of consent, loss to follow up, or study termination by Sponsor, whichever occurs first. All such medications should be reported to the investigator, and must be recorded on the appropriate Concomitant Medications eCRF.

4.4.1 Atezolizumab Concomitant Therapy

4.4.1.1 Permitted Therapy with Atezolizumab

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions.

Guidelines for medical management of infusion-related reactions during Cycle 1 are provided in Section 4.3.3.1.1. For subsequent cycles, infusion-related reactions should be managed according to institutional guidelines.

The following therapies should continue while patients are in the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level)
- Palliative radiotherapy (e.g., treatment of known bony metastases) provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion being irradiated is not the only site of disease, as that would render the patient not evaluable for response by tumor assessments according to RECIST v1.1).
- It is not a requirement to withhold atezolizumab during palliative radiotherapy.
- *Vaccinations (such as influenza, COVID-19). Live attenuated vaccines are not permitted (see Section 4.4.1.3).*
- Megastrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)
- Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency

In general, investigators should manage a patient's care with supportive therapies as clinically indicated per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H_2 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 10).

The concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, their use for patients in the study is allowed at the discretion of the investigator provided that there are no known interactions with any study treatment. As noted below, herbal therapies intended for the treatment of cancer are prohibited.

4.4.1.2 Cautionary Therapy for Atezolizumab-Treated Patients

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor alpha (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations where 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 treating physician.

Systemic corticosteroids or immunosuppressive medications are recommended, with caution at the discretion of the treating physician, for the treatment of specific adverse events when associated with atezolizumab therapy. Guidelines for the management of immune-mediated adverse events are described in Section 5.1.3.3 and in the Investigator's Brochure.

4.4.1.3 Prohibited Therapy with Atezolizumab

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the anti-cancer agent (see Section 4.1.2), and during study treatment until disease progression is documented and patient has discontinued study treatment. This includes, but is not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (unless otherwise noted).

The following medications are prohibited while in the study, unless otherwise noted:

- Any live, attenuated vaccine (e.g., FluMist®) within 4 weeks prior to randomization, during treatment, or within 5 months after the last atezolizumab dose (for patients randomized to atezolizumab).

- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

4.4.2 Chemotherapy Concomitant Therapy

Interactions common to all cytotoxics:

Due to the increased thrombotic risk in patients with cancer, the use of anticoagulation treatment is frequent. The high intra-individual variability of the coagulation status during diseases and the possibility of interaction between oral anticoagulants and anti-cancer chemotherapy require increased frequency of INR monitoring, if it is decided to treat the patient with oral anticoagulants.

4.4.2.1 Vinorelbine Concomitant Therapy

Vinorelbine should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy, or whose marrow function is recovering from the effects of previous chemotherapy. Administration of vinorelbine to patients with prior radiation therapy may result in radiation recall reactions.

Patients with a prior history or pre-existing neuropathy, regardless of etiology, should be monitored for new or worsening signs and symptoms of neuropathy while receiving vinorelbine.

Care must be taken to avoid contamination of the eye with concentrations of vinorelbine used clinically. Severe irritation of the eye has been reported with accidental exposure to another vinca alkaloid. If exposure occurs, the eye should immediately be thoroughly flushed with water.

For further details, see the local Prescribing Information for vinorelbine.

4.4.2.2 Gemcitabine Concomitant Therapy

Drug-induced liver injury, including liver failure and death, has been reported in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs. Administration of gemcitabine in patients with concurrent liver metastases or a pre-existing medical history or hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency. Assess hepatic function prior to initiation of gemcitabine and periodically during treatment. Discontinue gemcitabine in patients that develop severe liver injury.

Gemcitabine is not indicated for use in combination with radiation therapy.

For further details, see the local Prescribing Information for gemcitabine.

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of activities to be performed during the study.

Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

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

4.5.1 Informed Consent Forms and Screening Log

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

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

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies, procedures, and an assessment of tumor mutational status), reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit.

Cancer history will include prior cancer therapies, procedures, and tumor mutational status (e.g., EGFR mutation status, ALK fusion status).

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

4.5.3 Physical Examinations

A complete physical examination should include the assessment of height and weight, respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, 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.

4.5.4 Vital Signs

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

Vital signs will be measured and recorded for all patients as described in Table 12.

Table 12 Vital Signs Measurements at Cycle 1 and all Subsequent Cycles

Cycle 1 and all Subsequent Cycles	
Treatment Arm	**Timepoints**
Atezolizumab	• Within 60 minutes prior to atezolizumab infusion • During (every 15 [± 5] minutes) the infusion and within 30 (± 10) minutes after atezolizumab infusion, if clinically indicated
Chemotherapy	• Within 60 minutes prior to chemotherapy administration • Within 30 (± 10) minutes after chemotherapy administration
Subsequent Cycles	
Treatment Arm	Timepoints
Atezolizumab	• Within 60 minutes prior to atezolizumab infusion • During (every 15 [± 5] minutes) the infusion and within 30 (± 10) minutes after atezolizumab infusion, if clinically indicated or if symptoms occurred during prior infusion
Chemotherapy	• Within 60 minutes prior to chemotherapy administration • During infusion if clinically indicated or if symptoms occurred during the prior administrations • Within 30 (± 10) minutes after chemotherapy infusion if clinically indicated or if symptoms occurred during the prior administration

For patients in the atezolizumab arm, also refer to Section 4.3.2.1.

4.5.5 Tumor and Response Evaluations

Measurable and non-measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor assessments are to be performed at the timepoints specified in Appendix 1, regardless of drug delays or interruptions.

Screening assessments must include CT scans (with oral/IV contrast unless contraindicated) or MRIs of the chest and abdomen. A CT scan of the pelvis is required at screening and as clinically indicated or as per local practice at subsequent response evaluations. A spiral CT scan of the chest may be obtained but is not a requirement. MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may

be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance).

A CT (with contrast unless contraindicated) or MRI scan of the head must be done at screening to evaluate brain metastasis in all patients. In case of newly detected brain metastases, the patient must be treated and may then be included without the need for an additional brain scan prior to randomization, if all other criteria are met, including clinical confirmation of no evidence of interim disease progression. Patients with active or untreated CNS metastases are not eligible for the study (see Section 4.1.2.1).

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

Tumor assessments performed as standard-of-care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. It is recommended to have the screening/baseline tumor assessment done within 14 days before randomization, as close as possible to baseline. All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans).

Tumor assessments will be performed at baseline, every 6 weeks (± 5 days) following randomization for 48 weeks, and every 9 weeks (± 5 days) thereafter, with additional scans as clinically indicated. Assessments will continue until disease progression per RECIST v1.1. Patients randomized to atezolizumab who continue to receive atezolizumab following disease progression will undergo tumor assessments until treatment discontinuation. Tumor assessments should continue regardless of whether patients discontinue study treatment or start new anti-cancer therapy in the absence of disease progression unless they withdraw consent.

In all patients, response will be assessed by the investigator using RECIST v1.1 (see Appendix 3) until disease progression. Patients randomized to receive atezolizumab will additionally be assessed by modified RECIST criteria (see Appendix 4) until treatment discontinuation. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

4.5.6 Determination of EGFR and ALK Status

Patients known to have a sensitizing mutation in the EGFR gene or an ALK fusion oncogene are excluded from the study. Therefore, all patients with non-squamous NSCLC must have undergone EGFR and ALK analysis before study inclusion. Testing is not required for patients who have squamous NSCLC, except for patients who are never-smokers or who have a mixed histology.

EGFR and ALK may be assessed locally or at a central lab. Central testing for EGFR and ALK requires submission of tumor tissue to the central laboratory (1 FFPE tissue block or at least 7 slides cut from a tumor tissue block).

4.5.7 Tumor Tissue Requirements for Central PD-L1 Analysis (Stratification)

In order to perform prospective stratification by PD-L1 IC/TC status, patients must provide tumor tissue meeting the following requirements.

Tumor tissue must meet the following requirements:

- A representative FPPE tumor tissue block obtained during course of disease (archival tissue) or screening (tumor blocks are highly preferred); ideally, 3 cores should be submitted in case smaller core biopsies are available in order to have sufficient tumor cells available.
- In case the tumor block is not available, 10-15 unstained, consecutive slides not older than 60 days will be accepted. A minimum of five slides is mandated for PD-L1 analysis and patient stratification.
- If archival tissue (most recent sample) is unavailable, a pretreatment tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable.
- Tumor tissue from bone metastases are not acceptable.
- Tumor tissue should be of good quality based on total and viable tumor content (at least 300 viable tumor cells across cores are needed for determination of TC/IC status at low cut-offs).

During screening, 5 slides will be cut from the tumor block for analysis of PD-L1. Once the patient enters the study, additional 10 slides will be cut for exploratory analyses. Tissue blocks will be returned upon completion of exploratory biomarker analyses (as early as possible but no later than 5 years after blocks had been sent). Slides will not be returned unless requested by the site for diagnostic purpose.

Samples will be sent to a central laboratory for PD-L1 IHC analysis. Percent PD-L1 positive tumor and immune cells will be assessed and categorized based on predefined criteria (see Appendix 12).

The study will enroll all patients whose tissue is evaluable for PD-L1 analysis, regardless of PD-L1 status.

4.5.8 Laboratory Assessments and Biomarker Samples

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

- Hematology (complete blood count [CBC], including red blood cell count [RBC] count, hemoglobin, hematocrit, white blood cell (WBC) count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], platelet count and coagulation parameters [aPTT or INR]).
- Serum chemistry (glucose, blood urea nitrogen [BUN] or urea, creatinine, sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), calcium, phosphorus, total and direct bilirubin, ALT, AST, alkaline phosphatase, uric acid, LDH, total protein, and albumin)
- Serum and urine pregnancy tests for women of childbearing potential, including women who have had a tubal ligation. On study pregnancy tests must be performed prior to each treatment cycle (21-day cycle for atezolizumab and per relevant local guidelines and SmPC management for chemotherapy) while receiving the IMP. For female patients of childbearing potential, the pregnancy tests will be repeated during the Safety FU visit and then every 2 months during Follow-up for at least 5 months after the last dose of atezolizumab and for at least 6 months after the last dose of chemotherapy, respectively. Results from a treating physician can be used. The pregnancy test can be conducted with serum or urine. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  Childbearing potential is defined as not having undergone surgical sterilization, hysterectomy, and/or bilateral oophorectomy or not being postmenopausal (≥ 12 months of amenorrhea).
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood); dipstick permitted
- Thyroid function testing (thyroid-stimulating hormone [TSH], free triiodothyronine [T3] (or total T3 for sites where free T3 is not performed), free thyroxine [also known as T4])
- HIV testing: Testing is not required in the absence of clinical symptoms and signs suggestive of HIV infection or known HIV positivity. Patients with a past history of/or symptoms of HIV are eligible only if serological tests are negative.
- HBV serology: HBsAg, hepatitis B surface antibody, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

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

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

Samples for the following laboratory tests are mandatory and will be sent to one or several central laboratories or to the Sponsor for analysis:

- FFPE tumor tissue (archival or obtained at screening) for patient stratification based on PD-L1 IHC results (see Section 4.5.7). Residual samples will be used for exploratory research.
- Whole) blood (at baseline) for analysis of protein expression and gene expression of PBMCs
- Plasma (at baseline, Week 7 and at time of disease progression) for analysis of ctDNA using NGS (or other methods)

Exploratory biomarker research may include, but will not be limited to, the biomarkers listed in Table 13.

