PROTOCOL

TITLE:	**AN OPEN-LABEL, MULTICOHORT, PHASE II STUDY OF ATEZOLIZUMAB IN ADVANCED SOLID TUMORS**
PROTOCOL NUMBER:	MO29518
VERSION NUMBER:	8
EUDRACT NUMBER:	2015-000269-30
NCT NUMBER:	*NCT02458638*
IND NUMBER:	111271
TEST PRODUCT:	Atezolizumab (RO5541267)
MEDICAL MONITOR:	Dr. [redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 18-Jan-2015
DATE AMENDED:	Version 2: 20-May-2015 Version 3: 29-Sep-2015 Version 4: 19-Aug-2016 Version 5: 19-Jun-2017 Version 6: 01-Mar-2018 Version 7: 29-Oct-2018 Version 8: See electronic stamp below

Date and Time (UTC)	Title	Approver's Name
23-Oct-2019 14:11:35	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 8: RATIONALE

Specific changes in Version 8 of Protocol MO29518 and their rationale are as follows:

- Appendix 8: updated to include the changes in the Atezolizumab Investigator's Brochure version 15 (IB v15), including the guidelines for management of immune-mediated myositis and for suspected hemophagocytic lymphohistiocytosis or macrophage activation syndrome, removed description and management guidelines for systemic immune activation, updated terminology changing "immune-related" to "immune-mediated" (and wherever applicable throughout the protocol).

- Clarified provisions for post-trial access to atezolizumab to allow for continued treatment of patients following last patient last visit (LPLV), and regarding data collection during transition to the extension study.

- Change in Medical Monitor and addition of NCT number.

- Terminology update to align with recent changes in the atezolizumab IB v15 changed "immune-related" to "immune-mediated".

Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 8:
SUMMARY OF CHANGES

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

Update of Non-Serious Adverse Events of Special Interest (AESI) to align with Atezolizumab IB v15 and protocols across the Atezolizumab programme, adding AESIs identified more recently and minor terminology updates.

5.1.4 Management of Specific Adverse Events

Removal of term, description and management guidelines for systemic immune activation (SIA), and addition of the terms hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) as potential risks, together with diagnostic criteria and management guidelines for HLH and MAS.

SIA was defined by the Sponsor internally as an excessive activation of the immune system in the setting of combined immunomodulatory therapies (immune-doublets) characterized as systemic inflammation with fever, elevated inflammatory markers and multiple organ dysfunction in the absence of other etiologies. It was considered a clinical entity separate from other similar systemic immune entities (HLH) and (MAS) etc. As of today, SIA remains a Roche specific term and is not widely used in the medical community. It is a potential risk for Atezolizumab. The event is not described in the literature, hence no common definition or established guidelines for SIA exist unlike other established entities [HLH, MAS, or cytokine release syndrome (CRS)]. Evolving knowledge of safety profile of checkpoint inhibitors and a recent review of reported SIA cases conducted by the Sponsor did not reveal any case that is clearly differentiated from other established entities in the spectrum of systemic immune events (e.g. HLH, MAS, CRS). The current guidance in the IB and protocols for Atezolizumab has led to cases being reported as SIA (single agent atezolizumab or in combinations) even though meeting the criteria of other immune entities such as HLH, MAS or CRS. The IB version 15 and amendments of protocols and ICFs for Atezolizumab remove the term systemic immune activation (SIA), and add the terms HLH and MAS as potential risks, together with diagnostic criteria and management guidelines for HLH and MAS.

~~**5.1.4.1 Systemic Immune Activation**~~

~~Systemic immune activation (SIA) is a rare condition characterized by an excessive immune response. Given the mechanism of action of Atezolizumab, SIA is considered a potential risk when given with other immunomodulating agents. SIA should be included in the differential diagnosis for patients who, in the absence of an alternative etiology,~~

~~develop a sepsis-like syndrome after administration of Atezolizumab, and the initial evaluation should include the following:~~

- ~~CBC with peripheral smear~~
- ~~PT, PTT, fibrinogen, and D-dimer~~
- ~~Ferritin~~
- ~~Triglycerides~~
- ~~AST, ALT, and total bilirubin~~
- ~~LDH~~
- ~~Complete neurologic and abdominal examination (assess for hepatosplenomegaly)~~

~~If SIA is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations and management.~~

5.3.4 Post-Trial Access to Atezolizumab

Added language to clarify provisions for post-trial access to atezolizumab to allow for continued treatment of patients following LPLV, and regarding data collection during transition to the extension study.

> *Patients may also take part in an extension study if the patient is still benefiting from treatment (defined as no registered PD) at the time of planned Last Patient Last Visit date. If the extension study is not set-up in time for the patient to roll over by the planned protocol LPLV date, nor is there a Post-Trial Access Program available, the patient can continue treatment in the study until the extension study is opened at the patient's site. During the interim period between LPLV and a patient rolling over to the extension study, only safety data (AE including SAE and AESI) will continue to be collected in the eCRF. Other assessments (e.g. tumor assessment) can be performed as per standard of care.*

APPENDIX 1: Schedule of Assessments

Added footnote 24 to clarify assessments during transition to the extension study following LPLV.

> *During the interim period between LPLV and a patient rolling over to the extension study, only safety data (AE including SAE and AESI) will continue to be collected in the eCRF. Other assessments (e.g. tumor assessment) can be performed as per standard of care.*

APPENDIX 2: Schedule of Anti-Therapeutic Antibody, Pharmacodynamic and Pharmacokinetic Assessments

Addition to footnote 2 to clarify sample collection during transition to the extension study following LPLV.

For patients who discontinue the study treatment, ATA and PK samples are to be obtained at 120 days ± 30 days after the last dose of study treatment unless the patient dies or withdraws consent or the study closes *(during the interim period between LPLV and a patient rolling over to the extension study, ATA and PK samples do not need to be collected)*.

APPENDIX 8: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Added guidelines for management of immune-mediated myositis and for suspected hemophagocytic lymphohistiocytosis or macrophage activation syndrome (see rationale above), and updated terminology changing "immune-related" to "immune-mediated".

IMMUNE-MEDIATED MYOSITIS

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

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

Table 13 Management Guidelines for Immune-Mediated Myositis

Event	*Management*
Immune-mediated myositis, Grade 1	• *Continue atezolizumab.* • *Refer patient to rheumatologist or neurologist.* • *Initiate treatment as per institutional guidelines.*
Immune-mediated myositis, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset*[a] *and contact Medical Monitor.* • *Refer patient to rheumatologist or neurologist.* • *Initiate treatment as per institutional guidelines.* • *Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, resume atezolizumab.*[b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.*[c]

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

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

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

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

Immune-mediated myositis, Grade 3	• *Withhold atezolizumab for up to 12 weeks after event onset*[a] *and contact Medical Monitor.* • *Refer patient to rheumatologist or neurologist.* • *Initiate treatment as per institutional guidelines.* • *Respiratory support may be required in more severe cases.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, resume atezolizumab.*[b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.*[c] • *For recurrent events, treat as a Grade 4 event.*
Immune-mediated myositis, Grade 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.*[c] • *Refer patient to rheumatologist or neurologist.* • *Initiate treatment as per institutional guidelines.* • *Respiratory support may be required in more severe cases.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

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

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

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

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

- *Fever $\geq$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 $<100 \times 10^9$/L (100,000/μL)*
  - *ANC $<1.0 \times 10^9$/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 interleukin 2 (IL-2) receptor (soluble CD25) elevated $\geq$2 standard deviations above age-adjusted laboratory-specific norms*

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

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

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

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

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

HLH=hemophagocytic lymphohistiocytosis; MAS=macrophage activation syndrome.

REFERENCES

Added relevant references related to hemophagocytic lymphohistiocytosis and macrophage activation syndrome.

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–9.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, MULTICOHORT, PHASE II STUDY OF ATEZOLIZUMAB IN ADVANCED SOLID TUMORS**
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IND NUMBER:	111271
TEST PRODUCT:	Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return the signed original of this form to the Sponsor or their designee. Contact details will be provided to the investigator prior to the study start. Please retain a copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL, MULTICOHORT, PHASE II STUDY OF ATEZOLIZUMAB IN ADVANCED SOLID TUMORS**
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NCT NUMBER:	*NCT02458638*
IND NUMBER:	111271
TEST PRODUCT:	Atezolizumab (RO5541267)
PHASE:	II
INDICATION:	Advanced solid tumors
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To evaluate non-progression rate (NPR) at 18 weeks in patients with advanced solid tumors treated with Atezolizumab, defined as the percentage of patients with complete response (CR) partial response (PR) or stable disease (SD) as assessed by the Investigator according to Response Evaluation Criteria In Solid Tumors, Version 1.1 (RECIST, v1.1) (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7)

The secondary efficacy objectives for this study are as follows:

- To evaluate NPR at 24 weeks, overall response rate (ORR), best overall response (BOR), clinical benefit rate (CBR), duration of response (DOR), time to tumor progression (TTP) and progression-free survival (PFS), as assessed by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7)
- To evaluate NPR at 18 and 24 weeks, ORR, BOR, CBR, DOR, TTP and PFS, as assessed by the Investigator using modified RECIST (Appendix 3)
- To evaluate overall survival (OS)

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of Atezolizumab in patients with advanced solid tumors
- To characterize the immunogenic potential of Atezolizumab by measuring anti-Atezolizumab antibodies and to explore the potential relationship of the immunogenicity response with safety and efficacy

Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives for this study are as follows:

- To characterize the pharmacokinetics of Atezolizumab

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the relationship between tumor tissue PD-L1 expression and measures of efficacy, including NPR at 18 weeks and 24 weeks, ORR, BOR, CBR, DOR, TTP, PFS and OS
- To assess predictive and prognostic exploratory biomarkers (e.g. but not limited to protein and genetic markers on DNA and RNA) in archival and/or fresh tumor tissue and plasma and their association with disease status and/or response to study treatment
- To evaluate exploratory pharmacodynamic (PD) biomarkers (e.g., genetic markers, T, B and NK cell enumeration, T cell subpopulations like CD8+ T, effector/memory T cells, regulatory T cells, changes in expression of CD25 or human leukocyte antigen-DR [HLA-DR], interferon [IFN]-gamma production, IL-2 and other exploratory biomarkers) in tumor tissue, tumor microenvironment and plasma and their association with disease status, and/or response to study treatment, tumor immunobiology or tumor type

Study Design

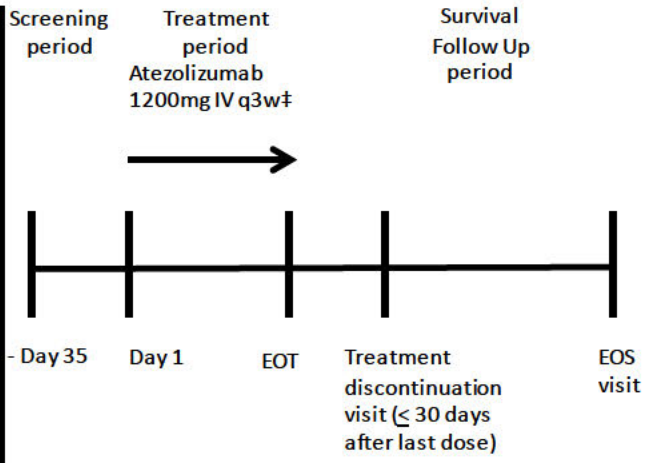
Description of Study

This will be an open-label, multicenter, multinational, multicohort, phase II study. For each cohort, the study will consist of a Screening Period (Day –35 to −1), a Treatment Period, a Treatment Discontinuation Visit occurring ≤ 30 days after the last dose of study medication and a 24-month Survival Follow-up Period (Figure 1). Day 1 (baseline) will be defined as the first day a patient receives study medication.

Synopsis Figure 1 Study Schema

Cohorts
n = 12 to 25

1 Cervical cancer
2 Nasopharyngeal carcinoma
3 Known MSI-H or MMR deficient colorectal cancer
4. Known BRCA 1/2 mutated cancers
   a. BRCA mutated ovarian cancer
   b. BRCA mutated breast cancers
5. Soft tissue, visceral and bone sarcomas
   a. Liposarcoma
   b. Leiomyosarcoma
   c. Gastrointestinal stromal tumor (GIST)
   d. Undifferentiated pleomorphic sarcoma
   e. Known translocation-related sarcomas
   f. Radiation induced sarcoma
   g. Osteosarcoma
   h. Chondrosarcoma
6. Mesothelioma
   a. Pleural mesothelioma
   b. Peritoneal mesothelioma
7. Cholangiocarcinoma/cancer of the biliary tract
8. Thyroid cancer
   a. Anaplastic thyroid cancer
   b. Follicular or papillary thyroid cancer
   c. Medullary thyroid cancer and mixed medullary and follicular or papillary thyroid cancer
9. Gastric adenocarcinoma/adenocarcinoma of GEJ
10. [Other solid tumors] †
11 Malignant germ cell tumors
12 ER+/HER2- MBC with known high mutation load (>100 mutations by local test)
13. Thymoma and thymic cancer
   a. Thymoma
   b. Thymic cancer
14 Gastroenteropancreatic (GEP) and lung neuroendocrine tumors (NETs)
   a. Low and intermediate grade any location (NET-GEP or typical / atypical lung carcinoid)
   b. Poorly differentiated grade any location (excluding SCLC)
15. Known HPV induced squamous cell carcinoma
   a. Head and neck
   b. Penile cancer
   c. Vaginal cancer/ vulvar cancer
   d. Anal cancer
16. Known MSI high or MMR deficient tumors (excluding colorectal and gastric cancers)



EOT end of treatment, EOS end of study

† Cohort closed to recruitment from Protocol Version 4 onwards

‡ Atezolizumab treatment may be continued as long as patients are experiencing clinical benefit (see Sections 3.1 and 4.6.2).

The study will include 16 cohorts of patients with the following solid cancers:

1. Cervical cancer
2. Nasopharyngeal carcinoma
3. Known high microsatellite instability (MSI-H) or mismatch repair (MMR) deficient colorectal cancer
4. Known BRCA 1/2 mutated cancers
    a. BRCA mutated ovarian cancer
    b. BRCA mutated breast cancers
5. Soft tissue, visceral and bone sarcomas
    a. Liposarcoma
    b. Leiomyosarcoma
    c. Gastrointestinal stromal tumor (GIST)
    d. Undifferentiated pleomorphic sarcoma
    e. Known translocation-related sarcomas
    f. Radiation induced sarcoma
    g. Osteosarcoma
    h. Chondrosarcoma
6. Mesothelioma
    a. Pleural mesothelioma
    b. Peritoneal mesothelioma
7. Cholangiocarcinoma/cancer of the biliary tract
8. Thyroid cancer
    a. Anaplastic thyroid cancer
    b. Follicular or papillary thyroid cancer
    c. Medullary thyroid cancer and mixed medullary and follicular or papillary thyroid cancer
9. Gastric adenocarcinoma/adenocarcinoma of the gastro-esophageal junction
10. Other solid tumors – closed to recruitment from Protocol Version 4 onwards.
11. Malignant germ cell tumors
12. ER+/HER2- metastatic breast cancer with known high mutation load (>100 mutations) by local test
13. Thymoma and thymic cancer
    a. Thymoma
    b. Thymic cancer
14. Gastroenteropancreatic (GEP) and lung neuroendocrine tumors (NETs)
    a. Low and intermediate grades - (typical or atypical carcinoid)
    b. Poorly differentiated grade (excluding SCLC)
15. Known HPV induced squamous cell carcinomas
    a. Head and neck
    b. Penile cancer
    c. Vaginal cancer / vulvar cancer
    d. Anal cancer
16. Known MSI-H or MMR deficient tumors (excluding colorectal and gastric cancers)

In addition, only patients whose tissue is available for biomarker assessment testing will be eligible.

Enrolled patients will receive Atezolizumab at a fixed dose of 1200 mg administered intravenously on the first day of each cycle. One cycle of therapy will be defined as 21 days

(± 3 days). Patients treated with Atezolizumab who have no post-baseline tumor assessment (per protocol mandated timelines), and enrolled patients who do not receive any dose of Atezolizumab will be replaced.

Atezolizumab treatment may be continued as long as patients are experiencing clinical benefit, as assessed by an investigator, in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available) and clinical status.

Patients will be permitted to continue Atezolizumab treatment after RECIST v1.1 criteria (or disease-specific criteria for patients with prostate cancer [Appendix 6] and malignant pleural mesothelioma [Appendix 7]) for progressive disease are met if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the Investigator
- Absence of symptoms and signs (including worsening of laboratory values, e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease
- 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 treated with Atezolizumab in whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the Investigator if they continue to meet the above criteria.

If an individual patient continues to experience clinical benefit beyond 2 years of radiologic progressive disease, it lies within the discretion of each investigator to continue study treatment based on a positive risk benefit assessment by the investigator.