See the laboratory manual for additional details on laboratory assessments and sample handling.

Table 13 Proposed Biomarkers for Exploratory Research

Sample Type	Timing	Proposed Biomarkers
FFPE Tissue Block (or 10-15 slides)	Pre-treatment (archival tissue or screening)	PD-L1 IHC (stratification) RNA expression (T-effector signature and/or analysis of cancer-related mutations (incl. mutational load)
Whole blood (PBMC Whole Blood) for isolation of PBMCs and their derivatives	Baseline	RNA expression analysis (including but not limited to PD-L1, IFNγ)
Plasma for extraction of cell-free DNA and/or RNA	Baseline, Week 7 and at time of disease progression	Cancer-related, disease specific mutations using NGS

FFPE = formalin fixed paraffin embedded; IFNγ= interferon gamma; IHC = immunohistochemistry; NGS = next generation sequencing; NSCLC = non-small cell lung cancer; PBMC = peripheral blood mononuclear cell; PD-L1 = programmed death-ligand 1.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- FFPE tissue blocks from screen failed patients will be returned within 6 weeks (unstained slides will not be returned but destroyed at the central lab).
- FFPE tissue blocks from eligible patients will be returned as early as possible but no later than 5 years after blocks had been sent. Leftover slides will be destroyed within 2 years after the date of final closure of the clinical database and will not be returned.

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.

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

4.5.9 Electrocardiograms

A twelve-lead electrocardiogram (ECG) is required at screening and as clinically indicated at other time points, as indicated in the Schedule of Activities (Appendix 1). ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

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

4.5.10 Patient-Reported Outcomes

PRO data will be collected via questionnaires to document the treatment benefit and treatment safety. The PRO questionnaires will be completed with each tumor assessment until disease progression per RECIST v1.1, even if patients discontinue study treatment for any reason other than progressive disease or loss of clinical benefit.

The questionnaires, translated into the local language as required, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, each questionnaire will be self-administered or interviewer-administered (as appropriate) before the patient or clinician receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

PRO data will be collected via the EORTC QLQ-C30, the EORTC QLQ-LC13, and EQ-5D-5L to more fully characterize the clinical profile of atezolizumab.

The EORTC QLQ-C30 (see Appendix 6) is a validated and reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), 3 symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scale scores can be obtained for the multi-item scales. The EORTC QLQ-C30 module takes approximately 15 minutes to complete.

The EORTC QLQ-LC13 (see Appendix 7) module incorporates one multiple-item scale to assess dyspnea and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. The EORTC QLQ-LC13 module takes approximately 15 minutes to complete.

The EQ-5D-5L is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that is used to build a composite of the patient's health status (see Appendix 8). The EQ-5D-5L will be utilized in this study for economic modeling.

Adverse event reports will not be derived from PRO data by the Sponsor. However, any PRO responses suggestive of a possible adverse event that are identified during site review of the PRO data should be reported as outlined in Section 5.3.5.13.

4.5.11 Samples for Research Biosample Repository (RBR)

4.5.11.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to NSCLC:

- Remaining or unused fluids (plasma, PBMCs, blood cell derivatives) after study-related tests have been performed
- Remaining or unused FFPE tissue slides and/or derivatives thereof obtained during screening (with the exception of archival FFPE blocks, which will be returned to sites) after study-related tests have been performed

The above samples may be sent to one or more laboratories for DNA extraction to enable analysis of germline mutations, somatic mutations via whole genome sequencing (WGS), or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical

data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens 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.

Given the complexity and exploratory nature of the analyses, data derived from RBR 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.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, as appropriate.

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

4.5.11.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data.

If a patient wishes to withdraw consent to the testing of his or her samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address: *global.rcr-withdrawal@roche.com*. The patient will be provided with instructions on how to withdraw consent after the trial is closed.

A patient's withdrawal from Study MO29872 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study MO29872.

4.5.11.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice (GCP) by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.5.12 Timing of Assessments

4.5.12.1 Screening/Baseline Assessments

Screening tests and evaluations will be performed within 28 days prior to Cycle 1, Day 1. Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment. Results of standard-of-care tests or examinations performed prior to

obtaining informed consent and within 28 days prior to Cycle 1, Day 1 may be used; such tests do not need to be repeated for screening.

See Appendix 1 for the schedule of screening assessments.

4.5.12.2 Assessments During Study Treatment

All visits must occur ± 5 days from the scheduled date unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment administration unless otherwise noted.

If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing continuing per original schedule. If treatment was postponed for fewer than 3 days, the patient can resume the original schedule.

After completion of single agent chemotherapy treatment (for patients in the chemotherapy arm) or after five cycles (for patients in the atezolizumab arm), one of 3 cycles may be delayed by 1 week (28 days instead of 21 days for one cycle) to allow for vacations/holidays.

Following the delay, the next atezolizumab cycle must be delivered 21 days from the previous dose administration. Two consecutive 28-day atezolizumab cycles are not permitted.

If a dose modification is required due to toxicity, refer to Section 5.1.

Tumor assessments will be done at baseline, every 6 weeks (± 5 days) following randomization for 48 weeks, and every 9 weeks (± 5 days) thereafter, with additional scans as clinically indicated. Assessments will continue until disease progression per RECIST v1.1. Patients randomized to atezolizumab who continue to receive atezolizumab following disease progression will undergo tumor assessments until treatment discontinuation. Tumor assessments should continue regardless of whether patients discontinue study treatment or start new anti-cancer therapy in the absence of disease progression unless they withdraw consent. In all patients, response will be assessed by the investigator using RECIST v1 until disease progression. Patients randomized to receive atezolizumab will additionally be assessed by modified RECIST criteria until treatment discontinuation.

The following assessments should be performed ≤ 96 hours before Day 1 of each cycle (for the Cycle 1, Day 1 treatment administration, the following Day 1 procedures should occur after randomization but before study treatment is administered):

- ECOG performance status

- Limited physical examination
- Local laboratory tests

See Appendix 1 for the schedule of assessments during treatment.

4.5.12.3 Assessments at Treatment Discontinuation Visit

Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit within 30 days after the last dose of study treatment, regardless of the reason for treatment discontinuation.

See Appendix 1 for assessments to be performed at the treatment discontinuation visit.

4.5.12.4 Assessments After Treatment Discontinuation Until Disease Progression

For all patients who discontinue study treatment for any reason other than progressive disease per RECIST v1.1, tumor assessments and PRO assessments will continue at the same frequency until progressive disease per RECIST v1.1.

See Appendix 1 for assessments to be performed for patients who discontinue study treatment for reasons other than progressive disease.

4.5.12.5 Follow-Up Assessments

After the Treatment Discontinuation Visit, adverse events should be followed as outlined in Section 5.3.

Follow-up data collection will include ongoing or new serious adverse events, adverse events of special interest or adverse events thought to be related to study treatment, which will be followed until the event has resolved to the baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that the study treatment or participation is not the cause of the adverse events.

Follow-up information, including subsequent anticancer therapies and adverse events (see Section 5.3.1 for adverse event reporting period), will be collected via telephone calls and/or clinic visits every 2 months (± 5 days) until death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor, or protocol-defined end of study, whichever comes first. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) when permissible, to obtain information about survival status and date only.

See Appendix 1 for assessments to be performed during Follow-up.

4.5.12.6 Assessments at Unscheduled Visits

Assessments for unscheduled visits related to a patient's underlying NSCLC, study treatment, or adverse events should be performed as clinically indicated and entered into Unscheduled Visit eCRFs.

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. 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.

4.6.2 Study Treatment Discontinuation

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

- Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status.
- Intolerable toxicity related to atezolizumab treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Intolerable toxicity related to chemotherapy treatment
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Use of another non-protocol anti-cancer therapy (see Section 4.4.1.3)
- Pregnancy

Patients randomized to the atezolizumab treatment arm may continue study treatment beyond disease progression per RECIST v1.1 until loss of clinical benefit, unacceptable toxicity, withdrawal of consent, death, study termination by the Sponsor, or protocol-defined end of study, whichever occurs first, if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator (i.e., in the absence of symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], clinical status, and of laboratory values)
- Absence of unacceptable toxicity
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial progression.

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

After termination of study treatment, all patients can be treated with locally approved chemotherapy or other treatments. All patients will remain in this study until withdrawal of consent, death, loss to follow-up, study termination by the Sponsor, or protocol-defined end of study, whichever occurs first.

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

Atezolizumab was approved by the U.S. FDA in May 2016 for the treatment of patients with locally advanced or mUC who 1) have disease progression during or following platinum-containing chemotherapy or 2) have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

On October 18, 2016, the FDA approved atezolizumab (Tecentriq®) also for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab.

The following information is based on results from nonclinical and clinical studies and published data on similar molecules.

5.1 SAFETY PLAN

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (see Section 4.1.1 and Section 4.1.2) and close monitoring (as indicated below and in Section 4.5). See Section 5.3 (Methods and Timing for Capturing and Assessing Safety Parameters) for complete details regarding safety reporting for this study.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. All serious adverse events and adverse events of special interest will be recorded during the trial and for up to 90 days after the last dose of study treatment or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events will be recorded during the trial and for up to 30 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first.

Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study. The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

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 COVID-19 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 COVID-19, 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 COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

5.1.1 Risks Associated with Investigational Medicinal Products

5.1.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 13 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Guidelines for managing patients who experience anticipated adverse events are provided in Appendix 13. To date, there are no additional identified risks/ADRs specific to the combination of atezolizumab when given with another therapeutic agent. The identified risks/ADRs of other therapeutic agents used in combination with atezolizumab can be found in their respective Investigator's Brochures or local Prescribing Information.

5.1.1.2 Risks Associated with Vinorelbine

Vinorelbine (soft capsule for oral administration, concentrate for intravenous administration) should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy, or whose marrow function is recovering from the effects of previous chemotherapy. Vinorelbine should not be administered to patients with granulocyte counts < 1,000 cells/mm^3. Patients developing severe granulocytopenia should be monitored carefully for evidence of infection and/or fever.

In case of oral administration of the soft capsules, caution must be taken not to damage the capsule. If the patient chews or sucks the capsule by error, the liquid is an irritant. Please refer to the Navelbine® 30 mg soft capsule SmPC for further information.

Patients treated with vinorelbine should be frequently monitored for myelosuppression both during and after therapy. Granulocytopenia is dose-limiting. Granulocyte nadirs

occur between 7 and 10 days after dosing with granulocyte count recovery usually within the following 7 to 14 days. Complete blood counts with differentials should be performed and results reviewed prior to administering each dose of vinorelbine.

Patients with a prior history or pre-existing neuropathy, regardless of etiology, should be monitored for new or worsening signs and symptoms of neuropathy while receiving vinorelbine. Care must be taken to avoid contamination of the eye with concentrations of vinorelbine used clinically. Severe irritation of the eye has been reported with accidental exposure to another vinca alkaloid. If exposure occurs, the eye should immediately be thoroughly flushed with water.

Adverse reactions reported as more than isolated cases following intravenous vinorelbine administration as single agent are listed in Table 14. Adverse reactions reported as more than isolated cases following oral vinorelbine administration as single agent are listed in Table 15. Additional adverse reactions from post marketing experience *have* been added according to the MedDRA classification with the frequency Not known.

Table 14 Adverse Reactions for Vinorelbine as Single Agent (Intravenous)

Adverse Reactions for intravenous Vinorelbine as single agent by System Organ Class and by the MedDRA Frequency	
Infections and infestations	
Common	• Infection bacterial, viral or fungal at different sites mild to moderate and usually reversible with an appropriate treatment
Uncommon	• Severe sepsis sometimes with other organ failure • Septicaemia
Very rare	• Complicated septicaemia and sometimes fatal
Not known	• Neutropenic sepsis • Neutropenic infection G3-4
Blood and lymphatic system disorders	
Very common	• Bone marrow depression resulting mainly in neutropenia (G3: 24.3%; G4: 27.8%) reversible within 5 to 7 days and noncumulative over time. • Anaemia (G3-4: 7.4%)
Common	• Thrombocytopenia (G3-4: 2.5%) may occur but are seldom severe
Not known	• Febrile neutropenia • Pancytopenia • Leucopenia.G1-4
Immune system disorders	
Not known	• Systemic allergic reactions as anaphylaxis, anaphylactic shock or anaphylactoïd type reaction.

Table 14 Adverse Reactions for Vinorelbine as Single Agent (Intravenous)

Adverse Reactions for intravenous Vinorelbine as single agent by System Organ Class and by the MedDRA Frequency	
Endocrine disorders	
Not known	• Inappropriate antidiuretic hormone secretion (SIADH).
Metabolism and nutrition disorders	
Rare	• Severe hyponatremia
Not known	• Anorexia
Nervous system disorders	
Very common	• Neurologic disorders (G 3-4: 2.7%) including loss of deep tendon reflexes. • Weakness of the lower extremities has been reported after a prolonged chemotherapy.
Uncommon	• Severe paresthesias with sensory and motor symptoms are infrequent, generally reversible.
Not known	• Headache • Dizziness • Ataxia
Cardiac disorders	
Rare	• Ischemic heart disease: angina pectoris, myocardial infarction (sometimes fatal).
Very rare	• Tachycardia, palpitation and heart rhythm disorders
Not known	• Heart failure
Vascular disorders	
Uncommon	• Arterial hypotension, arterial hypertension, flushing and peripheral coldness.
Rare	• Severe hypotension, collapse.
Respiratory system, thoracic and mediastinal disorders	
Uncommon	• Dyspnoea and bronchospasm may occur in association with vinorelbine treatment as with other vinca alkaloids.
Rare	• Interstitial pneumonopathy sometimes fatal has been reported.
Not known	• Cough G1-2
Gastrointestinal disorders	
Very Common	• Stomatitis (G1-4: 15%, with vinorelbine as single agent). • Nausea and vomiting (G 1-2: 30.4% and G 3-4: 2.2%). Anti-emetic therapy may reduce their occurrence. • Constipation is the main symptom (G 3-4: 2.7%) which rarely progresses. to paralytic ileus with vinorelbine as single agent and (G3-4: 4.1%), with the combination of vinorelbine and other chemotherapeutic agents
Common	• Diarrhoea usually mild to moderate may occur.

Table 14 Adverse Reactions for Vinorelbine as Single Agent (Intravenous)

Adverse Reactions for intravenous Vinorelbine as single agent by System Organ Class and by the MedDRA Frequency	
Rare	• Paralytic ileus, treatment may be resumed after recovery of normal bowel mobility. • Pancreatitis has been reported.
Not known	• Gastrointestinal bleeding • Severe diarrhoea • Abdominal pain
Hepatobiliary disorders	
Very common	• Transient elevations of liver function tests (G1-2) without clinical symptoms were reported (SGOT in 27.6% and SGPT in 29.3%).
Not known	• Hepatic disorder
Skin and subcutaneous tissue disorders	
Very common	• Alopecia, usually mild in nature, may occur (G3-4: 4.1% with vinorelbine as single chemotherapeutic agent).
Rare	• Generalized cutaneous reactions have been reported with vinorelbine.
Not known	• Erythema on hands and feet (Palmer-plantar erythrodysesthesia syndrome).
Musculoskeletal and connective tissue disorders	
Common	• Arthralgia including jaw pain and myalgia.
General disorders and administration site conditions	
Very common	• Reactions at the injection site may include erythema, burning pain, vein discoloration and local phlebitis (G 3-4: 3.7% with vinorelbine as single chemotherapeutic agent).
Common	• Asthenia, fatigue, fever, pain at different sites including chest pain and pain at the tumor site.
Rare	• Local necrosis has been observed. Proper positioning of the cannula in the vein before starting to infuse vinorelbine followed by liberal flushing of the vein can limit these effects.
Not known	• Chills G1-2
Investigations	
Not known	• Weight loss

Frequencies are defined as: Very common: ≥ 1/10; Common: ≥ 1/100 to < 1/10; Uncommon: ≥ 1/1000 to < 1/100; Rare: ≥ 1/10,000 to < 1/1000; Very rare: < 1/10,000, including isolated reports; Not known: Post marketing reports.

Source: Navelbine® Summary of Product Characteristics [27 Jul 2020], Available from: https://www.medicines.org.uk/emc/medicine/16029#CONTRAINDICATIONS.

Table 15 Adverse Reactions for Vinorelbine as Single Agent (Soft Capsule)

Adverse Reactions for oral Vinorelbine as single agent by System Organ Class and by the MedDRA Frequency	
Infections and infestations	
Very common	• Bacterial, viral or fungal infections without neutropenia at different sites: G1-4: 12.7%; G3-4: 4.4%
Common	• Bacterial, viral or fungal infections resulting from bone marrow depression and/or immune system compromise (neutropenic infections) are usually reversible with an appropriate treatment • Neutropenic infection: G3-4: 3.5%
Not known	• Neutropenic sepsis • Complicated septicaemia and sometimes fatal • Severe sepsis sometimes with other organ failure • Septicaemia
Blood and lymphatic system disorders	
Very common	• Bone marrow depression resulting mainly in neutropenia G1-4: 71.5%; G3: 21.8%; G4: 25.9%, is reversible and is the dose limiting toxicity. • Leucopenia: G1-4: 70.6%; G3: 24.7%; G4: 6% • Anaemia: G1-4: 67.4%; G3-4: 3.8% • Thrombocytopenia: G1-2: 10.8%
Common	• G4 Neutropenia associated with fever over 38°C including febrile neutropenia 2.8%.
Not known	• Thrombocytopenia G3-4 • Pancytopenia
Metabolism and nutrition disorders	
Very common	• Anorexia: G1-2: 34.5%, G3-4: 4.1%
Not known	• Severe hyponatraemia
Psychiatric disorders	
Common	• Insominia: G1-2: 2.8%
Nervous system disorders	
Very common	• Neurosensory disorders: G1-2: 11.1%, generally limited to loss of tendon reflexes and infrequently severe
Common	• Neuromotor disorders: G1-4: 9.2%; G3-4:1.3%. • Headache: G1-4: 4.1%, G3-4: 0.6%. • Dizziness: G1-4: 6%; G3-4: 0.6%. • Taste disorders: G1-2:3.8%
Uncommon	• Ataxia grade 3: 0.3%
Eye disorders	
Common	• Visual impairment: G1-2: 1.3%.
Cardiac disorders	
Uncommon	• Heart failure and cardiac dysrhythmia

Table 15 Adverse Reactions for Vinorelbine as Single Agent (Soft Capsule)

Adverse Reactions for oral Vinorelbine as single agent by System Organ Class and by the MedDRA Frequency	
Not known	• Myocardial infarction in patients with cardiac medical history or cardiac risk factors.
Vascular disorders	
Common	• Arterial hypertension: G1-4: 2.5%; G3-4: 0.3%. • Arterial hypotension: G1-4: 2.2%; G3-4: 0.6%.
Respiratory system, thoracic and mediastinal disorders	
Common	• Dyspnoea: G1-4: 2.8%; G3-4: 0.3%. • Cough: G1-2: 2.8%.
Gastrointestinal disorders	
Very common	• Nausea: G1-4: 74.7% ; G3-4: 7.3% • Vomiting: G1-4: 54.7%; G 3-4: 6.3%, Supportive treatment such as 5HT3 antagonists (ondansetron) may reduce the occurrence of nausea and vomiting • Diarrhoea: G1-4: 49.7%; G3-4: 5.7% • Stomatitis: G1-4:10.4%; G3-4: 0.9% • Abdominal pain: G1-4: 14.2% • Constipation: G1-4: 19%; G3-4: 0.9%, Prescription of laxatives may be appropriate in patients with prior history of constipation and/or who receive concomitant treatment with opioid analgesics • Gastric disorders: G1-4: 11.7%
Common	• Oesophagitis: G1-3: 3.8%; G3: 0.3% • Dysphagia: G1-2: 2.3%.
Uncommon	• Paralytic ileus: G3-4: 0.9% [rarely fatal], treatment may be resumed after recovery of normal bowel mobility.
Not known	• Gastro-intestinal bleeding.
Hepatobiliary disorders	
Common	• Hepatic disorders: G1-2: 1.3%.
No known	• Transient elevations of liver function tests G1-2
Skin and subcutaneous tissue disorders	
Very common	• Alopecia usually mild in nature G1-2: 29.4%, may occur.
Common	• Skin reactions: G1-2: 5.7%.
Musculoskeletal and connective tissue disorders	
Common	• Arthralgia including jaw pain • Myalgia: G1-4: 7 %, G3-4: 0.3%.
Renal and urinary disorders	
Common	• Dysuria: G1-2: 1.6%. • Other genitourinary disorders: G1-2: 1.9%
General disorders and administration site conditions	

Table 15 Adverse Reactions for Vinorelbine as Single Agent (Soft Capsule)

Adverse Reactions for oral Vinorelbine as single agent by System Organ Class and by the MedDRA Frequency	
Very common	• Fatigue/malaise: G1-4: 36.7%; G3-4: 8.5%. • Fever: G1-4: 13.0%, G3-4: 12.1%).
Common	• Pain including pain at the tumour site: G1-4: 3.8%, G3-4: 0.6%. • Chills: G1-2: 3.8%.
Investigations	
Very common	• Weight loss: G1-4: 25%, G3-4: 0.3%.
Common	• Weight gain: G1-2: 1.3%.

Frequencies are defined as: Very common: ≥ 1/10; Common: ≥ 1/100 to < 1/10; Uncommon: ≥ 1/1000 to < 1/100; Rare: ≥ 1/10,000 to < 1/1000; Very rare: < 1/10,000, including isolated reports; Not known: Post marketing reports.

Source: Navelbine 30 mg soft capsule Summary of Product Characteristics, Last Updated on eMC 27 May 2020 (Available from: https://www.medicines.org.uk/emc/medicine/1604).

Information on vinorelbine dose modification and the management of specific adverse events is provided in Section 5.1.3.4. For more details regarding the safety profile of vinorelbine, see the respective Navelbine® Prescribing Information (intravenous or oral administration).

5.1.1.3 Risks Associated with Gemcitabine

Infusion times of gemcitabine longer than 60 minutes and more frequent than weekly dosing have been shown to increase toxicity.

Pulmonary toxicity has been reported with the use of gemcitabine. In cases of severe lung toxicity, gemcitabine therapy should be discontinued immediately and appropriate supportive care measures instituted.

Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia has been reported with gemcitabine as a single agent or in combination with other cytotoxic drugs. Monitoring for myelosuppression should occur prior to each cycle.