The primary objective of this study is to evaluate Investigator-determined non-progression rate (NPR) at 18 weeks in the individual cohorts using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7). Secondary efficacy variables (including ORR, BOR, CBR, DOR, TTP and PFS) will be recorded using RECIST, v1.1, (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7), and modified RECIST (see Appendix 3)

Safety will be monitored by assessing AEs, serious AEs (SAEs), AEs of special interest (AESIs), laboratory findings and electrocardiogram. The National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE, v4.0) will be used to quantify the intensity of AEs occurring during treatment. Incidence, type and severity of AEs, SAEs, incidence of AEs and SAEs leading to Atezolizumab interruption or discontinuation and cause of death will be reported. In addition, to characterize the immunogenic potential and the pharmacokinetic properties of Atezolizumab, blood samples will be taken at various time points before and after study treatment administration (see Appendix 2 for a detailed description of the assessments).

This study will also have an exploratory analysis examining biomarkers. These analyses will be conducted on archival tissue specimens (required for patient inclusion), as well as prospectively-collected plasma/blood samples and freshly obtained tumor specimens. Collected samples will be analyzed at a central laboratory for PD-L1 expression, as well as other potential markers (e.g. but not limited to protein or genetic markers), to assess relationships between biomarker expression and patient outcomes including, but not limited to, response and disease progression.

All patients will be monitored for survival for a minimum period of 24 months after the last patient has been enrolled in each cohort or until all patients have died, withdrawn consent or are lost to follow up, or the Sponsor decides to end the study, whichever occurs first. Survival follow-up information will be collected via clinic visits, telephone calls and/or review of patient medical records approximately every 3 months from study treatment discontinuation until patient death, loss to follow-up, withdrawal of consent or until the study is terminated by the Sponsor. Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments approximately every 3

months until death, disease progression, initiation of further systemic cancer therapy or study closure, whichever occurs first.

Enrollment in this study will be based on Simon's optimal two-stage design (Simon 1989). Accordingly, 12 fully-evaluable patients will be enrolled in each cohort in the first stage. If 3 or more of these patients exhibit non-progressive disease at the end of Stage I, then an additional 13 fully-evaluable patients will be enrolled in Stage II. Thus, approximately 725 patients are expected to participate in the study. However, if positive efficacy signals are observed in any of the other cohorts that include different tumor types or in a specific subgroup of patients within other cohorts (e.g. biomarker positive subgroup), the Sponsor in discussion with the Steering Committee may decide to extend the enrolment of the individual tumor type or subgroup of patients based on methodology explained in the Determination of Sample Size (Section 6.1).

Please refer to the Schedule of Assessments (Appendix 1) for a detailed description of the assessments to be carried out in this study.

Number of Patients

Based on Simon's optimal two-stage design (Simon 1989), approximately 12 to 25 fully evaluable patients per individual tumor type will be included.

Allowing for expansion of cohorts into further sub-cohorts of individual tumor types and possible further expansion into subgroups of responders, the projected total number of patients enrolled in this study is approximately 725. However, cohorts may be expanded under certain conditions (see Section 6.1).

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Ability to comply with protocol
3. Male or female, 18 years of age or older
4. Histologically documented solid tumors that are advanced (i.e. Stages III and IV disease) and
   - meet one of the cohort specifications in Section 4.1.3
   - have progressive disease at study entry
   - have received at least one line of prior systemic therapy or for which alternative therapy does not exist which is known to prolong survival
5. Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (preferred) or, in exceptional cases, 15 freshly cut and unstained slides, with an associated pathology report (in local language), for central testing. Detection of tumor in the provided block (or slide) needs to be confirmed by the central pathology laboratory prior to study enrollment.
   - Only tissue from core needle, punch or excisional biopsy sample collection will be accepted. For core-needle biopsy specimens, at least three cores should be submitted for evaluation. Fine-needle aspiration, brushing, bone tissue, and lavage samples are not acceptable
   - Patients who do not have tissue specimens meeting eligibility requirements must undergo a biopsy during the screening period. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions
6. Measurable disease as defined by RECIST, v1.1. (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7)
7. ECOG Performance Status of 0 or 1

8. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 3 days prior to the first study treatment (Cycle 1, Day 1):
   - Absolute neutrophil count (ANC) ≥ 1500 cells/µL (without granulocyte colony-stimulating factor support within 2 weeks before Cycle 1, Day 1)
   - Lymphocyte count ≥ 500/µL
   - White blood cell counts > 2500/µL
   - Platelet count ≥ 100,000/µL (without transfusion within 2 weeks before Cycle 1, Day 1)
   - Hemoglobin ≥ 9.0 g/dL (patients may be transfused or receive erythropoietic treatment to meet this criterion)
   - Serum bilirubin < 1.5 × upper limit of normal (ULN), with the following exception:

     Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled
   - Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase ≤ 2.5 × ULN, with the following exceptions:

     Patients with liver involvement: AST and/or ALT ≤ 5 × ULN

     Patients with liver or bone metastases: alkaline phosphatase ≤ 5 × ULN
   - Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 30 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation: (140 − age) × (weight in kg) × (0.85 if female)/72 × (serum creatinine in mg/dL)
   - International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN. This applies only to patients who do not receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation (such as low−molecular weight heparin or warfarin) should be on a stable dose
   - Serum albumin level > 3.2 g/dL
9. 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
10. For female patients of childbearing potential, agreement (by patient) to use a highly effective form(s) of contraception that results in a low failure rate (< 1% per year) when used consistently and correctly, and to continue its use for 5 months after the last dose of Atezolizumab. 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. Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drug.
11. Life expectancy > 3 months.

<u>Exclusion Criteria</u>

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

1. Malignancies other than disease under study within 5 years prior to Cycle 1 Day 1, 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 surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
2. Uncontrolled tumor-related pain
   - Patients requiring pain medication must be on a stable regimen at study entry
   - Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment

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

3. 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
4. Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab
   - Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible
   - Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while on study
5. History of treated asymptomatic or symptomatic CNS metastasis or presence of CNS metastases as determined by CT scan or MRI evaluation during screening or at prior radiographic assessments.
6. Leptomeningeal disease
7. 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 Cycle 1, Day 1
8. Any approved anticancer therapy, including chemotherapy, hormonal therapy or radiotherapy, within 3 weeks prior to initiation of study treatment; however, the following are allowed:
   - Hormone-replacement therapy or oral contraceptives
   - Palliative radiotherapy for bone metastases > 2 weeks prior to Cycle 1, Day 1
9. Acute toxicities from previous therapy that have not resolved to Grade ≤ 1, except for alopecia
10. Pregnant and lactating women
11. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)
12. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to Cycle 1, Day 1, unstable arrhythmias or unstable angina
    - Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded
    - Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate
13. Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia or severe pneumonia
14. Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1
    - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible
15. Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study
16. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
17. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or to any component of the Atezolizumab formulation

18. 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 anti-phospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 5 for a more comprehensive list of autoimmune diseases)
    - Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible
    - Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen are eligible
    - Patients with eczema, psoriasis, 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:
        - Rash must cover less than 10% of body surface area (BSA).
        - Disease is well controlled at baseline and only requiring low potency topical steroids.
        - No acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high-potency or oral steroids)
19. Prior allogeneic bone marrow transplantation or prior solid organ transplantation
20. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan
    - History of radiation pneumonitis in the radiation field (fibrosis) is permitted
21. Any other diseases, metabolic dysfunction, physical examination finding or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complication
22. Positive test for HIV
23. Patients with active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C
    - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible
    - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA
24. Active tuberculosis
25. Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1
26. Administration of a live, attenuated vaccine within 4 weeks prior to Cycle 1, Day 1 or anticipation that such a live attenuated vaccine will be required during the study.
    - Influenza vaccination should be given during influenza season only (example: approximately October to March in the Northern Hemisphere). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study treatment or within 5 months after the last dose of atezolizumab
27. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti−PD1, or anti− PD-L1 therapeutic antibodies
    - Patients who have received prior treatment with anti−CTLA-4 may be enrolled, provided at least 5 half-lives (approximately 75 days) have elapsed from the last dose of anti-CTLA-4 to the first dose of Atezolizumab and there was 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 interferon-alpha (IFN-α) and interleukin-2 (IL-2) within 4 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1
29. Treatment with an investigational agent within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer)
30. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor [TNF] agents) within 2 weeks prior to Cycle 1, Day 1, or anticipated requirement for systemic immunosuppressive medications during the trial
    - 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
    - The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, low-dose supplemental corticosteroids for adrenocortical insufficiency and topical steroids for cutaneous diseases are allowed

Length of Study

The study is expected to last approximately 5 years.

End of Study

The end of cohort will occur when all patients have been followed for survival for a minimum of 24 months after the last patient has been enrolled in the cohort or until all patients have died, withdrawn consent or are lost to follow up, or the Sponsor decides to end the study, whichever occurs first.

Recruitment/enrollment in any of the cohorts may present some challenges. Therefore, a permanent stop rule may be applied if the recruitment rate is too low after any of the individual cohorts have been completely enrolled, which could result in stopping further enrolment in some of the remaining cohorts (Section 4.6.3), based on regular review of the recruitment rate After a cohort has been opened for at least 4 months, it may be closed early if the recruitment is less than 2 patients per month on average from the opening of the cohort. This decision will be made by the Sponsor. The overall end of study will occur when the end of cohort has occurred for all of the individual cohorts, as described above.

Outcome Measures

Efficacy Outcome Measures

The primary efficacy outcome measure for this study is as follows:

- Non progression rate (NPR) at 18 weeks is defined as the percentage of patients with CR, PR or SD at 18 weeks, as determined by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7). Patients treated with Atezolizumab who have no post-baseline tumor assessment (per protocol mandated timelines), and enrolled patients who do not receive any dose of Atezolizumab will be replaced

The secondary efficacy outcome measures for this study are as follows:

- Non progression rate (NPR) at 24 weeks is defined as the percentage of patients with CR, PR or SD at 24 weeks, as determined by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7). Patients treated with Atezolizumab who have no post-baseline tumor assessment (per protocol mandated timelines), and enrolled patients who do not receive any dose of Atezolizumab will be replaced

- Overall response rate (ORR) is defined as the proportion of patients with a CR or PR, as assessed by the Investigator using RECIST v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7)
- Best overall response (BOR) is defined as the proportion of patients with the best response obtained throughout the trial, as determined by the Investigator using RECIST v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7)
- Clinical benefit rate (CBR) is defined as the proportion of patients whose BOR, as determined by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7), is either CR, PR or SD lasting for at least 6 weeks
- Duration of objective response (DOR) is defined as the time from the first occurrence of a documented objective response to the time of progression, as determined by the by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7), or death from any cause, whichever occurs first. For patients who do not die or experience disease progression before the end of the study or who are lost to follow-up, duration of objective response will be censored at the day of the last tumor assessment
- Progression-free survival (PFS) is defined as the time from the first day of study treatment to the first occurrence of disease progression, as determined by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7), or death from any cause, whichever occurs first. A patient without a PFS event will be censored at the time of the last evaluable tumor assessment. Patients with no tumor assessment after the baseline visit will be censored at the time of the first day of study treatment plus 1 day
- Time to progression (TTP) is defined as time from the first day of study treatment to the first occurrence of progressive disease, as determined by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7), or death due to reason of disease progression, whichever occurs first. Patients who have not progressed or died due to disease progression at the time of study completion or who are lost to follow-up will be censored at the date of the last evaluable tumor assessment. Patients with no tumor assessment after the baseline visit will be censored at the time of the first day of study treatment plus 1 day
- Overall survival (OS) is defined as the time from the first day of study treatment to death from any cause. Patients for whom no death is captured on the clinical database will be censored at the most recent date they were known to be alive

NPR at 18 and 24 weeks, ORR, BOR, CBR, PFS and TTP will also be determined by the by the Investigator using modified RECIST (see Appendix 3).

Safety Outcome Measures

The safety and tolerability of Atezolizumab will be assessed using the following safety outcome measures:

- Incidence, nature, and severity of adverse events graded according to the NCI CTCAE, v4.0
- Number of cycles and dose intensity
- Incidence of anti-Atezolizumab antibodies and the potential correlation with pharmacokinetics and safety parameters

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Maximum serum Atezolizumab concentration (C_{max}) after infusion on Day 1 of Cycle 1
- Minimum serum Atezolizumab concentration (C_{min}) prior to infusion on Day 1 of Cycles 1, 2, 3, 4, 8 and every eight cycles thereafter and at study termination

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Status of PD-L1 expression and other exploratory biomarkers (e.g. but not limited to protein and genetic markers) in archival and/or freshly obtained tumor tissues and plasma collected pre-treatment and during treatment with Atezolizumab
- Association of PD-L1 expression and other exploratory biomarkers (e.g. but not limited to protein and genetic markers) with disease status and/or response or resistance to Atezolizumab
- Status of exploratory biomarkers in plasma (including but not limited to genetic markers and cytokines such as IFN-gamma) collected pre-treatment and during treatment/at progression/study discontinuation with Atezolizumab
- Association of exploratory biomarkers in plasma with disease status and/or response or resistance to Atezolizumab, tumor immunobiology or tumor type

Investigational Medicinal Products

Test Product (Investigational Drug)

The dose of Atezolizumab in this study will be 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by intravenous infusion every 3 weeks (21 [± 3] days).

Administration of Atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

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

The initial dose of Atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes.

For first infusion of study treatment, the patient's vital signs must be determined within 60 minutes before the infusion; during, and after the infusion if clinically indicated. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and at the end of the infusion, if clinically indicated.

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

No premedication will be allowed for the first dose of Atezolizumab. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The management of infusion-related reactions will be according to severity as described in section 5.1.4.

For anaphylaxis precautions, see Appendix 4.

Guidelines for dosage modification, treatment interruption or discontinuation and the management of specific adverse events are provided in Sections 5.1.3 and in the Atezolizumab Investigator's Brochure.

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

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

Comparator
Not applicable

Non-Investigational Medicinal Products
Not applicable

Statistical Methods

Primary Analysis

The primary analysis will be based on NPR at 18 Weeks for each cohort, as assessed by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7). This endpoint will be assessed at Stage I and Stage II.

At the conclusion of this study, Atezolizumab will be declared effective or ineffective for each cohort based on rules for Stage II.

The final analysis for each cohort will take place when all patients in that cohort have been followed for survival for a minimum of 24 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow up, or if the cohort is stopped due to safety or efficacy reasons or the Sponsor decides to end the cohort, whichever occurs first.

Hypothesis Testing

A Simon optimal two-stage design will be used to test whether Atezolizumab yields a NPR that is of clinical interest. In this Phase II study, an NPR of 20% is a level of activity that is not of interest for further clinical development, whereas an NPR of 40% is of clinical interest.

The study hypotheses are:

- H_0: $\pi \leq \pi_0$
- H_1: $\pi > \pi_1$

Where $\pi_0 = 20\%$ and the assumed NPR under the alternative is $\pi_1 = 40\%$.

The type I error will be 10% and the study will have 80% power to reject the null hypothesis when the true NPR is 40%.

The hypothesis and clinical assumptions will be applied to all cohorts separately.

Determination of Sample Size

The sample size for this phase II study is based on Simon's optimal two-stage design (Simon 1989).

In this Phase II study, an NPR of 20% is a level of activity that is not of interest for further clinical development, whereas an NPR of 40% is of clinical interest. The type I error will be 10% and the study will have 80% power to reject the null hypothesis when the true NPR is 40%.

The Simon design in this study requires 12 fully evaluable patients for the first stage. If at the end of the first stage there are 0, 1 or 2 patients with non-progressive disease at Week 18, the enrollment into this cohort will be terminated (or the cohort may be expanded as described below). Otherwise, if more than 2 patients with non-progressive disease are observed at the end of Stage I, an additional 13 fully-evaluable patients may be enrolled into Stage II. The study drug will be considered of clinical interest in this cohort if, at the end of the second stage, there are 8 or more patients with non-progressive disease out of 25 total fully-evaluable patients.

It can be assumed that some patients will not be evaluable for NPR. A patient will be considered evaluable for NPR if they received study drug, have a baseline tumor assessment and at least one tumor assessment post-baseline- (per protocol mandated timelines). Thus,

more than 25 patients may be needed to be enrolled per cohort to obtain 25 fully-evaluable patients.

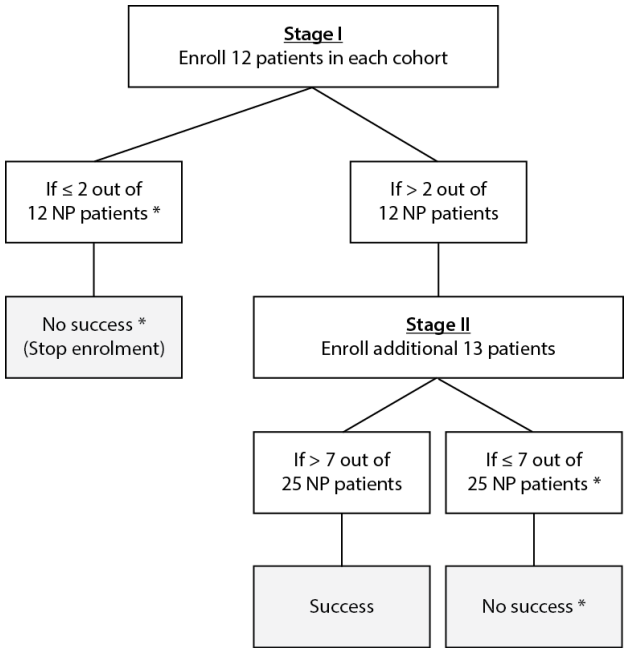
The hypotheses and clinical assumptions will be applied to all cohorts individually.

Statistical analyses will be based on patients with the same individual tumor type and may be based on pre-defined cohorts or on sub-cohorts.

Allowing for expansion of cohorts into further sub-cohorts of individual tumor types and possible further expansion into subgroups of responders, the projected total number of patients enrolled in this study is approximately 725 (see Figure 2).

If a clear clinical benefit has been observed for a defined subgroup of patients at the end of Stage I within a cohort that did not meet the criteria for continuation (as described in Section 6.2.1), then enrolment into Stage II might still be allowed in this cohort for this specific subgroup after discussion with the Sponsor and the study Steering Committee. Similarly, if a clear clinical benefit has been observed for a defined subgroup of patients at the end of Stage II within a cohort that did not meet the criteria for success (as described in Section 6.2.2), then enrolment into Stage II might continue in this cohort for this specific subgroup after discussion with the Sponsor and the study Steering Committee.

Synopsis Figure 2. Sample Size for Each Cohort in Stage I/II



NP = non-progressors; NPR = non-progression rate.

Assumptions: H0 = NPR 20%; H1 = NPR 40%; power = 80%; alpha = 10%.

The sample size was estimated using Simon's optimal two-stage design (Simon 1989).

* And no additional clinical benefit in a subgroup.

Interim Analyses

The study will be analyzed for efficacy at Stage I and Stage II. All cohorts will also be analyzed at Week 24 (6 months) and at the end of cohort for each cohort. No additional interim analysis for efficacy will be performed in this study.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
+	censored value
AC	atypical carcinoids
AE	adverse event
AESI	adverse event of special interest
ASA	abnormal self antigen
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATA	anti-therapeutic antibody
BOR	best overall response
BRCA1/2	breast cancer type 1/2 susceptibility protein
BS	bone sarcoma
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CBR	clinical benefit rate
CHO	Chinese hamster ovary
CL	mean apparent clearance
ClinRO	clinician-reported outcome
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRO	contract research organization
CT	computed tomography
CTCAE	Common TerminologyCriteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DOR	duration of response
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DTC	differentiated thyroid cancers
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	electrocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ePRO	electronic patient-reported outcome
ER	estrogen receptor
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FOLFOX	folinic acid/fluorouracil/oxaliplatin
GEJ	gastro-esophageal junction
GEP-NETs	neuroendocrine gastroenteropancreatic tumors
GCT	germ cell tumors
GGT	gamma-glutamyl transferase
GIST	gastrointestinal stromal tumors
HBc	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA-DR	human leukocyte antigen-DR
HNSCC	head and neck squamous cell carcinoma
HPV	human papilloma virus
HR	hormone receptor
IC	PD-L1-positive tumor-infiltrating immune cell
ICH	International Conference on Harmonisation
IFN-α	interferon-alpha
IFN-ɣ	interferon-gamma
Ig	immunoglobulin
IGF-1R	insulin-like growth-factor-1 receptor
IHC	immunohistochemistry
IL-2	interleukin-2
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous

LCNEC	large-cell neuroendocrine carcinoma
LDH	lactate dehydrogenase
LFT	liver function test
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MFH	malignant fibrous histiocytoma
MMR	mismatch repair
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	high microsatellite instability
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MSKCC	Memorial Sloan-Kettering Cancer Center
NA	not applicable
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NETs	neuroendocrine tumors
NPR	non-progression rate
NSCLC	non-small cell lung cancer
ORR	overall response rate
NSE	neuron-specific enolase
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamic or progressive disease
PD-1	programmed cell death 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PI3K	phosphoinositide 3-kinase
PNECs	pulmonary neuroendocrine cells
PR	partial response or partial receptor
PRO	patient-reported outcome
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time

PUVA	psoralen and ultraviolet A
QTcF	QT interval corrected using Fridericia's formula
q3w	every 3 weeks
RBC	red blood cell
RCC	renal cell carcinoma
RCR	Roche Clinical Repository
RECIST, v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RIS	radiation induced sarcoma
SCLC	small-cell lung cancer
SD	stable disease
SAE	serious adverse event
SCFR	stem cell factor receptor
SEER	Surveillance, Epidemiology and End Results
~~SIA~~	~~systemic immune activation~~
STS	soft tissue sarcoma
T3	triiodothyronine
T4	thyroxine
TC	tumor cells or typical carcinoids
TGCT	testicular germ cell tumors
TILS	tumor-infiltrating lymphocytes
TNF	tumor necrosis factor
TSA	tumor-specific antigen
TSH	thyroid-stimulating hormone
TTP	time to tumor progression
UBC	urothelial bladder cancer
ULN	upper limit of normal
US	United States
Vss	volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND

1.1 BACKGROUND ON ADVANCED SOLID TUMORS

This study will assess the efficacy and safety of the anti-PD-L1 therapeutic antibody Atezolizumab for the treatment of a diverse array of advanced solid tumors. The tumors were selected based on the characteristics of their pathology that suggest a potential susceptibility to immunotherapy with Atezolizumab. Specifically, the tumors were chosen based on their potential for high immunogenicity, and on published evidence linking PD-L1 expression to pathogenesis.

The tumors included in this study, as well as a brief description of their epidemiology and prognoses, are presented in Table 1. Full details of the histological types / subtypes and markers mandated for each cohort are described in Section 4.1.3.

Table 1. Summary of the Advanced Solid Tumors Examined in This Study

Cervical cancer (Colombo et al. 2012) (http://globocan.iarc.fr) (http://www.cancer.org/cancer/cervicalcancer/detailedguide/cervical-cancer-survival)	• Cervical cancer is the fourth most common cancer in women, and the seventh overall • Around 528,000 new cases were diagnosed worldwide in 2012, approximately 85% of which occurred in less developed regions. Incidence in Europe ranged from 3.6 (Switzerland) to 28.7 (Romania) per 100,000 women. Incidence rates in the United States (US), Japan and China were 6.6, 10.9 and 7.5 per 100,000 women, respectively • Around 266,000 deaths occurred worldwide in 2012 due to cervical cancer. Mortality rates in Europe ranged from 0.4 (Iceland) to 10.8 (Romania) per 100,000 women. Mortality rates in the US, Japan and China were 2.7, 2.8 and 3.4 per 100,000 women, respectively • The 5-year survival rate is 32%–35% for Stage III disease and 15%–16% for Stage IV disease • Human papilloma virus (HPV) is detected in 99% of cervical tumors, in particular the oncogenic subtypes (e.g., HPV 16 and 18)

Table 1. Summary of the Advanced Solid Tumors Examined in This Study (Cont.)

Nasopharyngeal cancer (Chan et al. 2012) (Lin et al. 2004) (http://globocan.iarc.fr/ia) (http://www.cancer.org/cancer/nasopharyngealcancer/detailedguide/nasopharyngeal-cancer-survival-rates)	• Around 87,000 new cases of nasopharyngeal cancer were diagnosed worldwide in 2012. Incidence rates in Europe ranged from 0 (Iceland) to 2.9 (Malta) per 100,000 men and 0 (Iceland) to 0.6 (Malta) per 100,000 women. Incidence rates were 0.7, 0.4 and 2.7 per 100,000 men and 0.3, 0.1 and 1.1 per 100,000 women in the US, Japan and China, respectively • Around 51,000 deaths occurred worldwide in 2012 due to nasopharyngeal cancer. Mortality rates in Europe ranged from 0 (Iceland) to 1 (Romania) per 100,000 men and 0 (Iceland) to 0.3 (Albania) per 100,000 women. Mortality rates were 0.2, 0.2 and 1.7 per 100,000 men and 0.1, 0.1 and 0.6 per 100,000 women in the US, Japan and China, respectively • The 5-year survival rate is 62% for Stage III disease and 38% for Stage IV disease • Epstein-Barr virus (EBV) is detectable in approximately 95% of patients
MSI-H or MMR-deficient colorectal cancer (Van Cutsem et al. 2010) (Poynter et al. 2008) (Sinicrope et al. 2011) (http://globocan.iarc.fr/ia)	• Microsatellite instability (MSI) occurs in approximately 10% to 20% of colorectal cancer cases • Magnetic resonance imaging (MMR)-deficient colon cancers have reduced rates of tumor recurrence, delayed time to recurrence and improved survival rates relative to MMR-proficient disease • The 5-year survival rates are 23% for localized disease, 12% for intra-abdominal disease and 8% for distant disease
BRCA 1/2 mutated cancers (Goodwin et al. 2012) (Bolton et al. 2012) (http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA) (http://www.ncbi.nlm.nih.gov/books/NBK1247/) (http://globocan.iarc.fr/ia) (http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-survival-by-stage)	• BRCA1 and BRCA2 mutations have been identified in approximately 5% to 10% of all breast cancers • BRCA1 and BRCA2 mutations have been identified in approximately 15% of all ovarian cancers • In patients with breast cancer, mortality rates of patients with BRCA1/2 mutations and patients with sporadic disease were similar. The 5-year survival rates are 72% for Stage III disease and 22% for Stage IV disease • In patients with ovarian cancer, BRCA1 and BRCA2 mutation carriers showed a more favorable survival than noncarriers (BRCA1: HR, 0.73; BRCA2: HR, 0.49). The 5-year overall survival was 36% for noncarriers, 44% for BRCA1 carriers, and 52% for BRCA2 carriers

Table 1. Summary of the Advanced Solid Tumors Examined in This Study (Cont.)

Soft tissue visceral and bone sarcomas (Kasper et al, 2007) (van Glabekke et al, 2002) (WHO classification of tumors) (ESMO European Sarcoma Network Working Group 2012) (Grimer et al. 2010) (http://www.cancer.org/cancer/sarcoma-adultsofttissuecancer/detailedguide/sarcoma-adult-soft-tissue-cancer-survival-rates)	• Adult sarcomas comprise a heterogeneous group of rare tumors. The most common soft tissue and visceral sarcoma types are malignant fibrous histiocytoma, liposarcoma and leiomyosarcoma and the most common types of bone and joint sarcoma are osteosarcoma and chondrosarcoma • The total estimated annual incidence of soft tissue and visceral sarcomas in Europe is 4–5/100,000 (approximately 1% of all adult cancers). In the US, the incidence of soft tissue and visceral sarcoma is 3.8 per 100,000 and the mortality rate is 1.5 per 100,000. The incidence of bone sarcoma is 0.9 per 100,000 and mortality is 0.4 per 100,000 • About 12,020 new soft tissue and visceral sarcomas and about 2,300 new cases of bone sarcoma were diagnosed in the US in 2014 and about 4,740 and 1,500 people died from soft tissue and bone sarcomas, respectively • Approximately half of all patients with intermediate or high-grade tumors develop metastatic disease requiring systemic treatment. The 5-year survival rate is around 10% for soft tissue sarcoma (STS) that have metastasized. After failure of first-line treatment the estimated 6-month progression-free survival rate is only 14% for agents deemed to be active in sarcoma • The 5-year survival rate for osteosarcoma with unresectable disease is between 7% and 19%. For chondrosarcoma the 5-year survival is 89% for grade 1 and 53% for combined grade 2 and 3
Pleural and Peritoneal Mesothelioma (Stahel et al. 2010) (Gregoire 2010) (Trupiano et al. 2004) (http://www.cancer.org/cancer/malignantmesothelioma/detailedguide/malignant-mesothelioma-survival-statistics)	• Malignant mesothelioma has an incidence of 1.25 per 100,000 in the UK, 1.1 per 100,000 in Germany and 1.0 per 100,000 in the US • Incidence is expected to double in many countries within the next 20 years • Median survival time is 16 months for Stage III disease and 12 months for Stage IV disease. The 5-year survival rate is < 5% • Exposure to asbestos is a well-established etiological factor, with occupational exposure being documented in 70%–80% of those affected • Survival ranges from 9 to 18 months for peritoneal mesotheliomas and 4 to 12 months for pleural mesotheliomas

Table 1. Summary of the Advanced Solid Tumors Examined in This Study (Cont.)

Cholangiocarcinoma/cancer of the biliary tract (Bridgewater et al. 2014) (http://www.cancer.org/cancer/bileductcancer/detailedguide/bile-duct-cancer-survival-by-stage)	• Cholangiocarcinoma, the second most common primary liver cancer after hepatocellular cancer, comprises a heterogeneous group of cancers with pathologic features of biliary tract differentiation • The incidence varies substantially worldwide, with the highest known rates in Northeast Thailand (> 80 per 100,000) and much lower rates in the Western world (e.g., Canada, 0.3 per 100,000) • Incidence rates are rising around the world. For example, incidence rates in the US increased from 0.3 per 100,000 in 1975–79 to 0.9 per 100,000 in 1995–99 • The 5-year survival rate is 30% for localized disease, 24% for regional disease and 2% for distant disease • Risk factors for cholangiocarcinoma, such as hepatobiliary flukes, primary sclerosing cholangitis, biliary tract cysts, hepatolithiasis and toxins, are associated with chronic biliary inflammation and increased cellular turnover
Thyroid cancer (Pacini et al. 2012) (http://www.cancer.org/cancer/thyroidcancer/detailedguide/thyroid-cancer-survival-rates)	• Thyroid cancer accounts for around 3.8% of all cancers in the US in 2016. The incidence was 13.9 per 100,000 per year and mortality was 0.5 per 100,000 per year in the US between 2009 and 2013. In Europe, incidence was 6.3 per 100,000 and mortality was 0.6 per 100,000 in 2012 • There are 4 types of thyroid cancers – papillary, follicular, medullar and anaplastic • Papillary and follicular thyroid cancers are differentiated tumors - Papillary thyroid cancer represents 70% to 80% of all thyroid cancers and follicular thyroid cancer represents 10% to15%. Differentiated tumors (papillary or follicular) have a 10-year survival rate of 90 - 95% but survival decreases to 50% at 5-year for metastatic disease • Medullary thyroid cancer makes up about 5 % to 10% of all thyroid cancers and has a 10-year survival rate of 75%; however, the 5-year survival rate is 5% for metastatic disease • Anaplastic thyroid cancer has an estimated incidence of 0.21 per 100,000 person-years, and comprises < 2% of all thyroid cancers. More women than men are affected (2–3:1). The 5-year survival rate is around 7%

Table 1. Summary of the Advanced Solid Tumors Examined in This Study (Cont.)

Gastric adenocarcinoma/ adenocarcinoma of the gastro-esophageal junction (http://globocan.iarc.fr/ia) (http://www.cancer.org/cancer/stomachcancer/detailedguide/stomach-cancer-survival-rates)	• Almost one million new cases of gastric cancer were estimated to have occurred in 2012 (952,000 cases, 6.8% of the total), making it the fifth most common malignancy in the world. More than 70% of cases (677,000 cases) occurred in developing countries (456,000 in men, 221,000 in women), and half the world total occurs in Eastern Asia (mainly in China) • Age-standardized incidence rates are about twice as high in men as in women • Incidence rates in Europe ranged from 4.9 (Sweden) to 29.1 (Belarus) per 100,000 men and 2.7 (Sweden) to 15.1 (Albania) per 100,000 women. Incidence rates were 5.3, 45.8 and 32.8 per 100,000 men and 2.7, 16.5 and 13.1 per 100,000 women in the US, Japan and China, respectively • Around 254,000 deaths occurred worldwide in 2012 due to gastric cancer. Mortality rates in Europe ranged from 3.0 (Iceland) to 24.6 (Belarus) per 100,000 men and 1.5 (Malta) to 12.6 (Albania) per 100,000 women. Mortality rates were 2.7, 18.8 and 25.5 per 100,000 men and 1.5, 7.3 and 10.7 per 100,000 women in the US, Japan and China, respectively • Five-year survival rates are 9%–20% for Stage III and 4% for Stage IV • Infection with Helicobacter pylori is the primary identified risk factor for gastric cancer
Other solid tumors	• NA
Germ cell tumors (Ferlay et al, 2004) (McGlynn et al. 2010) (Smith et al. 2006) (Oosterhuis et al, 2005)	• Germ cell tumors (GCT) include a group of gonadal and extragonadal tumors that are considered as one disease with separate entities that can manifest themselves in different anatomical sites. In men testicular germ cell tumors (TGCT) are the most common GCTs, whilst in women the most common are of ovarian origin. GCTs occur mostly in young adults and children. Malignant GCTs are rare, comprising only 0.7% of all cancers • GCTs account for 95 percent of testicular cancers and the terms “testicular cancer” and TGCT are often used interchangeably. The global incidence rate of testicular cancer is 1.5 per 100,000 men. Incidence rates of TGCT have been increasing for at least 50 years, but mortality rates, at least in developed countries, have been declining. In the US, the 5-year survival rate is over 95% • Female GCTs are rare. They are mostly of ovarian origin. The estimated incidence rate is about 0.3 per 100,000 women-years. The 5-year relative survival is about 84% • Extragonadal GCTs are very rare tumors that predominantly affect young males

Table 1. Summary of the Advanced Solid Tumors Examined in This Study (Cont.)