Hemolytic-uremic syndrome (HUS) and/or renal failure have been reported following one or more doses of gemcitabine. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS.

Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs.

Use caution in patients with pre-existing renal impairment or hepatic insufficiency.

Undesirable effects following gemcitabine administration and their frequencies based on data from clinical trials are presented in Table 16.

Table 16 Adverse Reactions for Gemcitabine Observed in Clinical Trials

Adverse Reactions in NSCLC for Gemcitabine in Clinical Trials System Organ Class and Frequency Grouping	
Blood and lymphatic system disorders	
Very common	• Leucopenia (Neutropenia Grade 3 = 19.3 %; Grade 4 = 6 %). Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count • Thrombocytopenia • Anaemia
Common	• Febrile neutropenia
Very rare	• Thrombocytosis • Thrombotic microangiopathy
Immune system disorders	
Very rare	• Anaphylactoid reaction
Metabolism and nutrition disorders	
Common	• Anorexia
Nervous system disorders	
Common	• Headache • Insomnia • Somnolence
Uncommon	• Cerebrovascular accident
Very rare	• Posterior reversible encephalopathy syndrome
Cardiac disorders	
Uncommon	• Arrhythmias, predominantly supraventricular in nature • Heart failure
Rare	• Myocardial infarct
Vascular disorders	
Rare	• Clinical signs of peripheral vasculitis and gangrene • Hypotension
Very rare	• Capillary leak syndrome
Respiratory, thoracic and mediastinal disorders	
Very common	• Dyspnoea -usually mild and passes rapidly without treatment
Common	• Cough • Rhinitis
Uncommon	• Interstitial pneumonitis

Table 16 Adverse Reactions for Gemcitabine Observed in Clinical Trials

Adverse Reactions in NSCLC for Gemcitabine in Clinical Trials System Organ Class and Frequency Grouping	
	• Bronchospasm -usually mild and transient but may require parenteral treatment
Rare	• Pulmonary oedema • Adult respiratory distress syndrome
Not known	• Pulmonary eosinophilia
Gastrointestinal disorders	
Very common	• Vomiting • Nausea
Common	• Diarrhoea • Stomatitis and ulceration of the mouth • Constipation
Very rare	• Ischaemic colitis
Hepatobiliary disorders	
Very common	• Elevation of liver transaminases (AST and ALT) and alkaline phosphatase
Common	• Increased bilirubin
Uncommon	• Serious hepatotoxicity, including liver failure and death
Rare	• Increased gamma-glutamyl transferase (GGT)
Skin and subcutaneous tissue disorders	
Very common	• Allergic skin rash frequently associated with pruritus • Alopecia
Common	• Itching • Sweating
Rare	• Severe skin reactions, including desquamation and bullous skin eruptions • Ulceration • Vesicle and sore formation • Scaling
Very rare	• Toxic epidermal necrolysis • Stevens-Johnson Syndrome
Not known	• Pseudocellulitis
Musculoskeletal and connective tissue disorders	
Common	• Back pain • Myalgia
Renal and urinary disorders	
Very common	• Haematuria • Mild proteinuria
Uncommon	• Renal failure • Haemolytic uraemic syndrome

Table 16 Adverse Reactions for Gemcitabine Observed in Clinical Trials

Adverse Reactions in NSCLC for Gemcitabine in Clinical Trials System Organ Class and Frequency Grouping	
General disorders and administration site conditions	
Very common	• Influenza-like symptoms - the most common symptoms are fever, headache, chills, myalgia, asthenia and anorexia. Cough, rhinitis, malaise, perspiration and sleeping difficulties have also been reported. • Oedema/peripheral oedema-including facial oedema. Oedema is usually reversible after stopping treatment
Common	• Fever • Asthenia • Chills
Rare	• Injection site reactions - mainly mild in nature
Injury, poisoning, and procedural complications	
Rare	• Radiation toxicity • Radiation recall
Infections and infestations	
Common	• Infections
Not known	• Sepsis

Frequencies are defined as: Very common: > 1/10; Common: > 1/100 to < 1/10; Uncommon: > 1/1000, < 1/100; Rare: ≥ 1/10,000, < 1/1000; Very rare: < 1/10,000, including isolated reports; Not known: Post marketing experience.

Source: Gemzar® Summary of Product Characteristics [July 2019]. Available from: https://www.medicines.org.uk/emc/product/4483/smpc

Information on gemcitabine dose modification and the management of specific adverse events is provided in Section 5.1.3.5. For more details regarding the safety profile of vinorelbine, see the Gemzar® Prescribing Information.

5.1.2 General Plan to Manage Safety Concerns

5.1.2.1 Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events defined and graded according to NCI CTCAE v4.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Laboratory values must be reviewed prior to each study drug administration.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Appendix 1 for the list and timing of study assessments).

During the study, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

All serious adverse events and protocol-defined events of special interest (see Section 5.2.2 and Section 5.2.3) will be reported in an expedited fashion. In addition, the iDMC and Medical Monitor will review and evaluate observed adverse events on a regular basis.

Patients will be followed for serious adverse events and adverse events of special interest for 90 days after their last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. For all other adverse events, patients will be followed for 30 days after their last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study.

Patients who have an ongoing study treatment-related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

5.1.3 Dose Modifications and Management of Special Adverse Events

5.1.3.1 General Notes Regarding Dose Modification

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF. The severity of adverse events will be graded according to the NCI CTCAE v4.0 grading system.

- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes.
- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.

The investigator may use discretion in modifying or accelerating the dose modification guidelines described below depending on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing patient compliance and access to supportive care.

5.1.3.2 Atezolizumab Dose Modification

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment for up to 12 weeks after event onset if they experience an adverse event that requires a dose to be withheld. If atezolizumab is withheld because

of adverse events for > 12 weeks after event onset, then the patient will be discontinued from atezolizumab treatment and will be followed for safety and efficacy as specified in Section 5.2.1.

If a patient must be tapered off steroids used to treat adverse events, atezolizumab may be withheld for additional time > 12 weeks after event onset until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

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

Management of atezolizumab-specific adverse events is present in Section 5.1.3.3.

5.1.3.3 Management of Atezolizumab-Specific Adverse Events

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 determine a possible immunogenic etiology.

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

The investigator should consider the benefit-risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the event can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor..

For the management of other adverse events associated with atezolizumab, refer to the Atezolizumab Investigator's Brochure.

For the management of infusion-related reactions, see Section 4.3.3.1.

5.1.3.4 Vinorelbine Dose Modification and Management of Specific Adverse Events

5.1.3.4.1 Intravenous Vinorelbine

The usual initial dose of single-agent vinorelbine is 30 mg/m^2 administered weekly.

If administered intravenously, intravenous injection is done over 6 to 10 minutes. In controlled trials, single-agent vinorelbine was given weekly until progression or dose-limiting toxicity.

Most drug-related adverse events of vinorelbine are reversible. If severe adverse events occur, vinorelbine should be reduced in dosage or discontinued and appropriate corrective measures taken. Reinstitution of therapy with vinorelbine should be carried out with caution and alertness as to possible recurrence of toxicity.

The dosage should be adjusted according to hematologic toxicity or hepatic insufficiency, whichever results in the lower dose for the corresponding starting dose of vinorelbine, as shown in Section 5.1.3.4.2 and Section 5.1.3.4.3. If Grade ≥ 2 neurotoxicity develops, vinorelbine should be discontinued.

For more details regarding the dose modifications and the management of specific adverse events, see the Navelbine® Prescribing Information.

5.1.3.4.2 Hematologic Toxicity – Intravenous Vinorelbine

Granulocyte count should be ≥ 1,000 cells/mm^3 prior to the administration of vinorelbine. Adjustments in the dosage of vinorelbine should be based on granulocyte counts obtained on the day of treatment according to Table 17.

Table 17 Intravenous Vinorelbine Dose Adjustments Based on Granulocyte Counts

Granulocytes on Day of Treatment (cells/mm^3)	Percentage of Starting Dose of Vinorelbine
≥ 1,500	100%
1,000 to 1,499	50%
< 1,000	Do not administer. Repeat granulocyte count in 1 week. If 3 consecutive weekly doses are held because granulocyte count is < 1,000 cells/mm^3, discontinue vinorelbine.
Note: For patients who, during treatment with vinorelbine, experienced fever and/or sepsis while granulocytopenic or had 2 consecutive weekly doses held due to granulocytopenia, subsequent doses of vinorelbine should be:	
≥1,500	75%
1,000 to 1,499	37.5%
<1,000	See above

5.1.3.4.3 Hepatic Insufficiency - Intravenous Vinorelbine

Vinorelbine should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinemia during treatment with vinorelbine, the dose should be adjusted for total bilirubin according to Table 18.

Table 18 Intravenous Vinorelbine Dose Adjustments for Hepatic Insufficiency

Total Bilirubin (mg/dL)	Percentage of Starting Dose of Vinorelbine
≤ 2.0	100%
2.1 to 3.0	50%
> 3.0	25%

5.1.3.4.4 Oral Vinorelbine

If administered orally, vinorelbine is administered once weekly at 60mg/m² of body surface area for the first three administrations. Beyond the third administration, it is recommended to increase the dose of vinorelbine to 80 mg/m² once weekly except in those patients for whom the neutrophil count dropped once below 500/mm^3 or more than once between 500 and 1000/mm^3 during the first three administrations at 60 mg/m².

Table 19 Oral Vinorelbine Dose Adjustments during First Three Weeks Based on Neutrophils

Neutrophil count during the first 3 administrations of 60 mg/m^2/week	Neutrophils > 1000	Neutrophils ≥ 500 and < 1000 (1 episode)	Neutrophils ≥ 500 and < 1000 (2 episodes)	Neutrophils < 500
Recommended dose starting with the 4th administration	80	80	60	60

For any administration planned to be given at 80 mg/m², if the neutrophil count is below 500/mm^3 or more than once between 500 and 1000/mm^3 the administration should be delayed until recovery and the dose reduced from 80 to 60 mg/m^2 per week during the 3 following administrations.

If the neutrophil count is below 1500/mm^3 and/or the platelet count below 100000/mm^3, then the treatment should be delayed until recovery.

Table 20 Oral Vinorelbine Dose Adjustments beyond Fourth Week Based on Neutrophils

Neutrophil count beyond the 4th administration of 80 mg/m^2/week	Neutrophils > 1000	Neutrophils ≥ 500 and < 1000 (1 episode)	Neutrophils ≥ 500 and < 1000 (2 episodes)	Neutrophils < 500
Recommended dose starting with the next administration	80		60	

It is possible to re-escalate the dose from 60 to 80 mg/m^2 per week if the neutrophil count did not drop below 500/mm^3 or more than once between 500 and 1000/mm^3 during 3 administrations given at 60 mg/m^2 according to the rules previously defined for the first 3 administrations.

5.1.3.4.5 Special Warnings - Oral Vinorelbine

If the patient chews or sucks the capsule by error, the liquid is an irritant. Proceed to mouth rinses with water or preferably a normal saline solution.

In the event of the capsule being cut or damaged, the liquid content is an irritant, and so may cause damage if in contact with skin, mucosa or eyes. Damaged capsules should not be swallowed and should be returned to the pharmacy or to the doctor in order to be properly destroyed. If any contact occurs, immediate thorough washing with water or preferably with normal saline solution should be undertaken.