Estrogen receptor positive, HER2 negative breast cancer with > 100 mutations (Haricharan et al, 2014) (Stephens et al. 2012) (Disis et al, 2015)	• Estrogen receptor (ER) positive, HER2 negative breast cancer represents 40 to 55% of breast cancers and the overall 5-year survival is estimated to be over 90%; however, this group of tumors is heterogeneous and prognosis and management varies based on criteria other than ER and HER2 • Somatic mutation load (SML) may constitute an important immunogenic signature for a subset of ER positive, HER2 negative patients with a poorer prognosis. There are currently no epidemiologic data for the ER positive, HER2 negative breast cancer with a high mutation load
Thymoma / Thymic cancer (PDQ®: Health Professional Version. Thymoma and Thymic CarcinomaTreatment - Cancer Information Summaries: NCI; 2002-2015 (Rosai et al, 1999) (http://www.cancer.net/cancer-types/)	• Invasive thymoma and thymic cancer are relatively rare tumors, which together represent about 0.2% to 1.5% of all malignancies • The overall incidence of thymoma is 0.15 cases per 100,000, based on SEER data. The 5-year overall survival of thymoma varies according to histological subtype but remains above 90% at 10 years for all subtypes • Thymic carcinoma accounts for only 0.06% of all thymic neoplasms. The 5-year overall survival is 30% to 50% for thymic carcinoma
Gastroenteropancreatic (GEP) and lung neuroendocrine tumors (NETs) **Low and intermediate grades (typical or atypical carcinoid)** **Poorly differentiated grade (excluding SCLC)** (http://www.neuroendocrinetumor.com/health-care-professional/mortality-associated-with-nets.jsp)	• Neuroendocrine gastroenteropancreatic tumors constitute a heterogeneous group of tumors with their origin in neuroendocrine cells of the embryological gut. Most commonly, the primary lesion is located in the gastric mucosa, the small and large intestine, the rectum and pancreas. The incidence has significantly increased over the last years and is estimated to be 5.25/100,000/year • Neuroendocrine tumors (NETs) of the lung comprise a heterogeneous population of tumors ranging from well differentiated bronchial NETs to highly malignant such as large-cell neuroendocrine carcinoma (LCNEC). The incidence of pulmonary NETs is low, although reported to have increased over the past 30 years. According to the SEER database, in 2003, the combined incidence was 1.57/100,000 inhabitants • The 5-year survival rates for metastatic disease varies according to tumor characteristics with e.g. 35% for well-differentiated G1/G2 NETs and 4% for poorly differentiated disease

Table 1. Summary of the Advanced Solid Tumors Examined in This Study (Cont.)

Known HPV induced squamous cell carcinoma Head and neck Penile cancer Vaginal cancer Vulvar cancer Anal cancer (De Vuyst et al, 2009) (http://www.cancer.net/cancer-types/)	• The prevailing evidence favors human papillomavirus (HPV) as a causative factor in many genital tract carcinomas • An estimated 50% of penile, 88% of anal, 43% of vulvar, 70% of vaginal, and 13–56% of oropharyngeal cancers are attributable to HPV, primarily HPV-16 typically followed by HPV-18. • Head and neck squamous cell carcinoma (HNSCC) is the fifth most common cancer worldwide, with an annual incidence of about 60,000 cases annually in the US and Europe. The five-year survival rate is around 30% • Invasive penile cancer is a rare disease with an annual burden of 22,000 estimated cases. About 95% are squamous cell carcinoma • Carcinomas of the vagina are uncommon tumors comprising about 1% of the cancers that arise in the female genital system. About 85% are squamous cell carcinoma • Vulvar cancer accounts for about 5% of cancers of the female genital system in the US. About 90% are squamous cell carcinoma. The 5-year survival rate for women with vulvar cancer is 86% but decreases to 16% for metastatic tumors • Anal cancer accounts for about 4% of all cancers of the lower alimentary tract. Anal carcinomas are rare, with, an incidence of only 1 to 2.5 cases per 100,000 people per year in many countries; however, its incidence is growing. In the US in 2016, there will be 8,080 new cases of anal cancer and 1,080 deaths from it. The overall 5-year survival is 65.7% however the 5-year survival decreases to 21% for metastatic tumors. The majority of anal cancer (98%) are related to HPV
Known MSI high or MMR deficient tumors (excluding CRC and gastric cancer) (Hall et al, 2016)	• MSI is a hypermutable phenotype caused by the loss of DNA mismatch repair (MMR) activity and is detected in a wide range of human solid tumors. Its frequency is highly variable across tumor types and has not been evaluated for all tumor types. Frequencies assessed include: uterine 14.1%, small bowel 8.6%, prostate 6.2%, cancer of unknown primary origin 2.7%, hepatobiliary 2.3%, neuroendocrine 0.2%, pancreas 0.2%, NSCLC 0.2%, and breast 0.1%.

BRCA - breast cancer; CRC = colorectal cancer; HPV = human papilloma virus; MMR = mismatch repair; MSI-H = microsatellite instability, high; NA = not applicable; IV = intravenous; HER2 = human epidermal growth factor receptor 2

Please refer to Section 1.3 (Study Rationale and Benefit-Risk Assessment) for further information on the specific cancers included in this study.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a phage-derived human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids). Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated heavy chain that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations and eliminates the potential for antibody-dependent cell-mediated cytotoxicity. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptors, programmed death−1 (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.

1.2.1 Nonclinical Studies

The safety, pharmacokinetic (PK) and toxicokinetics of Atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in predicting 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, PK 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 down-modulating the PD-L1/PD-1 pathway and supported entry into clinical trials in patients.

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

1.2.2 Ongoing Clinical Studies

Atezolizumab is currently being tested in 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). Much of the safety and efficacy data summarized below are from the Phase Ia Study PCD4989g, a multicenter, first-in-human, open-label, dose-escalation trial evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics and preliminary evidence of biologic activity of Atezolizumab administered as a single agent by IV infusion every 3 weeks (q3w) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.

1.2.3 Clinical Safety

As of the cutoff date for the Investigator's Brochure version 9, Atezolizumab, (August 2016) has been administered to approximately 6053 patients with solid tumors and hematologic malignancies.

Safety information for Atezolizumab is also gleaned from studies in the entire development program, including those where Atezolizumab is investigated in combination with other unapproved agents.

Study PCD4989g, in which Atezolizumab is being used as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies, provides the majority of data (with 558 safety evaluable patients as of the data extraction date of 11 May 2015) for the safety profile of Atezolizumab as monotherapy. Currently, no maximum tolerated dose, no dose-limiting toxicities and no clear dose-related trends in the incidence of AEs have been determined. Fatigue, decreased appetite, nausea and cough were commonly reported adverse events in single and combination therapy. The overall immune-mediated adverse events reported for Atezolizumab were considered moderate in severity and majority of patients were able to continue on Atezolizumab therapy.

Adverse Events

In PCD4989g of the 558 safety evaluable treated patients 376 patients (67.4%) reported at least one treatment-related adverse event, Grade 3 - 4 AEs were reported in 239 patients (42.8%) of which 66 (11.8%) were considered related. Grade 3 and 4 AEs considered related by the investigator included dyspnea, pneumonitis, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased gamma-glutamyl transferase (GGT), lymphocyte count decreased, cardiac tamponade, asthenia, autoimmune hepatitis, pneumonia, influenza, and hypoxia. More detailed information is provided in the latest version of the IB.

Immune-mediated Adverse Events

Given the mechanism of action of Atezolizumab, events associated with inflammation and/or immune-mediated adverse events have been closely monitored during the Atezolizumab clinical program. These include potential dermatologic, hepatic, endocrine and respiratory events. Events of immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome / myasthenia gravis, meningoencephalitis and infusion-related reactions are considered adverse drug reactions associated with Atezolizumab.

Please refer to the Atezolizumab Investigator's Brochure for details regarding immune-mediated adverse events observed in patients treated with Atezolizumab.

1.2.4 Clinical Activity

1.2.4.1 Study PCD4989g

Anti-tumor activity, including Response Evaluation Criteria in Solid Tumors (RECIST)−based responses (i.e., RECIST v1.1 responses), have been observed in patients with different tumor types treated with Atezolizumab monotherapy in Study PCD4989g.

Among 345 evaluable patients treated by 21 October 2013 (data cutoff of 21 April 2014) with a median 30.4 weeks of follow-up, 62 experienced objective responses per RECIST v1.1 at an ORR of 18% (95% CI: 14.1%−22.3%). Objective responses with Atezolizumab monotherapy were observed in a broad range of malignancies including NSCLC, RCC, melanoma, bladder cancer, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. The majority of the responses have been durable, with a median DOR of 77.6 weeks (range: 6.4+ to 97.9+ weeks, where "+" denotes a censored value); 72.6% (45 of 62 patients) of these responses were ongoing as of the clinical cutoff date.

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

NSCLC

As of the 21 April 2014 cutoff, 88 patients with NSCLC who enrolled into Study PCD4989g and received their first dose of Atezolizumab by 21 October 2013 were evaluable for efficacy. The median age was 60.5 years. The group represented a heavily pre-treated patient population in that 84.1% of the patients had received ≥ 2 prior systemic therapies. Patients had a median duration of follow-up of 36.1 weeks. RECIST responses (confirmed) were observed in a total of 18 patients, inclusive of squamous and non-squamous histologies, and across all treatment cohorts (treatment dose levels of 1 to 20 mg/kg).

Preliminary results suggest that PD-L1 expression in tumor tissue is likely to be associated with response to Atezolizumab. A prototype IHC assay was used to measure specific PD-L1 signals in TCs and ICs. PD-L1 staining categories in TCs were defined as TC0, TC1, TC2, and TC3, and in ICs were defined as IC0, IC1, IC2, and IC3. Of note, an ORR of 50% (11 of 22 patients, 95% CI: 28.2%− 71.8%) and an ORR of 31.6% (12 of 38, 95% CI: 17.5%−48.6%) were observed in patients whose tumors were characterized by high levels of PD-L1 staining in TCs or ICs (TC3 or IC3 group and TC3 or IC2/3 group, respectively) compared with an ORR of 12.1% (7 of 58 patients, 95% CI: 5.7%−22.5%) in patients with low or no PD-L1 staining in TCs and ICs (TC0/1/2 and IC0/1/2 group) (Table 2).

As of the data cutoff of 21 April 2014, 11 of the 18 responding patients have continued to respond after 13.0+ weeks to 97.9+ weeks. The median DOR is 66.9 weeks. See the

Atezolizumab Investigator's Brochure for details on clinical activity in patients with NSCLC treated to date.

Table 2. Efficacy-Evaluable NSCLC Patients in Study PCD4989g: ORR by Tumor PD-L1 Expression and Objective Response Rate (per RECIST, Version 1.1)

PD-L1 IHC Expression Category	ORR (n=88)	PR	SD
TC3 or IC3	50% (11 of 22) 95% CI: 28.2%−71.8%	50% (11 of 22)	18.2% (4 of 22)
TC3 or IC2/3	31.6% (12 of 38) 95% CI: 17.5%−48.6%	31.6% (12 of 38)	28.9% (11 of 38)
TC0/1/2 and IC0/1/2	12.1% (7 of 58) 95% CI: 5.7%−22.5%	12.1% (7 of 58)	36.2% (21 of 58)
TC0/1/2 and IC0/1	14.3% (6 of 42) 95% CI: 6.4%−27.7%	14.3% (6 of 42)	33.3% (14 of 42)

IC = tumor-infiltrating immune cells; IHC = immunohistochemistry; TC = tumor cells; NSCLC = non−small cell lung cancer; ORR = objective response rate; PR = partial response; SD = stable disease; PD-L1 = programmed death− ligand 1; RECIST = Response Evaluation Criteria in Solid Tumors.
Note: This table is based on a data cutoff of 21 April 2014 of patients with NSCLC dosed by 21 October 2013. Objective response is per RECIST v1.1.

Urothelial Bladder Cancer

As of the clinical cut-off date of 21 April 2014, efficacy analyses had been performed on 70 patients (33 IHC 2/3, 36 IHC 0/1 and 1 unknown) with locally-advanced or metastatic urothelial bladder cancer (UBC) (all patients were dosed by 27 January 2014 and had a minimum of 12 weeks of follow-up). In these 70 patients, the median age was 65 years (range: 36−89 years). Sixty-four patients (91%) had received prior platinum-based chemotherapy. The majority of patients had at least one or more poor prognostic features (i.e., hemoglobin < 10 g/dL, Eastern Cooperative Oncology Group [ECOG] performance status [PS] ≥ 1, liver involvement) at baseline, with 52 patients (74%) having visceral metastases.

Among the 33 efficacy-evaluable IHC 2/3 patients, median follow-up was 6 months (range: 1+ – 12 months). The investigator-assessed ORR (unconfirmed) per Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST, v1.1]) was 52% (95% CI: 34%, 69%), with 3 complete responses (CRs) (Table 5). Among the 36 efficacy-evaluable IHC 0/1 patients, median follow-up was 4 months (range: 1+ to 7 months). The ORR was 14% (95% CI: 6%, 28%) (Table 3).

Table 3. Efficacy-Evaluable UBC Patients in Study PCD4989g: ORR per RECIST v1.1 According to PD-L1 Tumor Expression

IHC Score	ORR, Best Response % (95% CI)	PD-L1+ vs. PD-L1– ORR, Best Response % (95% CI)
IHC 3 (IC ≥ 10%)	60 (2, 85)	52 (34, 69)
IHC 2 (10% > IC ≥ 5%)	48 (27, 68)	
IHC 1 (5% > IC ≥ 1%)	17 (6, 37)	14 (6, 28)
IHC 0 (IC < 1%)	8 (0, 35)	

IC = PD-L1−positive tumor-infiltrating immune cell; IHC = immunohistochemistry; ORR, overall response rate; PD-L1 = programmed death−ligand 1; UBC = urothelial bladder cancer.
Note: This table is based on a data cutoff of 21 April 2014 of UBC patients dosed by 27 January 2014.

Median PFS was 24 weeks (range: 5 to 50+) in the IHC 2/3 cohort and 8 weeks (range: 0.1+ to 30+ weeks) in the IHC 0/1 cohort. Overall, median PFS appeared to be associated with PD-L1 expression. For the entire UBC population, 19 of 22 patients had ongoing responses at the time of data cut-off, and the median duration of response had not been reached.

Renal Cell Carcinoma

As of the clinical cut-off date of 21 April 2014, efficacy analyses had been performed on 69 patients with RCC (all patients were dosed by 21 October 2013). In these 69 patients, the median age was 61 years (range: 33−81 years). Sixty patients (87%) had received prior systemic therapies, including cytokine-based therapies (39%), tyrosine kinase inhibitors (58%) and mTOR inhibitors (25%). Eighteen patients (26%) were in the Memorial Sloan-Kettering Cancer Center (MSKCC) poor risk stratification group, while 71%, 23%, 35% and 4% of patients at enrolment had metastases in the lung, liver, bone and brain, respectively.

Among the 69 efficacy-evaluable patients, the median follow-up was 239 days (range: 21 to 834 days). The investigator-assessed ORR (confirmed) per RECIST, v1.1, was 15% (95% CI: 8%, 25%), including 1 CR. The ORRs in the IHC 1/2/3 and IHC 0 groups were 20% (95% CI: 9%, 37%) and 10% (95% CI: 2%, 30%), respectively. The PFS was 24 weeks (range: 5 to 98+ weeks), with a 24-week PFS rate of 51% (95% CI: 38%, 63%). The ORR for Fuhrman Grade 4 or sarcomatoid clear cell RCC (n=18) was 22% (95% CI: 8%, 47%).

Further analysis indicated that higher response rates were observed in MSKCC poor-risk patients with PD-L1 IHC 1/2/3 expression (Table 4).

Table 4. Efficacy-Evaluable RCC Patients in Study PCD4989g: ORR per MSKCC Risk Stratification and PD-L1 Tumor Expression

	All Patients		IHC 1/2/3 [a]	
MSKCC Risk Category	**n**	**ORR, n (%) 95% CI**	**n**	**ORR, n (%) 95% CI**
Overall	62	9 (15%) CI: 8%, 25% [1 CR and 8 PRs]	35	7 (20%) CI: 9%, 37% [1 CR and 6 PRs]
Favorable	10	2 (20%) CI: 4%, 56%	3	0% CI: 0%, 63%
Intermediate	36	3 (8%) CI: 2%, 21%	24	3 (13%) CI: 4%, 31%
Poor	15	4 (27%) CI: 10%, 55%	7	4 (57%) CI: 23%, 87%

MSKCC = Memorial Sloan-Kettering Cancer Center; IHC = immunohistochemistry; ORR, overall response rate; PD-L1 = programmed death−ligand 1; RCC = renal cell carcinoma.

a. One patient had unknown PD-L1 status.

Note: This table is based on a data cutoff of 21 April 2014 of RCC patients dosed by 21 October 2013.

1.2.4.2 Study GP28328

Study GP28328 is an ongoing Phase Ib study evaluating the safety and pharmacology of Atezolizumab administered with bevacizumab alone (Arm A) or with bevacizumab plus folinic acid/fluorouracil/oxaliplatin (FOLFOX) (Arm B) in patients with advanced solid tumors. As of the clinical cut-off date of 7 July 2014, 35 patients had enrolled in Arm A and 36 had enrolled in Arm B (safety-evaluable population). Sixty percent of patients in Arm A and 22% of patients in Arm B had received ≥ 3 prior systemic regimens.

Responses in the RCC and CRC cohorts are shown in Table 5.

Table 5. Efficacy-Evaluable RCC and CRC Patients in Study GP28328: Summary of Responses

	n	ORR
Atezolizumab + bevacizumab (Arm A)		
First-line RCC	10	40%
CRC	13	8%
Atezolizumab + bevacizumab + FOLFOX (Arm B)		
First-line CRC	18	44%
CRC	25	36%

CRC = colorectal cancer; RCC = renal cell carcinoma.
Note: This table is based on a data cutoff of 7 July 2014 of RCC and CRC patients dosed by 7 April 2013.

In Arm A, responses were also observed in melanoma (1/4 PR) and breast cancer (1/1 PR). In Arm B, responses were also observed in RCC (1/1 CR) and breast cancer (1/2 PR).

1.2.5 Clinical Pharmacokinetics

On the basis of available preliminary PK data (0.03−20 mg/kg), Atezolizumab appeared to show linear pharmacokinetics at doses ≥ 1 mg/kg. For the 1-mg/kg and 20-mg/kg dose groups, the mean apparent clearance (CL) and the mean volume of distribution at steady state (Vss) had a range of 3.11 to 4.14 mL/kg and 48.1 to 67.0 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

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

See the Atezolizumab Investigator's Brochure for additional details on clinical pharmacokinetics.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Rationale

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

PD-L1 is an extracellular protein that down-regulates immune responses primarily in peripheral tissues through binding to its two receptors PD-1 and B7.1. Many human tumors have been found to overexpress PD-L1, which acts to suppress anti-tumor immunity. 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 down-regulation 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.

Targeting the PD-L1 pathway with Atezolizumab has demonstrated activity in patients with advanced malignancies in patients who have failed standard of care therapies. In the PCD4989g Phase Ia dose-escalation and expansion study of 345 evaluable patients treated by 21 October 2013 (data cutoff of 21 April 2014) with a median 30.4 weeks of follow-up, 62 patients experienced objective responses per RECIST, v1.1, at an ORR of 18% (95% CI: 14.1%−22.3%). Objective responses with Atezolizumab monotherapy were observed in a broad range of malignancies including NSCLC, RCC, melanoma, bladder cancer, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. The median DOR was 77.6 weeks (range: 6.4+ to 97.9+ weeks, where "+" denotes a censored value). The majority of these responses have been durable, with 72.6% (45 of 62) of responses ongoing as of the clinical cutoff date.

Preliminary results from the Phase Ia Study PCD4989g suggest that PD-L1 expression in tumor tissue is likely to be associated with response to Atezolizumab. A prototype immunohistochemistry (IHC) assay was used to measure specific PD-L1 signals in tumor cells (TCs) and tumor-filtrating immune cells (ICs).

The basic approach of the study will be to examine the efficacy and safety of Atezolizumab patients with different advanced solid tumors. The cancer subtypes were chosen based on input from academic experts and relevant published literature. Two types of evidence were considered to be particularly relevant in the choice:

1. Does evidence exist that the tumor is immunogenic? Two basic categories of tumor antigens are thought to trigger anticancer immune surveillance: abnormal self antigens (ASAs), and tumor-specific antigens (TSAs) (Schreiber et al. 2010). ASAs are generated in a variety of ways, including induction of embryonal and developmental genes not normally expressed in adult tissues, expression of normal proteins with abnormal sugar moieties or expression of self proteins at abnormally

high levels. TSAs result from spontaneous somatic mutations or breaks in germline DNA that lead to missense mutations, frameshift errors or fusion proteins. Thus, advanced solid tumors having potentially high levels of ASAs and/or TSAs were considered to be suitable for inclusion in this study. A high level of tumor-infiltrating lymphocytes was also used as evidence of inherent immunogenicity, as it indicates a tumor microenvironment permissive for leukocyte trafficking and extravasation.

2. Does evidence exist that the PD-L1 checkpoint may play a role in the development of the tumor? Thus, tumors that have been shown in published reports to express PD-L1 in vivo were considered for inclusion in the study. This evidence was considered to be especially relevant if evidence also existed that the level of PD-L1 expression correlated with cancer grade and/or prognosis, implying a direct role for the PD-L1 pathway in tumor immunity.

Based on these considerations, as well as other tumor-specific issues that might suggest potential activity for Atezolizumab (see below), the solid cancers described in the following sections were chosen for study.

1.3.1.1 Cervical Cancer

A key step in an antitumor immune response is the production and recognition of ASAs and TSAs that are recognized by lymphocytes as foreign (non-self). Breaking self-tolerance is not as great of an obstacle for virally-induced cancers because viral antigens are inherently non-self, and virally-induced cancers are thus potentially highly immunogenic (Schreiber et al. 2010).

Human papilloma virus (HPV) is detected in 99% of cervical tumors, in particular oncogenic subtypes such as HPV 16 and 18 (Colombo et al. 2012). In addition, cervical cancer progression is associated with deregulated viral gene expression, which leads to (among other things) deficient DNA repair and the accumulation of genetic damage in the infected cell, both of which may increase the levels of TSAs (Doorbar et al. 2012).

Evidence in the literature also suggests that PD-L1-mediated immune checkpoints may play a role in cervical cancer progression. PD-L1 was found to be expressed on tumor cells in 19% to 29% of patients with cervical cancer (Karim et al. 2009; Grosso et al. 2013). PD-L1 expression on cervical T cells and dendritic cells, respectively, correlated positively with increasing grade (Yang et al. 2013) and inversely with spontaneous regression (Kojima et al. 2013).

1.3.1.2 Nasopharyngeal Carcinoma

As with cervical cancer, nasopharyngeal carcinoma is highly associated with viral infection, in this case Epstein-Barr virus (EBV), and thus has the potential to be highly immunogenic. In one study, plasma EBV was detectable before treatment in 94 of 99 patients with nasopharyngeal carcinoma, but not in 40 healthy controls or 20 cured patients (Lin et al. 2004). Median plasma EBV levels also correlated with disease stage.

Consistent with a role for immune checkpoints in the disease, PD-L1 was expressed on tumor cells in 68% to 100% of patients (Hsu et al. 2010; Yang et al. 2011). PD-L1 has also been shown to be highly expressed on tumor-infiltrating macrophages in patients with nasopharyngeal carcinoma (Chen et al. 2013). Finally, higher expression rate of PD-1 in intratumoral CD8+ T cells significantly correlated with poorer OS, disease-free survival and locoregional recurrence-free survival (Hsu et al. 2010).

1.3.1.3 MSI-H or MMR-Deficient Colorectal Cancer

In MSI-H colorectal cancer, the accumulation of errors in microsatellites that reside in gene exons leads to the generation of a large number of abnormal peptides due to frameshift mutations: the so-called "mutator phenotype" (Bodmer et al. 1994). Such an array of abnormal peptides represents a pool of potential TSAs that render MSI-H tumors inherently more detectable by the host immune system. In fact, epitope mapping based on results of The Cancer Genome Atlas (TCGA) estimated that approximately 7 TSAs are generated on average in individual colorectal tumors with appropriate anchor residues for MHC loading (Segal et al. 2008).

Consistent with potentially high immunogenicity, MSI-H colorectal cancer is associated with high numbers of tumor-infiltrating lymphocytes and a Crohn-like host response (Hutchins et al. 2011). PD-L1 immune checkpoint regulation has also been directly implicated in CRC pathogenesis. Thus, PD-L1 was expressed on tumor cells in 53% of patients with colon adenocarcinoma (Dong et al. 2002). A case report has been published describing a patient with PD-L1-positive MSI-H colorectal cancer who exhibited a long-term response with the anti-PD-1 antibody BMS-936558 (Lipson et al. 2013). Finally, the anti-PD-L1 antibody Atezolizumab demonstrated preliminary activity against colorectal cancer in Study PCD4989g as a single agent and in Study GP28328 in combination with bevacizumab ± FOLFOX (Section 1.2.4).

1.3.1.4 BRCA 1/2 Mutated Cancers

The BRCA 1/2 gene products play a central role in another DNA repair pathway, double-strand break repair (DSBR) (O'Donovan and Livingston 2010). While not as mutagenic as mismatch-repair mutants (see previous section), DSBR mutants do exhibit some increase in mutator activity, as well as a dramatic rise in genomic instability. This implies that BRCA 1/2 tumors may have high frequencies of induced TSAs (Schreiber et al. 2010). Consistent with this, it has been estimated that breast cancers accumulate on average 10 novel and unique TSAs (Segal et al. 2008). Furthermore, extensive tumor infiltration by cytotoxic CD8+ T cells was strongly associated with patient survival and response to therapy (Salgado et al. 2014). Thus, growth of these tumors may require a bypass of normal tumor immunity.

Evidence in the literature also suggests that PD-L1-mediated immune checkpoints may play a role in cancers commonly associated with BRCA 1/2 mutations. In one case series study (Ghebeh et al. 2006), PD-L1 was expressed in 22 of 44 breast cancer patients in both epithelial cells and tumor-infiltrating lymphocytes. Intra-tumor

expression of PD-L1 was significantly associated with histologic grade, while expression of PD-L1 in tumor-infiltrating lymphocytes was associated with large tumor size and histologic grade. In another case series study, PD-L1 was expressed in 152 (23.4%) of 650 breast cancer specimens; PD-L1 expression was associated with a significantly worse OS (Muenst et al. 2014).

In patients with ovarian cancer, higher expression of PD-L1 on tumor cells correlated with a significantly poorer prognosis than lower expression, while a significant inverse correlation was observed between PD-L1 expression and the intraepithelial CD8+ T lymphocyte count (Hamanishi et al. 2007). Ovarian cancer-infiltrating dendritic cells progressively expressed increased levels of PD-L1 over time. Accumulation of PD-L1 in the tumor was associated with suppression of T cell activity and decreased infiltrating T cells in advancing tumors (Krempski et al. 2011). Finally, in a Phase I dose-escalation study of 207 patients treated with the anti-PD-L1 antibody BMS-936559, a response rate of 6% was observed in patients with ovarian cancer (Brahmer et al. 2012).

1.3.1.5 Soft Tissue, Visceral and Bone Sarcomas

Adult soft tissue sarcoma (STS) and bone and joint sarcoma (BS) constitute a rare group of heterogeneous mesenchymal cancers originating from connective tissue. There are multiple histological subtypes of STS and BS.

Soft-tissue sarcoma comprises a generally aggressive set of diseases characterized by multiple histological subtypes generally categorized according to the normal tissue they mimic and the most common types are malignant fibrous histiocytoma, liposarcoma and leiomyosarcoma. Genomic profiling indicates that many soft tissue sarcomas contain translocations, mutations, amplifications or other more complex and chaotic karyotypes (Maki 2001; Linch et al. 2014). Consequently, this broad class of tumors may be rich sources of TSAs, implying a bypass of tumor immunity may be necessary for progression. Moreover, dendritic cells have been shown to induce an effective antitumor immune response in both animal models and human sarcoma trials, suggesting that boosting immune responses may have therapeutic value in this setting (Indelicato and Finkelstein 2012).

Radiation induced sarcomas (RIS) are well-characterized and constitute about 3% of all sarcomas. They are more aggressive than other sarcomas. One of the most significant effects of radiation therapy on normal tissues is mutagenesis and genomic instability which is the basis for radiation-induced malignancies. A high frequency of MYC amplifications has been described in radiation-induced angiosarcomas, but not in primary angiosarcomas and other somatic mutations have been described. Many tumors that respond to PD-1/PD-L1 inhibitors are those with a high mutation load or that are commonly associated with mutations.

The most common types of bone sarcoma are osteosarcoma and chondrosarcoma. PD-L1 expression in osteosarcoma has been described as 36% in 161 patients with osteosarcoma (Raj et al. 2014).

Evidence that PD-L1 specifically plays a role in inhibiting immune surveillance in soft tissue sarcoma comes from the observation that the protein was expressed on tumor cells in 58% of patients with the disease (Kim et al. 2013). Moreover, PD-L1 expression was significantly associated with higher clinical stage, presence of distant metastasis, higher histological grade, poor differentiation of tumor and tumor necrosis, suggesting the protein is playing an active role in inducing immune checkpoints (Kim et al. 2013).

1.3.1.6 Mesothelioma

Chronic exposure to asbestos, a Group I carcinogen, induces genetic alterations in lung epithelial cells via at least two known mechanisms: direct DNA damage, and mutagenic asbestos-driven escape from apoptosis (Otsuki et al. 2007). The resulting genetic alterations are thought to drive the development of malignant mesothelioma. The same process might be expected to result in an increased rate of TSA production, as well, making mesothelioma a potentially good target for immunotherapeutic approaches.

Many of the epidemiologic associations pertaining to malignant pleural mesothelioma apply to malignant mesothelioma arising in the peritoneum. There are, however, several important site-specific differences in the demographic features, genetics, and distribution of histological subtypes between mesotheliomas arising in the pleural and peritoneal cavities that suggest fundamental biological disparities between tumors at these sites (Husain et al. 2013). Due to differences in biology and prognosis, two different cohorts have been implemented in this study: pleural mesothelioma and peritoneal mesothelioma.

Evidence that mesothelioma tumors are indeed immunogenic comes from studies demonstrating high levels of immune cell infiltration in mesothelioma tumors (Gregoire 2010). However, the relative levels of lymphocyte subtypes, as well as the cytokine levels, indicate that the immune infiltrate is in a relatively tolerogenic state (Hegmans et al. 2006; Gregoire 2010), i.e., that immune checkpoints may be required for tumorigenesis. PD-L1 may play a role in forming this tolerogenic state, as the protein has been found to be highly expressed on mesothelioma tumor cells and within the tumor stroma (Currie et al. 2009).

1.3.1.7 Cholangiocarcinoma/Cancer of the Biliary Tract

Long established risk factors for cholangiocarcinoma include hepatobiliary flukes, primary sclerosing cholangitis, biliary tract cysts, hepatolithiasis and toxins (Bridgewater et al. 2014). All of these etiologic factors are thought to lead to a chronic state of biliary inflammation and increased cellular turnover (Bridgewater et al. 2014). The chronic inflammation might be expected to down-regulate immune responses via immune checkpoint mechanisms, which in turn might help to promote carcinogenesis.

Several published studies support this model. For instance, resting human cholangiocytes in culture have been shown to induce PD-L1 protein expression following administration of interferon-gamma, which is known to be up-regulated in many tumor microenvironments (Gong et al. 2009). Expression of PD-L1 was also up-regulated in cholangiocarcinoma tissues compared with adjacent tissues (Ye et al. 2009). Tumor-related PD-L1 expression was significantly correlated with both tumor differentiation and stage and was inversely correlated with CD8+ tumor-infiltrating lymphocytes.

1.3.1.8 Thyroid Cancer

There are 4 types of thyroid cancers – papillary, follicular, medullar and anaplastic. Papillary and follicular thyroid cancers are usually considered together as differentiated thyroid cancer.

Most patients with differentiated thyroid cancer will evolve favorably with current therapy, which mostly includes surgery and radio-iodine treatment; however, 10–30% will present recurrent disease and may metastasize. Medullary thyroid cancer (MTC) usually presents low chemosensitivity and radiosensitivity and does not concentrate iodine.

1.3.1.8.1 Anaplastic thyroid cancer

Anaplastic thyroid cancer, one of the most aggressive human tumors, is characterized by multiple genetic mutations and chromosomal aberrations (Smallridge et al. 2009). DNA copy number changes were found in 11 out of the 13 patients with anaplastic thyroid cancer; gains were noted in 10 out of the 13, deletions in 3 out of the 13, both gains and deletions in two, and chromosome deletion in one (Hemmer et al. 1999). This high degree of genetic heterogeneity might be expected to associate with high numbers of TSAs, but the highly aggressive course indicates that the immune system is nonetheless unable to check the uncontrolled growth.