In the case of vomiting within a few hours after drug intake, do not re-administer. Supportive treatment such as metoclopramide or 5HT3 antagonists (e.g., ondansetron, granisetron) may reduce the occurrence of this. Vinorelbine soft capsules are associated with a higher incidence of nausea/vomiting than the intravenous formulation. Primary prophylaxis with antiemetics and administration of the capsules with some food is recommended as this has also been shown to reduce the incidence of nausea and vomiting.

Patients receiving concomitant morphine or opioid analgesics: laxatives and careful monitoring of bowel mobility are recommended. Prescription of laxatives may be appropriate in patients with prior history of constipation.

For further information see the Navelbine® soft capsule SmPC.

5.1.3.5 Gemcitabine Dose Modification and Management of Specific Adverse Events

Dose modification guidelines for gemcitabine are described in Table 21, Table 22, and Table 23. Additionally, manufacturer's instructions as well as local hospital or clinical practice will also be followed.

5.1.3.5.1 Hematologic Toxicity

Dose adjustments for hematologic toxicity may be required for gemcitabine. Gemcitabine dosage adjustments for hematologic toxicity are based on the granulocyte and platelet counts taken on Days 1 and Week 3 of therapy. Patient receiving gemcitabine should be monitored prior to each dose with a CBC, including differential and platelet counts. If bone marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 21 and Table 22.

Table 21 Dose Modification Guidelines for Hematological Toxicities on Day 1 of Gemcitabine

Absolute Granulocyte Count (x 10^6/L)		Platelet Count (x 10^6/L)	Gemcitabine % of full dose
≥ 1,500	and	≥ 100,000	100%
< 1,500	or	< 100,000	withhold

Table 22 Dose Modification Guidelines for Hematological Toxicities at Week 3 of Gemcitabine

Absolute Granulocyte Count (x 10^6/L)		Platelet Count (x 10^6/L)	Gemcitabine % of full dose
≥ 1000	and	≥ 100,000	100%
500-999	or	50,000−99,999	75%
< 500	or	< 50,000	Withhold

5.1.3.5.2 Dose Modifications Guidelines of Non-Hematologic Toxicity

In general, for severe (Grade 3 or 4) non-hematological toxicity, and nausea/vomiting, therapy with gemcitabine should be held or dose reduced by 50% depending on the judgment of the investigator.

- Permanently discontinue gemcitabine for any of the following:
- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary-leak syndrome
- Posterior reversible encephalopathy syndrome

Table 23 summarizes dose modifications guidelines for non-hematologic toxicities based on grade and severity.

Table 23 Gemcitabine Dose Modification Guidelines for Non-Hematological Toxicities

Toxicity	Grade 2	Grade 3	Grade 4
Non hematological toxicity, first appearance	Interrupt treatment until resolved to Grade 0-1 then continue at same dose with prophylaxis where possible	Interrupt treatment until resolved to Grade 0-1, then continue at 75% of original dose with prophylaxis where possible	Discontinue treatment unless investigator considers it to be in the best interest of the patient to continue at 50% of original dose, once toxicity has resolved to Grade 0-1 (after approval by the Sponsor)
Second appearance of same toxicity	Interrupt treatment until resolved to Grade 0-1, then continue at 75% of original dose	Interrupt treatment until resolved to Grade 0-1, then continue at 50% of original dose	
Third appearance of same toxicity	Interrupt treatment until resolved to Grade 0-1, then continue at 50% of original dose	Discontinue treatment permanently	
Fourth appearance of same toxicity	Discontinue treatment permanently		

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events, non-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 GCP, 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 Sections 5.3.5.9 and 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 study 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 study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study 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 NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hypothyroidism, hypophysitis, and hyperthyroidism
- Hepatitis, including AST or ALT > 10 x ULN
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies including rhabdomyolysis
- Grade ≥2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- *Myelitis*
- *Facial paresis*

5.3 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 to 5.6.

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

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study 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 serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug, regardless of time after study (see Section 5.6).

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

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

Table 24 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 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

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

- 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

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 study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), 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 3 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 study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × baseline value) in combination with either an elevated total bilirubin (> 2 × 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 × baseline value in combination with total bilirubin > 2 × ULN (of which ≥ 35% is direct bilirubin)
- Treatment-emergent ALT or AST > 3 × 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

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of NSCLC should be recorded on the Death Attributed to Progressive Disease eCRF. All other on-study deaths, 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). The iDMC will monitor the frequency of deaths from all causes.

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Non-Small Cell Lung Cancer

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device 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 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as 'special situations') are defined as follows:

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

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

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For atezolizumab, vinorelbine, or gemcitabine, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Overdose" box. If drug abuse is suspected, check the "Abuse" box. If drug abuse is not suspected, check the "Misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Overdose" and "Abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Overdose" and "Misuse" boxes.

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

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Overdose" box. If drug abuse is suspected, check the "Abuse" box. If drug abuse is not suspected, check the "Misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Overdose" and "Abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Overdose" and "Misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Misuse" box.

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

5.3.5.13 Patient-Reported Outcome Data

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

5.4 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 Sections 5.2.2 and 5.4.2 for further details)
- Adverse events of special interest (see Sections 5.2.3 and 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

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

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

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

5.4.1 Emergency Medical Contacts

5.4.1.1 Medical Monitor Contact Information for All Sites

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately. An Emergency Medical Call Center will be available 24 hours a day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

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

5.4.2.1 Events That Occur prior to Study 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 Clinical *Trial* Adverse Event/Special *Situation* 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, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study treatment, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first.

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the *Clinical Trial* Adverse Event/Special *Situation* 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 post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab or within 6 months after the last dose of single agent chemotherapy. A 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.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 5 months after the last dose of atezolizumab or within 6 months after the last dose of

single agent chemotherapy. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male 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).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all

serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

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

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

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, 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

Investigators are instructed to report all serious adverse events, and all adverse events of special interest that occur after the end of the adverse event reporting period (defined as 90 days after the last dose of study drug for serious adverse events and adverse events of special interest, and 30 days after the last dose of study drug for all other adverse events or initiation of new anti-cancer therapy, whichever occurs first), if the event is believed to be related to prior study drug treatment.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to Roche or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of 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 documents as a reference:

- Atezolizumab Investigator's Brochure
- Vinorelbine SmPC
- Gemcitabine SmPC

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.

An iDMC will monitor the safety data during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Primary and secondary analyses (OS, PFS) will be performed on all randomized patients (i.e., ITT) irrespective of whether the assigned treatment was actually received. ORR and DCR analyses will be performed on all randomized patients who have measurable disease at baseline. DOR analyses will be performed on the subset of patients who achieve an objective response. For all efficacy analyses, patients will be grouped according to the treatment assigned at randomization.

The safety population will include all randomized patients who received any amount of study treatment. Patients who are randomized into the study but did not receive any amount of study drug will not be included in the safety population. For safety analyses, patients will be grouped according to whether any amount of atezolizumab was received, including the case when atezolizumab was received in error.

6.1 DETERMINATION OF SAMPLE SIZE

This is a randomized, Phase III, global, multicenter, open-label study designed to evaluate the safety and efficacy of atezolizumab on duration of OS relative to the current treatment practice. Point and interval estimates of the true underlying hazard ratio will be obtained. Assuming a 10% withdrawal rate and accrual duration of 24 months, approximately 441 patients will be randomized in a 2:1 ratio to atezolizumab (294 patients) or chemotherapy (147 patients). A total of 380 OS events will provide 90% power to detect a significant improvement in the primary endpoint (median OS) for treatment with atezolizumab versus chemotherapy from 7 months to 10 months (i.e., hazard ratio [HR] of 0.7) for a two-sided log-rank test at an alpha level of 5%. One interim analysis for OS in the ITT population will be conducted when approximately 304 events have been reached. Operating characteristics are provided in Table 25.

Table 25 Operating Characteristics for Proposed Study Design

Sample Size Calculation Parameters	Values
Randomization ratio (atezolizumab vs chemotherapy)	2:1
Type 1 error (2-sided)	5%
Power	90%
Accrual duration	24 months
Duration until OS interim analysis	30 months
Duration until OS final analysis	42 months
Assumed drop-out rate	10%
Median control	7 months
Median atezolizumab	10 months
Hazard ratio	0.7
Number of events at interim analysis	304
Number of events at final analysis	380
Number of patients	441

Note: This is assuming validity of proportional Hazards assumption.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study drug administration, and discontinuation from the study will be summarized by treatment arm. The incidence of study drug discontinuation for reasons other than disease progression will be tabulated. Protocol deviations, including major deviations of inclusion/exclusion criteria, will be summarized.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables such as age, sex, race/ethnicity, stratification factors (histologic subtype, PD-L1 status, brain metastases), baseline and disease characteristics (e.g., PD-L1 status, cancer histology, ECOG performance status) will be summarized by treatment arm for the ITT population. Continuous variables will be summarized using means, standard deviations, medians, and ranges. Categorical variables will be summarized by proportions.

The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment, unless otherwise noted.

6.4 EFFICACY ANALYSES

Primary and secondary efficacy analyses will be based on the assigned treatment at randomization and will include all randomized patients (the ITT population).

6.4.1 Primary Efficacy Endpoint

The primary efficacy analysis is the comparison of OS between the two treatment arms (atezolizumab arm and single agent chemotherapy arm).

For OS, patients without a date of death will be censored on the date a patient was last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization plus 1 day.

The null and alternative hypotheses for OS analysis can be phrased in terms of comparison of survival function S(t) for the two treatment arms:

Ho: $S_{chemo}(t) = S_{Atezo}(t)$ vs

H1: $S_{chemo}(t) \neq S_{Atezo}(t)$.

The HR will be estimated using a stratified Cox regression model including 95% CIs. The stratification factors will be: histologic subtype (non-squamous/squamous), PD-L1 IHC status (positive/negative/unknown) and brain metastases (yes/no).

An unstratified analysis will also be performed.

Kaplan-Meier methodology will be used to construct survival curves by treatments arms. The median OS and corresponding 95% CI will be provided for each treatment arm.

If non proportionality of Hazard Ratio is detected, then further analyses and tests will be run. Further details on this scenario will be provided in the SAP.

A group sequential design will be used for testing OS at the interim analysis. Details on the timing of the interim analysis and stopping boundaries are provided in Section 6.8. Details on the hypothesis testing will be provided in the SAP.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Six month, 12 month, 18 month and 24 month Landmark OS

The rates of OS at various timepoints (i.e., every 6 months after randomization until 24 months) will be estimated by the Kaplan-Meier methodology for each arm and the 95% CI will be calculated using Greenwood's formula. The 95% CIs for the difference in OS rates between the two arms will be estimated using the normal approximation method.

6.4.2.2 Objective Response Rate

ORR is defined as the proportion of patients who had an objective response. The analysis population for ORR will be all randomized patients with measurable disease at baseline. An estimate of ORR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms will be determined using the normal approximation to the binomial distribution.

The ORR will be compared between the two arms using z-statistics and the normal approximation.

6.4.2.3 Progression-Free Survival

PFS is defined as the time (in months) between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Disease progression will be determined based on investigator assessment using RECIST v1.1. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of last tumor assessment. Patients with no postbaseline tumor assessment will be censored at the randomization date plus 1 day.

6.4.2.4 Duration of Response

DOR is defined as the time from initial response to disease progression or death among patients who have experienced a complete or partial response during the study. Patients who have not progressed at the time of analysis will be censored at the time of the last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a complete or partial response, DOR will be censored at the date of the first occurrence of a complete or partial response plus 1 day.