The inability of the immune system to slow anaplastic thyroid cancer might be attributable, at least in part, to the PD-L1/PD-1 pathway and is supported by several observations. First, in a study of 407 thyroid nodule tissue samples, including 293 differentiated thyroid carcinoma samples, malignant tissues displayed more intense PD-L1 staining levels than benign tissues (both $p<0.0001$) (Cunha et al. 2013). Second, elevated levels of PD-L1 protein were associated with the presence of CD4+ and CD8+, lymphocytes ($p<0.05$); tumor-associated macrophages ($P<0.0001$); and the presence of myeloid-derived suppressor cells ($P=0.03256$) (Cunha et al. 2013). Finally, Stage II–IV thyroid cancer patients presented with higher PD-L1 mRNA levels than stage I cases ($p=0.03522$) (Cunha et al. 2013).

1.3.1.8.2 Follicular and papillary thyroid cancers

Associations between inflammation and differentiated thyroid cancers have been reported and evidenced by a mixture of immune cells frequently found within, inside, or even surrounding primary thyroid tumors (Ward et al. 2014). In papillary thyroid cancer, PD-L1 expression correlates with a greater risk of recurrence, poorer prognosis and

shortened disease free survival (Chowdhury et al, 2016). Preliminary results of a study of pembrolizumab in a cohort of 22 patients with advanced papillary or follicular thyroid cancer, who failed standard therapy, reported 2 partial responses and a stable disease rate of 54.5% (Mehnert et al, 2016).

1.3.1.8.3 Medullary thyroid cancer and mixed medullary and follicular or papillary carcinoma

Medullary thyroid carcinoma (MTC), arising from parafollicular, calcitonin-producing C cells, represents an aggressive, usually slow-growing tumor occurring in both sporadic and familial forms. Sporadic MTC harbors RET gene somatic mutations in up to 50% of cases, and RAS family gene mutations occur in about 10%.

The immune system has been shown to play a role in MTC as evidenced by an increase of FoxP3+ lymphocytes in peripheral blood of patients with MTC, which correlated with prognosis (Ward et al, 2014).

1.3.1.9 Gastric Adenocarcinoma/Adenocarcinoma of the Gastro-Esophageal Junction

Infection with Helicobacter pylori (H. pylori), a type of bacterium found in the stomach of about two-thirds of the world's population, is a major cause of gastric cancer. A 2001 combined analysis of 12 case-control studies estimated that the risk of non-cardia gastric cancer (cancer in all areas of the stomach, except for the top portion near the esophagus) was nearly six times higher for H. pylori-infected people than for uninfected people (Helicobacter and Cancer Collaborative 2001). Similarly, in prospective cohort studies, H. pylori-infected individuals had a nearly eight-fold increased risk for non-cardia gastric cancer (Kamangar et al. 2006). A general atrophy of the stomach lining caused by H. pylori is thought to be the root cause of carcinogenesis in gastric cancer, although more direct interactions mediated by the bacterium have also been posited (Atherton 2006).

As with other bacterial infections, H. pylori induces a robust immune reaction in the host (Atherton 2006; Kusters et al. 2006). Unlike other bacterial infections, however, the immune response is primarily cellular, rather than humoral. Moreover, the cell-mediated immune reactions mounted by the host generally fail to clear the infection, due to H. pylori-induced products that interfere with local immune responses. Thus, gastric cancer develops in the presence of an induced cell-mediated immune response, but one which immune subtypes and cytokine levels indicate to be in a tolerogenic state. It is reasonable to hypothesize that the PD-L1/PD-1 pathway may be co-opted by the bacterium to help generate this anergy.

Consistent with this hypothesis, a number of studies have indicated a role for PD-L1 in gastric carcinogenesis. In case studies, PD-L1 was expressed on tumor cells in 42% to 65% of patients with gastric cancer (Wu et al. 2006; Geng et al. 2014; Wei et al. 2014). PD-L1 immunodetection was significantly correlated to tumor size, invasion, lymph node

metastasis and survival time of patients. PD-L1 immunolabeling was significantly enhanced (P<0.01) when the tumor infiltrated into the deep muscular layers, with lymph node metastasis or survival time of less than 2 years (Wu et al. 2006; Geng et al. 2014). High expression of PD-L1 was associated with poor prognosis (Geng et al. 2014). Finally, the anti-PD-L1 antibody Atezolizumab demonstrated preliminary activity against gastric cancer in Study PCD4989g.

1.3.1.10 Other Solid Tumors

This cohort has been closed to recruitment from Protocol Version 4 onwards.

Immune checkpoints and their involvement in tumor surveillance are highly complex, and many details of their regulation remain to be determined. Thus, other cancers than the ones included in the previous 9 cohorts are good targets for Atezolizumab, but might not be predicted to be so based on our current knowledge. In an effort to potentially capture other targetable cancers, the cohort enrolled patients with advanced solid tumors not included in the other cohorts. Any positive signals in Cohort 10 may be followed up in future clinical studies.

1.3.1.11 Malignant Germ Cell Tumors

Malignant germ cell tumors form a heterogeneous entity that is described by their histology. The tumors derive from embryonal cells and are located in the majority of cases in gonads (testis and ovary), but also in head and neck and mediastinum. Gonocytes have almost completely demethylated DNA, which facilitates the accumulation of mutations during cell replication and the development of intratubular germ cell neoplasia (Hanna et al. NEJM 2014). Frankhauser et al. have published PD-L1 expression in testicular germ cell tumors. They found 73% of all seminomas and 64% of all non-seminomas exhibited PD-L1 expression by multi-tissue microarray using a cut-off value of 5% (Frankhauser et al. BJC 2015).

1.3.1.12 ER+/HER2- Metastatic Breast Cancer with Known High Mutation Load (>100 mutations) by Local Test

Although several advances have been achieved, most of the patients with metastatic ER+/HER2- breast cancer will die after 4 years. One of the challenges is to identify new treatment for patients with ER+/HER2- mBC.

Whole exome sequencing of metastatic breast cancers has revealed that a subset of ER+/Her2- mBC present with high mutational load (Stephens et al. Nature 2012, M. Disis, ASCO 2015). This subset of patients might be more likely to benefit from immunotherapy due to increased number of mutations and neoantigens. Haricharan et al. demonstrated that ER+, but not ER-, tumors with a high somatic mutational load are associated with poor overall survival (HR = 2.02). These high mutation load tumors are enriched for coincident mutations in both DNA damage repair and ER signature genes (Haricharan et al. Breast Cancer Res Treat, 2014).

1.3.1.13 Thymoma and Thymic Cancer

Epithelial thymomas and thymic carcinomas include a variety of subtypes, well described in the World Health Organization (WHO) classification and must be differentiated from a number of nonepithelial thymic neoplasms, including (but not limited to) neuroendocrine tumors (NETs), germ cell tumors and lymphomas. In general, thymomas are indolent tumors with a tendency toward local recurrence rather than metastasis. Thymic carcinomas, however, are typically invasive, with a higher risk of relapse and a poorer prognosis.

Thymic carcinoma is often associated with an overexpression of growth factor receptors like epidermal growth factor receptor (EGFR), stem cell factor receptor (SCFR) and Insulin-like growth-factor-1 receptor (IGF-1R) and have been found to frequently harbor mutations in epigenetic regulatory genes.

In a sample of 38 thymic carcinoma patients, 70% stained positive for PD-L1 and in a sample of 101 thymomas, 23% stained positive for PD-L1 (Katsuyo et al. 2015).

1.3.1.14 Gastroenteropancreatic (GEP) and Lung Neuroendocrine Tumors (NETs)

Neuroendocrine tumors (NETs) are generally classified based on their anatomic site of origin. NETs can arise in many different areas of the body, and are most often located in the intestine, pancreas or the lungs. Due to the different etiology and biology, two different cohorts are implemented in this study: neuroendocrine gastroenteropancreatic tumors and neuroendocrine tumors of the lung (excluding small cell lung cancer, SCLC).

The WHO classification scheme places neuroendocrine tumors into three main categories, which emphasize the tumor grade rather than the anatomical origin: well-differentiated NETs (low grade), neuroendocrine carcinomas with low-grade malignant behavior and poorly differentiated (high grade) and neuroendocrine carcinomas, which are the large cell neuroendocrine and small cell carcinomas.

Neuroendocrine gastroenteropancreatic tumors (GEP-NETs) share a common phenotype with immunoreactivity for the so-called ‘pan-neuroendocrine’ markers including chromogranin A and synaptophysin. Neuron-specific enolase (NSE) and CD56 are often positive in GEP-NETs, but are not specific for this tumor entity. Pulmonary neuroendocrine cells (PNECs) express serotonin and NSE and also gastrin-releasing peptide (GRP) (Öberg et al. 2012).

In a cohort of 32 patients with metastatic GEP-NET, PD-L1 expression was reported in 21.9% of the patients (Kim et al. 2016).

1.3.1.15 HPV Induced Squamous Cell Carcinomas

As described for cervical cancer, HPV induced tumors have the potential to be highly immunogenic. An estimated 50% of penile, 88% of anal, 43% of vulvar, 70% of vaginal,

and 13–56% oropharyngeal cancers are attributable to HPV, primarily HPV-16 typically followed by HPV-18 (De Vuyst et al, 2009).

1.3.1.15.1 Head and Neck Squamous Cell Carcinoma (HNSCC)

During the past decade, infection with HPVs, in particular HPV16 has emerged as a risk factor for HNSCCs, specifically HNSCCs arising in the oropharynx (tonsil, base of tongue, and soft palate). Currently, up to 70% of oropharyngeal cancers in the US are HPV-mediated oropharyngeal squamous cell carcinomas. HPV-16 is detected in over 90% of HPV-induced HNSCC and data suggests that HPV-16 cancers may present more frequently with lymph node metastases and may have a poorer outcome compared with other HPV types (Nichols et al, 2013).

Recently several studies of PD-1–pathway inhibitors have reported overall response rates in the 20% range in relapsed HNSCC (Seiwert et al, 2015; Fury et al. 2014). Responses were observed in both HPV positive and HPV negative patients,

1.3.1.15.2 Penile Cancer

Penile carcinoma is mostly a squamous cell carcinoma (SCC) with several histological subtypes. In this study only HPV positive squamous cell penile carcinoma will be included. The current treatment of HPV-positive penile SCC is identical to other penile SCCs.

HPV DNA has been detected in approximately 40% to 50% of invasive penile cancer cases and in up to 90% of high-grade squamous intraepithelial lesions. The high-risk oncogenic subtypes 16 and 18 were detected in over 60% of HPV-positive specimens.

1.3.1.15.3 Vaginal and Vulvar Cancers

SCC accounts for approximately 85% of vaginal cancer cases and about 90% of vulvar carcinomas. In this study only HPV positive squamous cell carcinoma of the vagina and the vulva will be included. Both HPV 16 and 18 are commonly detected in HPV-induced vaginal or vulvar cancers. The treatment of HPV positive or negative SCC of the vagina and vulva are identical.

1.3.1.15.4 Anal Cancer

HPV infection is strongly associated with anal cancer development and may be a necessary step in its carcinogenesis. HPV16 is the most prevalent HPV subtype in anal carcinoma and is present in up to 89% of all patients with anal carcinoma (Serup-Hansen et al, 2014).

1.3.1.16 Known MSI High or MMR Deficient Tumors (excluding CRC and gastric cancers)

Microsatellite instability (MSI) is a hypermutable phenotype caused by the loss of DNA MMR activity and is detected in a wide range of human solid tumors. Its frequency is highly variable across tumor types and has not been evaluated for all tumor types. Frequencies assessed include: uterine 14.1%, small bowel 8.6%, prostate 6.2%, cancer

of unknown primary origin 2.7%, hepatobiliary 2.3%, neuroendocrine 0.2%, pancreas 0.2%, NSCLC 0.2% and breast 0.1% (Hall et al, 2016).

MSI has been linked to a number of phenotypic characteristics and clinicopathological features of tumors and its predictive relevance has been primarily studied in colorectal cancer. Recent data are suggestive of more pronounced efficacy of checkpoint inhibitors in patients with colorectal or gastric cancer whose tumors are MSI-high. MSI-H CRC is known to have an exceptionally high mutation burden. There is an increased presence of tumor-specific neoantigens in hypermutated tumors which is associated with an increased quantity of tumor-infiltrating lymphocytes (TILs) and overexpression of immune checkpoint receptors and ligands such as PD-1 and PD-L1 (Overman et al. 2016).

Overall the MSI status appears predictive of anti-PD-1/L1 therapy efficacy independently of tumor histology (Le et al., 2015).

1.3.2 Benefit-Risk

Prior to enrolment, most patients in this study will have received previous treatment including surgery, radiation therapy and/or systemic cytotoxic chemotherapy for the treatment of their solid tumor(s). Moreover, it is likely that all standard therapeutic options for their advancing, treatment-refractory disease will have been exhausted, necessitating enrolment into a clinical trial, and that their overall prognosis is consequently bleak.

Immunotherapy with Atezolizumab could provide substantial benefit to the advanced solid tumor patients enrolling in this study. In the ongoing Study PCD4989g, Atezolizumab has exhibited efficacy in a variety of solid tumors. For instance, in advanced NSCLC patients with IC ≥ 5%, the confirmed ORR was 26.5% (95% CI: 14.3%, 43.6%) and the 24-week PFS rate was 36.4% (95% CI: 19.95%, 52.74%). The DOR ranged from 12.3+ to 85.9+ weeks. In advanced NSCLC patients with IC < 5%, the confirmed ORR was 15.9% (95% CI: 7.2%, 29.0%) and the 24-week PFS rate was 41.1% (95% CI: 26.18%, 56.07%). The DOR ranged from 25.4+ to 70.6+ weeks.

Significant efficacy was also observed in Study PCD4989g in patients with advanced urothelial cancer (IHC 2/3, ORR = 52% [95% CI: 34%, 69%]; IHC 0/1, ORR = 4% [95% CI: 6%, 28%]) and advanced RCC (IHC 1/2/3, ORR = 20% [95% CI: 9%, 37%]; IHC 0, ORR = 10% [95% CI: 2%, 30%]) (Section 1.2.4.1). Thus, consistent with other studies in the literature (Brahmer et al. 2012), the anti-PD-L1 antibody Atezolizumab may act as a general anticancer immunotherapy that works across multiple solid tumor types.

Nonetheless, in order to maximize potential patient benefit, substantial effort has been made to choose patients for enrolment who are most likely to benefit from Atezolizumab therapy. To do so, academic experts were queried and relevant published literature was reviewed to identify solid tumors that: 1) were likely to have high immunogenicity and,

thus, to respond to therapies that increase antitumor immunity; and 2) had published evidence indicating a direct role of PD-L1 expression on clinical outcomes, including prognosis and treatment outcomes. Further detail on the reasons for choosing the included tumors in this study are presented in the previous section (Section 1.3.1).

Although Atezolizumab has been generally well tolerated (see Section 1.2.3), adverse events with potentially immune-mediated causes, including rash, hypothyroidism, hepatitis/transaminitis, colitis, and myasthenia gravis have been observed in Study PCD4989g. To date, these events have been monitorable and treatable (see Section 5.1.4 and the Atezolizumab Investigator's Brochure for more information on managing adverse events associated with Atezolizumab therapy).

In summary, then, treatment with Atezolizumab offers the potential for clinical benefit in many advanced solid tumors. Because most Atezolizumab-related toxicities observed to date have been mild, transient, and do not overlap with those of chemotherapy, patients who do not respond to study treatment are considered likely to be able to subsequently receive further therapies. Patients will be fully informed of the risk of continuing study treatment in spite of apparent radiographic progression, and investigators should make a careful assessment of the potential benefit of doing so, considering radiographic data and the clinical status of the patient.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To evaluate non-progression rate (NPR) at 18 weeks in patients with advanced solid tumors treated with Atezolizumab, defined as the percentage of patients with CR, PR or SD as assessed by the Investigator according to RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7).

The secondary efficacy objectives for this study are as follows:

- To evaluate NPR at 24 weeks, overall response rate (ORR), best overall response (BOR), clinical benefit rate (CBR), duration of response (DOR), time to tumor progression (TTP) and progression-free survival (PFS), as assessed by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7)
- To evaluate NPR at 18 and 24 weeks, ORR, BOR, CBR, DOR, TTP and PFS, as assessed by the Investigator using modified RECIST (Appendix 3)
- To evaluate overall survival (OS)

2.2 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of Atezolizumab in patients with advanced solid tumors
- To characterize the immunogenic potential of Atezolizumab by measuring anti-Atezolizumab antibodies and to explore the potential relationship of the immunogenicity response with safety and efficacy

2.3 PHARMACOKINETIC OBJECTIVES

The PK objectives for thi s study are as follows:

- To characterize the pharmacokinetics of Atezolizumab

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

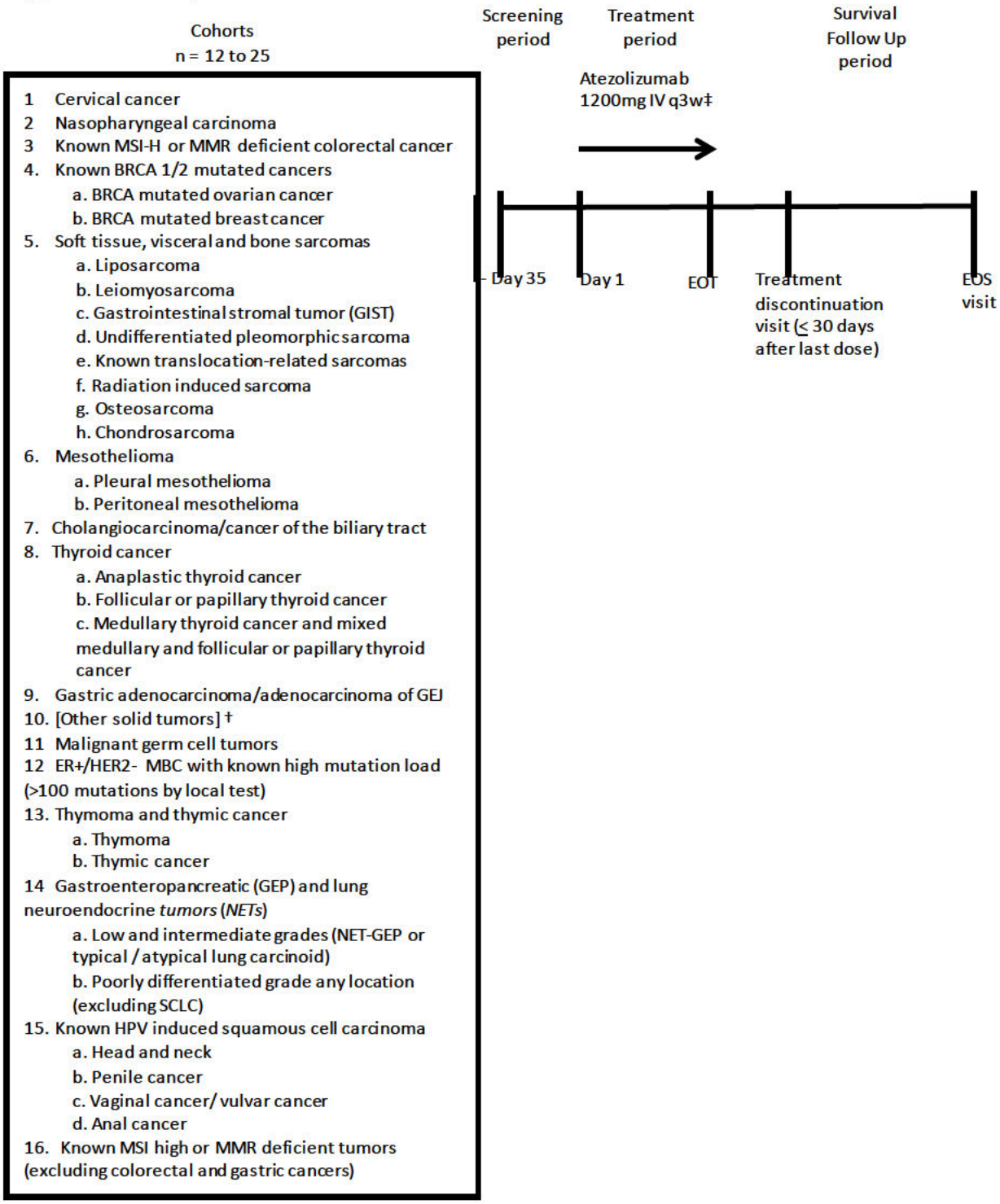
- To evaluate the relationship between tumor tissue PD-L1 expression and measures of efficacy, including NPR at 18 weeks and 24 weeks, ORR, BOR, CBR, DOR, TTP, PFS and OS.
- To assess predictive and prognostic exploratory biomarkers (e.g. but not limited to protein and genetic markers on DNA and RNA) in archival and/or fresh tumor tissue and plasma and their association with disease status and/or response to study treatment
- To evaluate exploratory pharmacodynamic (PD) biomarkers (e.g., genetic markers, T, B and NK cell enumeration, T cell subpopulations like CD8+ T, effector/memory T cells, regulatory T cells, changes in expression of CD25 or human leukocyte antigen-DR [HLA-DR], interferon [IFN]-gamma production, IL-2 and other exploratory biomarkers) in tumor tissue, tumor microenvironment and plasma and their association with disease status, and/or response to study treatment, tumor immunobiology or tumor type

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This will be an open-label, multicenter, multinational, multicohort, phase II study. For each cohort, the study will consist of a Screening Period (Day –35 to −1), a Treatment Period, a Treatment Discontinuation Visit occurring ≤ 30 days after the last dose of study medication and a 24-month Survival Follow-up Period (Figure 1). Day 1 (baseline) will be defined as the first day a patient receives study medication.

Figure 1. Study Schema



EOT end of treatment, EOS end of study
† Cohort closed to recruitment from Protocol Version 4 onwards
‡ Atezolizumab treatment may be continued as long as patients are experiencing clinical benefit (see Section 3.1, and Section 4.6.2).

The study will include 16 cohorts of patients with the following solid cancers:

1. Cervical cancer
2. Nasopharyngeal carcinoma
3. Known MSI-H- or MMR-deficient colorectal cancer
4. Known BRCA 1/2 mutated cancers
    a. BRCA mutated ovarian cancer
    b. BRCA mutated breast cancer
5. Soft tissue, visceral and bone sarcomas:
    a. Liposarcoma
    b. Leiomyosarcoma
    c. Gastrointestinal stromal tumors (GIST)
    d. Undifferentiated pleomorphic sarcoma
    e. Known translocation-related sarcomas
    f. Radiation induced sarcoma
    g. Osteosarcoma
    h Chondrosarcoma
6. Mesothelioma
    a. Pleural mesothelioma
    b. Peritoneal mesothelioma
7. Cholangiocarcinoma/cancer of the biliary tract
8. Thyroid cancer
    a. Anaplastic thyroid cancer
    b. Follicular or papillary thyroid cancer
    c. Medullary thyroid cancer and mixed medullary and follicular or papillary thyroid cancer
9. Gastric adenocarcinoma/adenocarcinoma of the gastro-esophageal junction
10. Other solid tumors – closed to recruitment from Protocol Version 4 onwards
11. Malignant germ cell tumors
12. ER+/HER2- metastatic breast cancer with known high mutation load (>100 mutations) by local test

13. Thymoma and thymic cancer
    a. Thymoma
    b. Thymic cancer
14. Gastroenteropancreatic (GEP) and lung neuroendocrine tumors (NETs)
    a. Low and intermediate grades (typical or atypical carcinoid)
    b. Poorly differentiated grade (excluding SCLC)
15. Known HPV induced squamous cell carcinomas
    a. Head and neck
    b. Penile cancer
    c. Vaginal cancer / vulvar cancer
    d. Anal cancer
16. Known MSI high or MMR deficient tumors (excluding colorectal and gastric cancers)

Full details of the histological types / subtypes and markers mandated for each cohort are described in Section 4.1.3.

In addition, only patients whose tissue is available for biomarker assessment testing will be eligible.

Enrolled patients will receive Atezolizumab at a fixed dose of 1200 mg administered intravenously on the first day of each cycle. One cycle of therapy will be defined as 21 days (± 3 days).

Patients treated with Atezolizumab who have no post-baseline tumor assessment (per protocol mandated timelines), and enrolled patients who do not receive any dose of Atezolizumab will be replaced.

Atezolizumab treatment may be continued as long as patients are experiencing clinical benefit, as assessed by an investigator, in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available) and clinical status.

Patients will be permitted to continue Atezolizumab treatment after RECIST v1.1 criteria (or disease-specific criteria for patients with prostate cancer [Appendix 6] and malignant pleural mesothelioma [Appendix 7]) for progressive disease are met if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the Investigator
- Absence of symptoms and signs (including worsening of laboratory values, e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease

- 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 treated with Atezolizumab in whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the Investigator if they continue to meet the above criteria.

If an individual patient continues to experience clinical benefit beyond 2 years of radiologic progressive disease, it lies within the discretion of each investigator to continue study treatment based on a positive risk benefit assessment by the investigator.

The primary objective of this study is to evaluate Investigator-determined non-progression rate (NPR) at 18 weeks in the individual cohorts using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7). Secondary efficacy variables (including ORR, BOR, CBR, DOR, TTP and PFS) will be recorded using RECIST, v1.1, (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7), and modified RECIST (see Appendix 3).

Safety will be monitored by assessing AEs, SAEs, AEs of special interest (AESIs), laboratory findings and electrocardiogram. The National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE, v4.0) will be used to quantify the intensity of AEs occurring during treatment. Incidence, type and severity of AEs, SAEs, incidence of AEs and SAEs leading to Atezolizumab interruption or discontinuation and cause of death will be reported. In addition, to characterize the immunogenic potential and PK of Atezolizumab, blood samples will be taken at various time points before and after study treatment administration (see Appendix 2 for a detailed description of the assessments).

This study will also have an exploratory analysis examining biomarkers. These analyses will be conducted on archival tissue specimens (required for patient inclusion), as well as prospectively-collected plasma/blood samples and freshly obtained tumor specimens. Collected samples will be analyzed at a central laboratory for PD-L1 expression, as well as other potential markers, to assess relationships between biomarker expression and patient outcomes including, but not limited to, response and disease progression.

All patients will be monitored for survival for a minimum period of 24 months after the last patient has been enrolled in each cohort or until all patients have died, withdrawn consent or are lost to follow up, or the Sponsor decides to end the study, whichever occurs first. Survival follow-up information will be collected via clinic visits, telephone

calls and/or review of patient medical records approximately every 3 months from study treatment discontinuation until patient death, loss to follow-up, withdrawal of consent or until the study is terminated by the Sponsor. Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments approximately every 3 months until death, disease progression, initiation of further systemic cancer therapy or study closure, whichever occurs first.

Enrollment in this study will be based on Simon's optimal two-stage design (Simon 1989). Accordingly, 12 fully-evaluable patients will be enrolled in each cohort in the first stage. If 3 or more of these patients exhibit non-progressive disease at the end of Stage I, then an additional 13 fully-evaluable patients will be enrolled in Stage II. Thus, approximately 725 patients are expected to participate in the study. However, if positive efficacy signals are observed in any of the other cohorts that include different tumor types or in a specific subgroup of patients within other cohorts (e.g. biomarker positive subgroup), the Sponsor in discussion with the Steering Committee may decide to extend the enrolment of the individual tumor type or subgroup of patients based on methodology explained in the Determination of Sample Size (Section 6.1).

Please refer to the Schedule of Assessments (Appendix 1) for more detail on the timing and nature of assessments to be carried out in this study.

3.2 END OF STUDY

The end of cohort will occur when all patients have been followed for survival for a minimum of 24 months after the last patient has been enrolled in the cohort or until all patients have died, withdrawn consent or are lost to follow up, or the Sponsor decides to end the study, whichever occurs first.

Recruitment/enrollment in any of the cohorts may present some challenges. Therefore, a permanent stop rule may be applied if the recruitment rate is too low after any of the individual cohorts have been completely enrolled, which could result in stopping further enrolment in some of the remaining cohorts (Section 4.6.3). This decision will be made by the Sponsor based on regular review of the recruitment rate. After a cohort has been opened for at least 4 months, it may be closed early if the recruitment is less than 2 patients per month on average from the opening of the cohort. The overall end of study will occur when the end of cohort has occurred for all of the individual cohorts, as described above.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Dose and Schedule

The fixed dose of 1200 mg (equivalent to an average body weight−based dose of 15 mg/kg) was selected on the basis of both nonclinical studies 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: 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 efficacy, safety, PK and immunogenicity data in humans. Thus, anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg. The MTD of Atezolizumab was not reached and no DLTs have been observed at any tested dose (0.03–20 mg/kg). Preliminary PK data from Study PCD4989g suggest that Atezolizumab exhibits pharmacokinetics that are both linear and consistent with typical IgG1 antibodies at doses ≥ 1 mg/kg. Patients dosed at 10-, 15-, and 20-mg/kg have maintained the expected target trough levels (6 µg/mL), despite the detection of some ATAs. To date, no relationship between the development of measurable ATAs and safety or efficacy has 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} 6 µg/mL and further safeguard against both interpatient variability and the potential effect of ATAs that might lead to subtherapeutic levels of Atezolizumab at the 10-mg/kg q3w dose level (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.

Finally, simulations do not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight (Bai et al. 2012). On the basis of the preceding analysis, a fixed dose of 1200 mg has been selected in this study (equivalent to an average body weight-based dose of 15 mg/kg).

Selection of an every-21-day dosing interval is supported by this preliminary pharmacokinetics evaluation and allows for a convenient integration with common chemotherapeutic regimens.

All available PK, ATA, safety, and efficacy data for Atezolizumab will continue to be evaluated as described above to support the proposed 1200-mg fixed dose.

3.3.2 Rationale for Patient Population and Analysis Groups

This study will assess the safety and efficacy of Atezolizumab in patients with a diverse array of advanced solid tumors. An increasing pool of data indicates that anti-PD-L1 therapy, by reinvigorating tumor-specific T-cell activity, has the potential to boost antitumor immunity against multiple cancers. A Phase I dose-escalation study of 207

patients treated with the anti-PD-L1 antibody BMS-936559 reported an ORR of approximately 17% in patients with melanoma, 12% in patients with renal cell carcinoma, 10% in patients with NSCLC and 6% in patients with ovarian cancer (Brahmer et al. 2012). Several durable responses were observed in this study, with partial responses and complete responses ongoing at over 18 months.

Similarly, in the ongoing Study PCD4989g, Atezolizumab exhibited efficacy in a variety of solid tumors, including NSCLC, bladder cancer and RCC (Section 1.2.4.1).

Although the response rate appears to correlate with PD-L1 expression in Phase I study PCD4989g, responses per RECIST v1.1 and prolonged stable disease have been observed in the subgroup of patients with low PD-L1 expression. Therefore, this trial will include patients with all levels of PD-L1 expression.

In order to maximize potential patient benefit, substantial effort has been made to choose patients for enrolment who are most likely to benefit from Atezolizumab therapy. To do so, academic experts were queried and relevant published literature was reviewed to identify solid tumors that: 1) were likely to have high immunogenicity and, thus, to respond to therapies that increase antitumor immunity; and 2) had published evidence indicating a direct role of PD-L1 expression on clinical outcomes, including prognosis and treatment outcomes. Further detail on the rationale for choosing the included tumors in this study are presented in Section 1.3.1.

3.3.3 Rationale for Biomarker Assessments

The development of advanced cancers is thought to occur by a complex, multi-step process involving diverse cell-biological functionalities. These include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, reprogramming of energy metabolism, evading immune destruction and activating invasion and metastasis (Hanahan and Weinberg 2011). Therefore, all patients may not be equally likely to benefit from treatment with Atezolizumab. Thus, this study will collect various tumor and blood samples at baseline in an effort to identify those patients with advanced solid tumors who respond most actively to Atezolizumab. Furthermore longitudinal sampling of both tumor and blood may help identifying changes induced by Atezolizumab and might help to understand potential escape mechanisms. Analysis and comparison of tumor and blood samples might additionally help to (further) develop diagnostic tools and techniques.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The primary efficacy outcome measure for this study is as follows:

- Non progression rate (NPR) at 18 weeks is defined as the percentage of patients with CR, PR or SD at 18 weeks, as determined by the Investigator using RECIST,

v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7). Patients treated with Atezolizumab who have no post-baseline tumor assessment (per protocol mandated timelines), and enrolled patients who did not receive any dose of Atezolizumab will be replaced

The secondary efficacy outcome measures for this study are as follows:

- Non progression rate (NPR) at 24 weeks is defined as the percentage of patients with CR, PR or SD at 24 weeks, as determined by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7). Patients treated with Atezolizumab who have no post-baseline tumor assessment (per protocol mandated timelines), and enrolled patients who did not receive any dose of Atezolizumab will be replaced
- Overall response rate (ORR) is defined as the proportion of patients with a CR or PR, as assessed by the Investigator using RECIST v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7)
- Best overall response (BOR) is defined as the proportion of patients with the best response obtained throughout the trial, as determined by the Investigator using RECIST v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7)
- Clinical benefit rate (CBR) is defined as the proportion of patients whose BOR, as determined by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7), is either CR, PR or SD lasting for at least 6 weeks
- Duration of objective response (DOR) is defined as the time from the first occurrence of a documented objective response to the time of progression, as determined by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7), or death from any cause, whichever occurs first. For patients who do not die or experience disease progression before the end of the study or who are lost to follow-up, duration of objective response will be censored at the day of the last tumor assessment
- Progression-free survival (PFS) is defined as the time from the first day of study treatment to the first occurrence of disease progression, as determined by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7), or death from any cause, whichever occurs first. A patient without a PFS event will be censored at the time of the last evaluable tumor assessment. Patients with no tumor assessment after the baseline visit will be censored at the time of the first day of study treatment plus 1 day

- Time to progression (TTP) is defined as time from the first day of study treatment to the first occurrence of progressive disease, as determined by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7), or death due to reason of disease progression, whichever occurs first. Patients who have not progressed or died due to disease progression at the time of study completion or who are lost to follow-up will be censored at the date of the last evaluable tumor assessment. Patients with no tumor assessment after the baseline visit will be censored at the time of the first day of study treatment plus 1 day
- Overall survival (OS) is defined as the time from the first day of study treatment to death from any cause. Patients for whom no death is captured on the clinical database will be censored at the most recent date they were known to be alive

NPR at 18 and 24 weeks, ORR, BOR, CBR, DOR, PFS and TTP will also be determined by the Investigator using modified RECIST (see Appendix 3).