DOR is based on a nonrandomized subset of patients (specifically, patients who achieve an objective response); therefore, formal hypothesis testing will not be performed for this endpoint.

6.4.2.5 OS and Investigator-assessed PFS in Patients with PD-L1 Positive Status

OS and investigator-assessed PFS according to RECIST v1.1 will be assessed in patients whose tumors express PD-L1 protein as measured by PD-L1 SP263 IHC assay (Ventana Medical Systems, Tucson, USA).

6.5 SAFETY ANALYSES

Safety analyses will include all randomized patients who receive at least one dose of study drug (the safety population), with patients allocated to the treatment arm associated with the regimen actually received.

Drug exposure will be summarized to include treatment duration, number of doses, and dose intensity. Verbatim description of adverse events will be mapped to MedDRA thesaurus terms and graded according to NCI CTCAE v4.0. All adverse events occurring during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade ≥ 3), adverse events of special interest, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity.

Laboratory data with values outside the normal ranges will be identified. In addition, selected laboratory data will be summarized by treatment arm and grade.

Changes in vital signs will be summarized by treatment arm and grade.

Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation will be summarized by treatment arm.

Additionally, safety data from the re-treatment period, which will include patients who qualified for re-treatment with atezolizumab and who received at least one dose, will be summarized and/or listed.

6.6 PATIENT-REPORTED OUTCOME ANALYSES

PROs of lung cancer-related symptoms (i.e., cough, dyspnea, fatigue, pain in chest; pain in arm/shoulder), patient functioning, and HRQoL will be assessed using the EORTC QLQ-C30 (Aaronson et al. 1993) and the QLQ-LC13 (Bergman et al. 1994).

Summary statistics (mean, standard deviation, median, and range) of linear transformed scores will be reported for all the items and subscales of the EORTC QLQ-C30 questionnaire and the QLQ-LC13 according to the EORTC scoring manual guidelines. The mean change of the linear transformed scores from baseline (and 95% CI using the normal approximation) will also be assessed. Line charts depicting the mean changes (and standard errors) over time from the baseline assessment of items and subscales will be provided for each treatment arm. The proportion of patients showing clinically meaningful change in selected items and subscales at each assessment timepoint will be calculated, with clinically meaningful defined as a change in symptoms/functioning (i.e., reduction or increase) from baseline to the threshold of 10 points or more (Osoba et al. 1998).

Completion rates will be summarized at each timepoint by treatment arm. Only patients with a baseline assessment and at least one post-treatment assessment will be included in the analyses. Summaries will be performed for the ITT population only.

6.7 EXPLORATORY ANALYSES

Analyses using modified RECIST criteria (atezolizumab arm only with no comparison to the chemotherapy arm): ORR, PFS and DOR will also be evaluated using definitions of response per modified RECIST criteria (see Appendix 4). The investigator-assessed ORR is defined as the proportion of patients whose confirmed best overall response is either a partial response or complete response per modified RECIST.

DCR is defined as the rate of patients with complete or partial response as best response or stable disease per RECIST v1.1. The analysis methods for DCR will be the same as those for the analysis of ORR.

Exploratory biomarker analyses will be performed in order to understand the association of these markers with study drug response, including efficacy and/or adverse events.

The exploratory biomarker analyses will include patients with biomarker assessment at baseline as well as analyses comparing pre- and post-dose samples to explore changes in biomarker expression over time, with patients grouped according to the treatment actually received. Tissue and blood samples will be analyzed by e.g., IHC, qRT-PCR, NGS and/or other methods to study tumor biomarkers and changes thereof on DNA, RNA and/or protein (or other analytes) derived from blood and tumor tissue samples to address exploratory objective.

EQ-5D-5L health status data will be used for obtaining utility measures for economic modeling. Patients without postbaseline assessments will be excluded from this analysis.

6.8 INTERIM AND FINAL ANALYSES

There will be one interim analysis of OS conducted when approximately 304 deaths have occurred in the ITT population. The final OS analysis will be conducted when 380 events have occurred in the ITT population or when the follow-up time reaches at least 54 months after first patient in, whichever occurs first.

A group sequential design (Lan-DeMets with O'Brien-Fleming stopping boundaries) will be used to control the overall type I error rate (Lan and DeMets 1983). The information fraction at the time of each analysis will be re-calculated using the actual number of events included in the analysis, and the nominal alpha level re-calculated accordingly. The stopping boundaries for the planned interim and final analyses are shown in Table 26.

Table 26 Analysis Timing and Stopping Boundaries for Interim and Final Analysis for Overall Survival

Analysis Timing	Time from First Patient In (months)	Information Fraction (number of events)	Stopping Boundary HR (p-value[a])
Interim Analysis	30	80% (304)	0.76 ($p \leq 0.0244$)
Final Analysis	42[b]	100% (380)	0.8 ($p \leq 0.0428$)

HR = hazard ratio
[a] Two-sided p-value
[b] A cut-off date for final analysis will be set at least 54 months after first patient in should 380 OS events not be reached

The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter. The decision to conduct the planned interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP. The iDMC charter will document potential recommendations the iDMC can make to the Sponsor as a result of the analysis and the iDMC charter will also be made available to relevant health authorities, if applicable.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

The CRO will produce eCRF Specifications for the study based on Sponsor's templates including quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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

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 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patient-reported data may be collected electronically through use of electronic devices provided by an electronic PRO (ePRO) vendor. The electronic device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 Code of Federal Regulations, Part 11).

If patient-reported data are collected electronically, the data will be transmitted to a centralized database at the ePRO vendor. The data from the ePRO devices are available for view access only via secure access to a Web portal provided by the ePRO vendor. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. Regular data transfers will occur from the centralized database at the vendor to the database at the Sponsor.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

Details regarding patient reported data and the electronic device is available in the Study Reference Manual. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.4 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor and collaborators 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.

7.5 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.

7.6 RETENTION OF RECORDS

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

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location. Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the U.S. 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 E.U. 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 a Mobile Nursing Informed Consent Form, if applicable) will be provided

to each site. 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.

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

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

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

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

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

For sites in the U.S., 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 investigational 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 Roche policy on study data publication (see Section 9.5).

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

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

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

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 F. Hoffmann-La Roche Ltd. Approximately 120 sites globally will participate in the study and approximately 631 patients will be screened in order to randomize the required 441 patients.

Randomization will occur through an IxRS. Central facilities will be used for study assessments throughout the study (e.g., specified laboratory tests). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. *Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:*

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

The results of this study may be published or presented at scientific congresses. For all clinical trials in 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 Window (Days)	Screening Period [a]	Treatment Period [w]		Treatment Discontinuation [b]	Follow-Up Period [c]
	Day –28 to Day –1	Baseline (Cycle 1 Day 1)	Cycles ≥ 2 (Day 1 ± 5 days)	≤ 30 Days after Last Dose	-
Signed Informed Consent Form(s) [a]	x				
Tumor Tissue for ALK/EGFR analysis, central PD-L1 IHC (stratification) and exploratory biomarkers [d]	x				
Review of eligibility criteria	x				
Medical, surgical, and cancer histories, including demographic information, EGFR, and ALK mutational status [e]	x				
HIV, HBV, HCV serology [f]	x [y]				
TSH, free T3 (or total T3), free T4 [g]	x [y]	x	Cycles 5, 9, 13 etc.	x	
Concomitant medications [h]	x	x	x	x	
Tumor response assessments [i, x]	x [i]		x		
Patient-reported outcomes [j]	x		With tumor response assessments [z]		
Complete physical examination [k]	x			x	
Limited physical examination [k]		x	x		
ECOG performance status [l]	x	x	x [m]	x	
Vital signs [n]	x	x	x	x	
12-lead electrocardiogram [o]	x	x	x	x	
Hematology [p]	x [y]	x	x	x	
Serum chemistry [q]	x [y]	x	x	x	

APPENDIX 1
SCHEDULE OF ACTIVITIES (CONT.)

Assessment Window (Days)	Screening Period [a]	Treatment Period [w]		Treatment Discontinuation [b]	Follow-Up Period [c]
	Day –28 to Day –1	Baseline (Cycle 1 Day 1)	Cycles ≥ 2 (Day 1 ± 5 days)	≤ 30 Days after Last Dose	-
Urinalysis [r]	x [y]	x	x	x	
Pregnancy test [s]	x [y]	Prior to each treatment cycle		x	x [s]
Coagulation (INR, aPTT)	x [y]			x	
Whole blood for PBMC (exploratory biomarker) [t]		x			
Plasma for exploratory biomarkers [u]		x	Week 7 and at PD		
Adverse events / adverse events of special interest [v]		x	x	x	x [v]
Study drug administration [w]		x	x		
Survival and anticancer therapy follow-up [c]					x

ALK = anaplastic lymphoma kinase; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus, IHC = immunohistochemistry; PBMC = peripheral blood mononuclear cell; PD = disease progression; PD-L1 = programmed cell death-ligand 1; q3w = every 3 weeks; TSH = thyroid-stimulating hormone; T3 = free triiodothyronine; T4 = free thyroxine.

Note: All assessments should be performed within ± 5 days of the scheduled visit, unless otherwise specified.

[a] Written informed consent is required for performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry (except where otherwise specified) may be used for screening assessments rather than repeating such tests.

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit ≤ 30 days after the last dose of study drug. The visit at which the decision is made to discontinue treatment (e.g., disease progression is determined or confirmed) may be used as the treatment discontinuation visit. After study drug discontinuation, patients will be treated at the discretion of the investigator according to local practice. The decision to continue treatment with atezolizumab (experimental arm only) beyond disease progression (RECIST v.1.1) is at the investigator's discretion for patients who can continue to benefit from the treatment (for criteria see Section 3.1).

[c] Required follow-up information, including subsequent anticancer therapies and any treatment related AEs, will be collected via telephone calls and/or clinic visits every 2 months (± 5 days) until death, withdrawal of consent, loss to follow-up, study termination by the Sponsor, or protocol-defined end of study, whichever comes first. In case of serious side effects during the study, follow-up examinations at the study site may be required.

APPENDIX 1
SCHEDULE OF ACTIVITIES (CONT.)

[d] Screening: A representative formalin-fixed paraffin-embedded (FPPE) tumor tissue block obtained during course of disease (archival tissue) or screening (tumor blocks are highly preferred; ideally, 3 cores should be submitted in case smaller core biopsies are available in order to have sufficient tumor cells available. In case the tumor block is not available, 10-15 unstained, consecutive slides not older than 60 days will be accepted. A minimum of five slides is mandated for PD-L1 analysis and patient stratification. If archival tissue (most recent sample) is unavailable, a pretreatment tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable. Tumor tissue from bone metastases or are not acceptable. Tumor tissue should be of good quality based on total and viable tumor content (at least 300 viable tumor cells across cores are needed for determination of TC/IC status at low cut-offs).

[e] Cancer history includes stage, date of diagnosis, results of EGFR mutation and ALK rearrangement testing (if available), and prior antitumor treatment. Demographic information includes sex, age, and self-reported race/ethnicity. Patients with non-squamous NSCLC and unknown EGFR or ALK status will be required to be tested at pre-screening/screening. Patients with squamous NSCLC and unknown EGFR or ALK status will not be required to be tested at pre-screening/ screening, except for patients who are never smokers or have mixed histology. EGFR and/or ALK may be assessed locally or at a central lab. Additional tissue will be required for central testing of EGFR and/or ALK. An FFPE tumor tissue block (or at least 7 slides) will be required for testing.

[f] Patients with a history of, or signs of active HIV or hepatitis B/C disease must be tested for seropositivity prior to the inclusion into the study. HIV-positive patients will be excluded from the clinical study. Patients with a positive hepatitis B surface antigen [HBsAg] test at screening will be excluded from this clinical study. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

[g] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening, on Day 1 of Cycle 1 and every four cycles thereafter (i.e., Cycles 5, 9, 13, etc.).

[h] Includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening until the treatment discontinuation visit. All such medications should be reported to the investigator and must be recorded on the appropriate Concomitant Medications eCRF.

[i] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. It is recommended to have the screening/baseline tumor assessment done within 14 days before randomization, as close as possible to baseline. All measurable and evaluable lesions should be assessed and documented at the screening visit. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Results must be reviewed by the investigator before dosing at the next cycle. All patients should undergo a brain scan at Screening. Patients with CNS metastases newly detected at the screening scan should have received radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to randomization, if all other criteria are met, including clinical confirmation of no evidence of interim disease progression.

[j] PRO assessments (EORTC QLQ-C30, QLQ-LC13, and EQ-5D-5L) will be completed before the patient receives any information on disease status and prior to the performance of non-PRO assessments and the administration of study treatment. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site.

[k] Complete and limited physical examinations are defined in Section 4.5.3.

[l] ECOG performance status, limited physical examination, local laboratory assessments may be obtained ≤ 96 hours before Day 1 of each cycle.

[m] ECOG PS is mandatory at all timepoints.

[n] Includes height, weight, respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and

neurological systems. Record abnormalities observed at baseline 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 AE eCRF.

[o] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. ECG recordings will be obtained as described in Section 4.5.9.

[p] Hematology includes complete blood count [CBC], including red blood cell count [RBC] count, hemoglobin, hematocrit, white blood cell (WBC) count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count

[q] Serum chemistry panel (serum or plasma) includes glucose, blood urea nitrogen [BUN] or urea, creatinine, sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), calcium, phosphorus, total and direct bilirubin, ALT, AST, alkaline phosphatase, uric acid, LDH, total protein, and albumin.

[r] Dipstick permitted: pH, specific gravity, glucose, protein, ketones, blood.

[s] A serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1. On study pregnancy tests must be performed prior to each treatment cycle (21-day cycle for atezolizumab and per relevant local guidelines and SmPC management for chemotherapy) while receiving the IMP. For female patients of childbearing potential, the pregnancy tests will be repeated during the treatment discontinuation visit and then every 2 months during follow-up for at least 5 months after the last dose of atezolizumab and for at least 6 months after the last dose of chemotherapy, respectively. Pregnancy tests during follow-up do not require on-site visits; results from a treating physician can be used. The pregnancy test can be conducted with serum or urine. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[t] 18 mL whole blood (ACD tubes) should be obtained pre-dose and shipped to the central laboratory for PBMC preparation, RNA isolation and gene expression analysis. Details are specified in a separate laboratory manual. If consented, residual material will be transferred to RBR.

[u] 20 mL whole blood (K3 EDTA tubes) for preparation of plasma should be obtained pre-dose. Plasma samples will be shipped to the central laboratory for exploratory biomarker analyses. If consented, residual material (including extracted RNA or DNA or other) will be transferred to RBR.

[v] 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 serious adverse events, and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After these respective periods, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug, regardless of time after study (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[w] Atezolizumab at a fixed dose of 1200 mg will be administered intravenously at the study site on Day 1 of each 21-day cycle. Single agent chemotherapy (vinorelbine, oral or intravenous, or gemcitabine) will be administered per relevant local guidelines and SmPC management. Chemotherapy cycles may be 3-weekly or 4-weekly. A 28-day assessment schedule will be followed for patients receiving 4-weekly chemotherapy cycles.

[x] Tumor assessments will be performed at baseline, every 6 weeks (± 5 days) following randomization for 48 weeks, and every 9 weeks (± 5 days) thereafter, regardless of dose delays, with additional scans as clinically indicated, until radiographic disease progression per RECIST v1.1 or (for patients who continue

atezolizumab after radiographic disease progression), loss of clinical benefit as determined by the investigator (see Section 3.1 and 4.5.5 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue study treatment for reasons other than disease progression or loss of clinical benefit, even if patients start new anti-cancer therapy. In all patients, response will be assessed by the investigator using RECIST v1.1 until disease progression. Patients randomized to receive atezolizumab will additionally be assessed by modified RECIST criteria until treatment discontinuation. Follow-up tumor assessments are not required after discontinuation of atezolizumab for patients continuing atezolizumab beyond PD.

[y] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[z] The EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires will be completed by the patients with each tumor assessment until disease progression per RECIST v1.1, even if patients discontinue study treatment for any reason other than progressive disease or loss of clinical benefit.

Appendix 2
American Joint Committee on Cancer Non−Small Cell Lung Cancer Staging, 7th Edition

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CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS	PATHOLOGIC *Extent of disease through completion of definitive surgery*
☐ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	TUMOR SIZE: _____ LATERALITY: ☐ left ☐ right ☐ bilateral	☐ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)	
☐ TX	Primary tumor cannot be assessed	☐ TX
☐ T0	No evidence of primary tumor	☐ T0
☐ Tis	Tis Carcinoma *in situ*	☐ Tis
☐ 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)*	☐ T1
☐ T1a	Tumor ≤2 cm in greatest dimension	☐ T1a
☐ T1b	Tumor > 2 cm but ≤3 cm in greatest dimension	☐ T1b
☐ T2	Tumor > 3 cm but ≤7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤ 5 cm) Involves main bronchus, ≥2 cm distal to the carina Invades visceral pleura (PL1 or PL2) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung	☐ T2
☐ T2a	Tumor > 3 cm but ≤5 cm in greatest dimension	☐ T2a
☐ T2b	Tumor > 5 cm but ≤7 cm in greatest dimension	☐ T2b
☐ T3	Tumor > 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (< 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe	☐ T3
☐ T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe	☐ T4
	* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.	
	REGIONAL LYMPH NODES (N)	
☐ NX	Regional lymph nodes cannot be assessed	☐ NX
☐ N0	No regional lymph node metastasis	☐ N0
☐ N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	☐ N1
☐ N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	☐ N2
☐ N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)	☐ N3
	DISTANT METASTASIS (M)	
☐ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
☐ M1	Distant metastasis	☐ M1
☐ M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion**	☐ M1a
☐ M1b	Distant metastasis (in extrathoracic organs)	☐ M1b
	**Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.	

APPENDIX 2
AMERICAN JOINT COMMITTEE ON CANCER NON−SMALL CELL LUNG CANCER STAGING, 7TH EDITION (CONT.)

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ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL				PATHOLOGIC			
GROUP	T	N	M	GROUP	T	N	M
☐ Occult	TX	N0	M0	☐ Occult	TX	N0	M0
☐ 0	Tis	N0	M0	☐ 0	Tis	N0	M0
☐ IA	T1a	N0	M0	☐ IA	T1a	N0	M0
	T1b	N0	M0		T1b	N0	M0
☐ IB	T2a	N0	M0	☐ IB	T2a	N0	M0
☐ IIA	T2b	N0	M0	☐ IIA	T2b	N0	M0
	T1a	N1	M0		T1a	N1	M0
	T1b	N1	M0		T1b	N1	M0
	T2a	N1	M0		T2a	N1	M0
☐ IIB	T2b	N1	M0	☐ IIB	T2b	N1	M0
	T3	N0	M0		T3	N0	M0
☐ IIIA	T1a	N2	M0	☐ IIIA	T1a	N2	M0
	T1b	N2	M0		T1b	N2	M0
	T2a	N2	M0		T2a	N2	M0
	T2b	N2	M0		T2b	N2	M0
	T3	N1	M0		T3	N1	M0
	T3	N2	M0		T3	N2	M0
	T4	N0	M0		T4	N0	M0
	T4	N1	M0		T4	N1	M0
☐ IIIB	T1a	N3	M0	☐ IIIB	T1a	N3	M0
	T1b	N3	M0		T1b	N3	M0
	T2a	N3	M0		T2a	N3	M0
	T2b	N3	M0		T2b	N3	M0
	T3	N3	M0		T3	N3	M0
	T4	N2	M0		T4	N2	M0
	T4	N3	M0		T4	N3	M0
☐ IV	Any T	Any N	M1a	☐ IV	Any T	Any N	M1a
	Any T	Any N	M1b		Any T	Any N	M1b
☐ Stage unknown				☐ Stage unknown			

Reference: Lung. In: Edge S, Byrd DR, Compton CC, et al, editors. AJCC Cancer Staging Manual, Seventh Edition. Chicago: Springer, 2010:267–70.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication

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Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized 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 computed tomography (CT) or magnetic resonance imaging (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

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

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 lung, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

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

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

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:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. 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 never more than 4 weeks before 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.

APPENDIX 3
RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: MODIFIED EXCERPT FROM ORIGINAL PUBLICATION (CONT.)

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

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

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan on the basis of the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, 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, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

APPENDIX 3
RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: MODIFIED EXCERPT FROM ORIGINAL PUBLICATION (CONT.)

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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 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.

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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").

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 during the 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 during the 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 during the 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 since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While in the 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 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 too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

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.

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- 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 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.

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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.

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.

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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.

c. 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 4
Modified Response Evaluation Criteria in Solid Tumors

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Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like *atezolizumab*, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment.

Modified Response Evaluation Criteria in Solid Tumors (RECIST) is derived from RECIST, Version 1.1 (v1.1) conventions[3] and immune-related response criteria[4] (irRC). When not otherwise specified, RECIST v1.1 conventions will apply.

Modified RECIST and RECIST v1.1: Summary of Changes

	RECIST v1.1	Modified RECIST
New lesions after baseline	Define progression	New measurable lesions are added into the total tumor burden and followed.
Non-target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of ≥20% increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease

RECIST=Response Evaluation Criteria in Solid Tumors.

A. DEFINITIONS OF MEASURABLE/NON-MEASURABLE LESIONS

All measurable and non-measurable lesions should be assessed at Screening and at the protocol-specified tumor assessment timepoints. Additional assessments may be performed, as clinically indicated for suspicion of progression.

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A.1 MEASURABLE LESIONS

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

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval 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)

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

A.2 NON-MEASURABLE LESIONS

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

A.3 SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions

Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

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Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as 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.

B. TUMOR RESPONSE EVALUATION

B.1 DEFINITIONS OF TARGET/NON-TARGET LESIONS

Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be 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 in addition, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance, the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the

diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

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

Non-Target Lesions

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.

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").

After baseline, changes in non-target lesions will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions) and will not be used to assess progressive disease.

New Lesions

During the study, all new lesions identified and recorded after baseline must be assessed at all tumor assessment timepoints. New lesions will also be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST, (e.g., non–lymph node lesions must be ≥ 10mm; see note for new lymph node lesions below). Up to a maximum of five new lesions total (and a maximum of two lesions per organ), all with measurements at all timepoints, can be included in the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the tumor response evaluation.

New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint will be measured from that point on and contribute to the sum

of longest diameters (SLD), if the maximum number of 5 measurable new lesions being followed has not been reached.

B.2 CALCULATION OF SUM OF THE DIAMETERS

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumor burden.

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Sum of the Diameters at Tumor Assessment: For every on-study tumor assessment collected per protocol or as clinically indicated the sum of the diameters at tumor assessment will be calculated using tumor imaging scans. All target lesions selected at baseline and up to five new measurable lesions (with a maximum of two new lesions per organ) that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment with use of modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

Note: In the case of new lymph nodes, RECIST v1.1 criteria for measurability (equivalent to baseline target lesion selection) will be followed. That is, if at first appearance the short axis of a new lymph node lesion ≥15 mm, it will be considered a measureable new lesion and will be tracked and included in the SLD. Thereafter, the lymph node lesion will be measured at subsequent timepoints and measurements will be included in the SLD, even if the short axis diameter decreases to <15 mm (or even <10 mm). However, if it subsequently decreases to <10 mm, and all other lesions are no longer detectable (or have also decreased to a short axis diameter of <10 mm if lymph nodes), then a response assessment of CR may be assigned.

If at first appearance the short axis of a new lymph node is ≥10 mm and <15 mm, the lymph node will not be considered measurable but will still be considered a new lesion. It will not be included in the SLD unless it subsequently becomes measurable (short axis diameter ≥15 mm).

The appearance of new lymph nodes with diameter <10 mm should not be considered pathological and not considered a new lesion.

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B.3 RESPONSE CRITERIA

Timepoint 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.

Complete Response (CR): Disappearance of all target and non-target lesions. Lymph nodes that shrink to <10 mm short axis are considered normal.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.

Note: the appearance of new measurable lesions is factored into the overall tumor burden, but *does not automatically qualify as progressive disease* until the sum of the diameters increases by ≥20% when compared with the sum of the diameters at nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the diameters while in the study.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and selected new measurable lesions, taking as reference the smallest sum during the study (nadir SLD; this includes the baseline sum if that is the smallest during the study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Impact of New Lesions on Modified RECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumor response.

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is considered not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE 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 only happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed but

those gave a sum of 80 mm, the patient will be assigned PD status, regardless of the contribution of the missing lesion.

Table 1 Modified RECIST Timepoint Response Definitions

% Change in Sum of the Diameters [a]	Non-Target Lesion Response Assessment	Overall Modified RECIST Timepoint Response
−100% from baseline [b]	CR	CR
−100% from baseline [b]	Non-CR or not all evaluated	PR
≤ −30% from baseline	Any	PR
> −30% to <+20%	Any	SD
Not all evaluated	Any	NE
≥ +20%from nadir SLD	Any	PD

CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; SLD=sum of the longest diameter.

[a] Percent change in sum of the diameters (including measurable new lesions when present).

[b] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm in order to meet the definition of CR.

Appendix 5
Anti-PD-L1 Immunohistochemistry

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OVERVIEW

The Ventana anti–programmed death ligand–1 (PD-L1) (SP142) rabbit monoclonal primary antibody immunohistochemistry (IHC) assay will be used to determine PD-L1 IHC status. The anti–PD-L1 (SP142) rabbit monoclonal antibody IHC assay is currently being developed by Ventana Medical Systems as a companion diagnostic to *atezolizumab*. For Study GO29432, the anti–PD-L1 (SP142) IHC assay will be used for investigational purposes only.

The Ventana anti–PD-L1 (SP142) rabbit monoclonal primary antibody is intended for laboratory use in the semi-quantitative immunohistochemical assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded non–small cell lung cancer (NSCLC) tissue stained on a Ventana BenchMark ULTRA automated slide stainer. It is indicated as an aid in the selection of patients with NSCLC with locally advanced or metastatic disease who might benefit from treatment with *atezolizumab*.

This assay is for investigational use only. The performance characteristics of this product have not been established.

DEVICE DESCRIPTION

The Ventana anti–PD-L1 (SP142) rabbit monoclonal primary antibody is a pre-dilute, ready-to-use antibody product optimized for use with the Ventana Medical Systems OptiView DAB IHC Detection Kit and the OptiView Amplification Kit on Ventana Medical Systems automated BenchMark ULTRA platforms. One 5-mL dispenser of anti–PD-L1 (SP142) rabbit monoclonal primary antibody contains approximately 36 µg of rabbit monoclonal antibody directed against the PD-L1 protein and contains sufficient reagent for 50 tests. The reagents and the IHC procedure are optimized for use on the BenchMark ULTRA automated slide stainer, utilizing Ventana System Software (VSS).

SCORING SYSTEM

PD-L1 staining with anti–PD-L1 (SP142) rabbit monoclonal primary antibody in NSCLC can be observed in both tumor cells and tumor-infiltrating immune cells.

Appendix 6
EORTC QLQ-C30

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EORTC QLQ-C30 (version 3)

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

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

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 7
EORTC QLQ-LC13

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EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Appendix 8
EuroQoL 5 Dimension, 5 Level Questionnaire

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Health Questionnaire

(English version for the US)

APPENDIX 8
EUROQOL 5 DIMENSION, 5 LEVEL QUESTIONNAIRE (CONT.)

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Figure 1: EQ-5D-5L (UK English sample version)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

ANXIETY / DEPRESSION

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

APPENDIX 8
EUROQOL 5 DIMENSION, 5 LEVEL QUESTIONNAIRE (CONT.)

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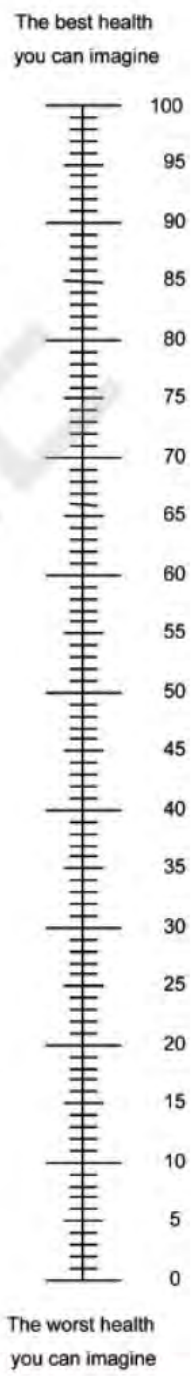
- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the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

YOUR HEALTH TODAY = ☐



Appendix 9
Eastern Cooperative Oncology Group Performance Status Scale

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Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 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 10
Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

1. Stop the study drug infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
5. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 11
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously expereinced a servere or life-threatening skin adverse reaction *or pericardial disorder* while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Anti-phospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • *Autoimmune myelitis* • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cholangitis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • *Granulomatosis with polyangiitis*

Appendix 12
PD-L1 IHC Scoring Criteria

- Tumor area is defined as tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma.
- Immune Cell (IC) Score includes the assessment of PD-L1 positive tumor-infiltrating immune cells relative to the tumor area.
- Tumor Cell (TC) score is the assessment of PD-L1 positive tumor cells relative to the total number of tumor cells.

PD-L1 Immune Cell (IC) Positivity	
IC0	Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering **< 1%** of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma
IC1	Presence of discernible PD-L1 staining of any intensity in tumor-filtrating immune cells covering between **≥ 1% and < 5%** of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma
IC2	Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering between **≥ 5% and < 10%** of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma
IC3	Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering **≥ 10%** of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma

PD-L1 Tumor Cell (TC) Positivity	
TC0	Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in **< 1%** tumor cells
TC1	Presence of discernible PD-L1 staining of any intensity in **≥ 1% and < 5%** tumor cells
TC2	Presence of discernible PD-L1 staining of any intensity in **≥ 5% and < 50%** tumor cells
TC3	Presence of discernible PD-L1 staining of any intensity in **≥ 50%** tumor cells

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

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

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

documented by the investigator. The Medical Monitor is available to advise as needed.

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit-risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study {and will have computed tomography (CT) scans of the chest performed at every tumor assessment}.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. *COVID-19 evaluation should be performed per institutional guidelines where relevant*. Management guidelines for pulmonary events are provided in Table 1

.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL *with or without transbronchial biopsy*. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • 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	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c, d] • *Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment.* • Bronchoscopy or BAL *with or without* transbronchial *biopsy* is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methyprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

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

HEPATIC EVENTS

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

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

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

Table 2 Management Guidelines for Hepatic Events

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

Table 2 Management Guidelines for Hepatic Events

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

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table 3.

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

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

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • *If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • Patient referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. *If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • If event resolves to Grade 1 or better, resume atezolizumab. [b]

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

Event	Management
	• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to GI specialist for evaluation and *confirmatory* biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of

thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• *Consider withholding atezolizumab.* • *Initiate treatment with thyroid replacement hormone.* • *Monitor TSH closely.* • *Consider patient referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled, and thyroid function is improving.*

Table 4 Management Guidelines for Endocrine Events

Event	• Management
Grade 3 and 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • *Refer* to *an* endocrinologist. • *Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status).* • Resume atezolizumab when symptoms are *controlled,* and thyroid function is improving. • *Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism.* [c]
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for *Grade 2* hyperthyroidism. • Consider patient referral to endocrinologist.
Grade 2 hyperthyroidism	• *Consider withholding atezolizumab.* • *Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.* • *Consider patient referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled, and thyroid function is improving.*
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug*s* such as methimazole or carbimazole as needed. • *Refer* to endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab and contact *the* Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

Table 4 Management Guidelines for Endocrine Events

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms *resolve,* and glucose levels are stable.

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

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 4 Management Guidelines for Endocrine Events

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

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

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

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

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table 6.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type matriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis *or associated with pericarditis (see section on pericardial disorders below)* and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

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

IMMUNE-MEDIATED PERICARDIAL DISORDERS

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

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

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

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

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated

according to the guidelines in Table 6. *Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.*

Table 6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2-4 *Immune-mediated pericardial disorders, Grades 2-4*	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD *or pericardiocentesis* as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretic *medication*s, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

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

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

with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

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

Severe COVID-19 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 COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator's judgement. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

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

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretics *medications*, and/or analgesics, and monitor closely for IRRs and/or CRS.

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

Event	Management
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically *indicated and* manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS 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 *the* Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic *medications*, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact *the* Medical Monitor.

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

Event	Management
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact *the* 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.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [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.

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

Event	Management

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 *the* NCCN guidelines for *the* 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 ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

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

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

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

- [f] Refer to Riegler et al. (2019).

PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8 .

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

GI = gastrointestinal.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

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

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

DERMATOLOGIC EVENTS

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

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis, 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 prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit-risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10 *, with specific guidelines for myelitis provided in Table 11*.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • *Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.*
Immune-mediated neuropathy, *including facial paresis,* Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • *For general immune-mediated neuropathy:* – If event resolves to Grade 1 or better, resume atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • *For facial paresis:* – *If event resolves fully, resume atezolizumab* [b] • *If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated neuropathy, *including facial paresis,* Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 11 Management Guidelines for Immune-Mediated Myelitis

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

IMMUNE-MEDIATED MENINGOENCEPHALITIS

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12 .

Table 12 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

RENAL EVENTS

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

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED MYOSITIS

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

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

Table 14 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact *the* Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact *the* Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.

Table 14 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor.[c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH).

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

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

- Fever ≥ 38.5°C
- Splenomegaly

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

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

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
- Platelet count ≤ 181×10^9/L (181,000/μL)
- AST ≥ 48 U/L
- Triglycerides > 1.761 mmol/L (156 mg/dL)
- Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 15 .

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

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact *the* Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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