3.4.2 Safety Outcome Measures

The safety and tolerability of Atezolizumab will be assessed using the following safety outcome measures:

- Incidence, nature, and severity of adverse events graded according to the NCI CTCAE, v4.0
- Number of cycles and dose intensity
- Incidence of anti-Atezolizumab antibodies and the potential correlation with pharmacokinetics and safety parameters

3.4.3 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Maximum serum Atezolizumab concentration (C_{max}) after infusion on Day 1 of Cycle 1
- Minimum serum Atezolizumab concentration (C_{min}) prior to infusion on Day 1 of Cycles 1, 2, 3, 4, 8 and every eight cycles thereafter and at study termination

3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Status of PD-L1 expression and other exploratory biomarkers (e.g. but not limited to protein and genetic markers) in archival and/or freshly obtained tumor tissues and plasma collected pre-treatment and during treatment with Atezolizumab
- Association of PD-L1 expression and other exploratory biomarkers (e.g. but not limited to protein and genetic markers) with disease status and/or response or resistance to Atezolizumab
- Status of exploratory biomarkers in plasma (including but not limited to genetic markers and cytokines such as IFN-gamma) collected pre-treatment and during treatment/at progression/study discontinuation with Atezolizumab

Association of exploratory biomarkers in plasma with disease status and/or response or resistance to Atezolizumab, tumor immunobiology or tumor type

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Ability to comply with protocol
3. Male or female, 18 years of age or older.
4. Histologically documented solid tumors that are advanced (i.e. Stages III or IV disease) and:
   - meet one of the cohort specifications in Section 4.1.3
   - have progressive disease at study entry
   - have received at least one line of prior systemic therapy or for which alternative therapy does not exist which is known to prolong survival.
5. Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (preferred) or, in exceptional cases, 15 freshly cut and unstained slides, with an associated pathology report (in local language), for central testing. Detection of tumor in the provided block (or slide) needs to be confirmed by the central pathology laboratory prior to study enrollment.
   - Only tissue from core needle, punch or excisional biopsy sample collection will be accepted. For core-needle biopsy specimens, at least three cores should be submitted for evaluation. Fine-needle aspiration, brushing, bone tissue, and lavage samples are not acceptable
   - Patients who do not have tissue specimens meeting eligibility requirements must undergo a biopsy during the screening period. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions
6. Measurable disease as defined by RECIST, v1.1. (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7)
7. ECOG Performance Status of 0 or 1
8. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 3 days prior to the first study treatment (Cycle 1, Day 1):
   - Absolute neutrophil count (ANC) ≥ 1500 cells/µL (without granulocyte colony-stimulating factor support within 2 weeks before Cycle 1, Day 1)

- Lymphocyte count ≥ 500/μL
- White blood cell counts > 2500/μL
- Platelet count ≥ 100,000/μL (without transfusion within 2 weeks before Cycle 1, Day 1)
- Hemoglobin ≥ 9.0 g/dL (patients may be transfused or receive erythropoietic treatment to meet this criterion)
- Serum bilirubin < 1.5 × upper limit of normal (ULN), with the following exception:

  Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled
- Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase ≤ 2.5 × ULN, with the following exceptions:

  Patients with liver involvement: AST and/or ALT ≤ 5 × ULN

  Patients with liver or bone metastases: alkaline phosphatase ≤ 5 × ULN
- Serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 30 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:
  (140 − age) × (weight in kg) × (0.85 if female)/72 × (serum creatinine in mg/dL)
- International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN. This applies only to patients who do not receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation (such as low−molecular weight heparin or warfarin) should be on a stable dose
- Serum albumin level > 3.2 g/dL

9. 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
10. For female patients of childbearing potential, agreement (by patient) to use a highly effective form(s) of contraception that results in a low failure rate (< 1% per year) when used consistently and correctly, and to continue its use for 5 months after the last dose of Atezolizumab. 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. Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drug.
11. Life expectancy > 3 months

4.1.2 Exclusion Criteria

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

1. Malignancies other than disease under study within 5 years prior to Cycle 1 Day 1, 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 surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
2. Uncontrolled tumor-related pain
   - Patients requiring pain medication must be on a stable regimen at study entry
   - Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment
   - Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment
3. 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
4. Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or Ca >12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab
   - Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible
   - Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while on study
5. History of treated asymptomatic or symptomatic CNS metastasis or presence of CNS metastases as determined by CT scan or MRI evaluation during screening or at prior radiographic assessments.
6. Leptomeningeal disease
7. 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 Cycle 1, Day 1
8. Any approved anticancer therapy, including chemotherapy, hormonal therapy or radiotherapy, within 3 weeks prior to initiation of study treatment; however, the following are allowed:
   - Hormone-replacement therapy or oral contraceptives
   - Palliative radiotherapy for bone metastases > 2 weeks prior to Cycle 1, Day 1

9. Acute toxicities from previous therapy that have not resolved to Grade ≤ 1, except for alopecia
10. Pregnant and lactating women
11. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)
12. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to Cycle 1, Day 1, unstable arrhythmias or unstable angina
    - Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded
    - Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate
13. Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia or severe pneumonia
14. Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1
    - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible
15. Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study
16. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
17. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or to any component of the Atezolizumab formulation
18. 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 anti-phospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 5 for a more comprehensive list of autoimmune diseases)
    - Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible
    - Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen are eligible

- Patients with eczema, psoriasis, 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:
    - Rash must cover less than 10% of body surface area (BSA).
    - Disease is well controlled at baseline and only requiring low potency topical steroids.
    - No acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high-potency or oral steroids)

19. Prior allogeneic bone marrow transplantation or prior solid organ transplantation
20. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan
    - History of radiation pneumonitis in the radiation field (fibrosis) is permitted
21. Any other diseases, metabolic dysfunction, physical examination finding or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complication
22. Positive test for HIV
23. Patients with active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C
    - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible
    - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA
24. Active tuberculosis
25. Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1
26. Administration of a live, attenuated vaccine within 4 weeks prior to Cycle 1, Day 1 or anticipation that such a live attenuated vaccine will be required during the study
    - Influenza vaccination should be given during influenza season only (example: approximately October to March in the Northern Hemisphere). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study treatment or within 5 months after the last dose of atezolizumab
27. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti−PD-1, or anti−PD-L1 therapeutic antibodies

- Patients who have received prior treatment with anti−CTLA-4 may be enrolled, provided at least 5 half-lives (approximately 75 days) have elapsed from the last dose of anti-CTLA-4 to the first dose of Atezolizumab and there was 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 interferon-alpha (IFN-α) and interleukin-2 (IL-2) within 4 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1
29. Treatment with an investigational agent within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer)
30. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor [TNF] agents) within 2 weeks prior to Cycle 1, Day 1, or anticipated requirement for systemic immunosuppressive medications during the trial
    - 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
    - The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, low-dose supplemental corticosteroids for adrenocortical insufficiency and topical steroids for cutaneous diseases are allowed

4.1.3 Cohort Specifications

Any cancer where the primary tumor is not clearly identified is not eligible for the cohorts described below (cohorts 1 to 9 and 11 to 16).

Cohort	Included histological types / subtypes and marker specifications	Excluded histological types / subtypes and excluded conditions
1 Cervical cancer	- squamous cell carcinoma - adenocarcinoma - adenosquamous carcinoma - non-squamous carcinoma of the cervix	- small cell carcinoma - sarcomas - adenoid cystic carcinoma - adenoid basal carcinoma - undifferentiated carcinoma
2 Nasopharyngeal cancer	- non-keratinizing carcinoma - keratinizing squamous cell carcinoma - basaloid squamous cell carcinoma of the nasopharynx	- nasopharyngeal papillary adenocarcinoma - salivary gland carcinomas - squamous cell carcinoma of the head and neck

Cohort	Included histological types / subtypes and marker specifications	Excluded histological types / subtypes and excluded conditions
3 MSI-H or MMR-deficient colorectal cancer	- adenocarcinoma of the colon (including cecum and sigmoid) or the rectum - MSI-H- or MMR-deficient tumor with details of results available prior to inclusion: - tissue tested (tumor / non-tumor) - type of test performed - summary of all identified mutations	- any histology other than adenocarcinoma - MSI or MMR test: - no test performed - no test results provided - MSI low or MMR proficient
4 Known BRCA 1/2 mutated cancer 4a. Ovarian cancer 4b. Breast cancer	4a. Epithelial ovarian, fallopian tube or primary peritoneal cancer 4b. Adenocarcinoma of the breast with BRCA 1 and/or BRCA 2 mutation - with details of results available prior to inclusion: - type of test performed - summary of identified mutations	4a: Tumors of malignant mixed mesodermal or mucinous subtypes, or non-epithelial ovarian cancers (e.g. Brenner tumors, sex-cord tumors) 4b: Any histology other than adenocarcinoma BRCA test: - no BRCA mutation identified - no test performed - no test results provided
5 Sarcoma 5a. Liposarcoma 5b. Leiomyosarcoma 5c. Gastrointestinal stromal tumor (GIST) 5d. Undifferentiated pleomorphic sarcoma 5e. Known translocation related sarcoma 5f. Radiation induced sarcoma 5g. Osteosarcoma 5h. Chondrosarcoma	5a. Liposarcoma 5b. Leiomyosarcoma 5c. stromal tumor of the esophagus, stomach, small intestine, colon and rectum 5d. undifferentiated pleomorphic sarcoma 5e. any sarcoma type (including existing cohorts) with details of the following results available prior to inclusion: - tissue tested and type of test performed - translocation detected 5f. Any sarcoma type with a documented history of prior irradiation that includes: - treatment with therapeutic irradiation at least 1 year prior to development of sarcoma - sarcoma arising within the field of previous therapeutic irradiation - differing histology between the sarcoma and the tumor that required radiotherapy 5g. Osteosarcoma 5h. Chondrosarcoma	- all sarcoma types not explicitly listed in cohorts 5a to 5h 5c: Any location other than the esophagus, stomach, small intestine, colon and rectum 5e: Assessment of translocation: - no translocation identified - chromosome abnormalities or mutations other than translocations - no test performed - no test results provided 5f: No prior irradiation or irradiation within less than 3 years prior to study entry - no tumor within the previously irradiated field or no clear record of the previously irradiated field - same histology as a prior tumor or no details on the histology of prior cancers 5g: and 5h: Ewing sarcoma

Cohort	Included histological types / subtypes and marker specifications	Excluded histological types / subtypes and excluded conditions
6 Mesothelioma 6a. Pleural mesothelioma 6b. Peritoneal mesothelioma	6a. Pleural mesothelioma 6b. Peritoneal mesothelioma	Any location other than the pleura or the peritoneum
7 Cholangiocarcinoma /cancer of the biliary tract	Adenocarcinoma of the intrahepatic, perihilar, and distal extrahepatic bile ducts	Any tumor originating outside of the bile ducts Any histology other than adenocarcinoma
8 Thyroid cancer 8a. Anaplastic 8b. Differentiated 8c. Medullary and mixed medullary	8a. Anaplastic 8b. Follicular or papillary 8c. Medullary or mixed medullary and follicular or papillary carcinoma of the thyroid	- any location other than the thyroid - poorly differentiated thyroid carcinoma - and any other histology that is not a carcinoma
9 Gastric adenocarcinoma /adenocarcinoma of the gastro-esophageal junction (GEJ)	- adenocarcinoma of the - stomach - lower esophagus up to 5 cm above the GEJ	- squamous cell carcinoma and - any histology other than adenocarcinoma, - adenocarcinoma located in the esophagus more than 5 cm above the anatomic GEJ or in the duodenum
11 Malignant germ cell tumors	Specific to germ cell testicular tumors: - intratubular germ cell neoplasia, unclassified type - seminoma (including cases with syncytiotrophoblastic cells) - spermatocytic seminoma Specific to germ cell ovarian tumors - dysgerminoma Common histologies - embryonal carcinoma - yolk sac tumor - choriocarcinoma - teratoma (mature, immature, with malignant component) - tumors with more than one histological type	- epithelial tumors of the ovary and peritoneum - sex cord/gonadal stromal tumors, - carcinoma /adenocarcinoma, - trophoblastic tumors

Cohort	Included histological types / subtypes and marker specifications	Excluded histological types / subtypes and excluded conditions
12 ER+/HER2- breast cancer with high mutation load (>100 mutations) by local test	- adenocarcinoma of the breast - Mutational status - > 100 mutations detected - summary of results (exact number of mutations) available prior to inclusion and report available upon request - type of test performed and location of tested tumor tissue - ER positive and HER2 negative with test results available prior to inclusion	-any histology other than adenocarcinoma - assessment of mutational load - mutations load ≤ 100 - no test performed -results of test not available - ER and HER2 test: - ER negative and / or HER2 positive - no test performed - no test results provided
13 Thymoma and thymic cancer	13 a. all subtypes of thymoma 13 b. all subtypes of thymic carcinoma	- Lipoadenoma - Neuroendocrine epithelial tumors - any other tumor that is not a thymoma or thymic carcinoma
14 Gastroenteropancreatic (GEP) and lung neuroendocrine tumors (NETs) 14a. Low and intermediate grade (typical or atypical carcinoid) 14b. Poorly differentiated grade (excluding SCLC)	14 a. Carcinoid NET (atypical or not) of any GEP or lung locations 14 b. Poorly differentiated grade of any GEP or lung locations (excluding SCLC)	- Small cell carcinoma of the lung (SCLC) - locations other than gastroenteropancreatic or pulmonary
15 Known HPV induced squamous cell carcinoma	Squamous cell carcinoma of: 15 a. Oropharynx, oral cavity, hypopharynx, or larynx 15 b. Penis 15 c. Vagina or vulva 15 d. Anal canal - with HPV16 detected on tumor tissue for oropharynx, oral cavity, hypopharynx or larynx or with HPV16 or 18 detected on tumor tissue for penile, vaginal, vulvar and anal carcinomas - using ISH or PCR-based test - with details of test results (summary of identified serotypes) available prior to inclusion	- Any non-squamous histology Depending on tumor types, this may include (without being limited to): - adenocarcinomas, - sebaceous, clear cell, basal cell, small cell and undifferentiated carcinomas - 15a. tumor located in the nasopharynx or the salivary glands (any histology) - HPV test: - No HPV detection on tumor tissue - HPV test not performed on tumor tissue - determination of HPV status not performed by ISH or PCR-based tests - no test results provided

Cohort	Included histological types / subtypes and marker specifications	Excluded histological types / subtypes and excluded conditions
16 Known MSI- high or MMR deficient solid tumors, excluding colorectal and gastric cancers	- any solid tumor that is not originating in the colon, the rectum, the stomach or the gastrointestinal junction - MSI-H- or MMR-deficient tumor with detailed test results available prior to inclusion: - tissue tested (tumor / non-tumor) - type of test performed - summary of all identified mutations	- any tumor originating in the colon, the rectum, the stomach or the gastrointestinal junction - MSI or MMR test: - no test performed - no or incomplete test results - MSS or MMR proficient

The WHO Classification of Tumours will be used as a reference - http://publications.iarc.fr/Book-And-Report-Series/Who-Iarc-Classification-Of-Tumours

For cohort 16, known MSI-H/MMR-deficiency will take precedence over histological subtype in patient cohort assignment.

If the Sponsor identifies that a patient has not been assigned to the right cohort, this patient can be re-assigned to the adequate cohort.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This will be an open-label, unblinded trial. All patients will receive intravenous Atezolizumab at a fixed dose of 1200 mg q3w.

4.3 STUDY TREATMENT

4.3.1 Atezolizumab Formulation, Packaging, and Handling

The Atezolizumab drug product will be provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20.0 mL (1200 mg) of Atezolizumab solution, but may contain more than the stated volume to enable delivery of the entire 20.0 mL volume. The Atezolizumab drug product is formulated as 60 mg/mL Atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

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

For further details, see the Atezolizumab Pharmacy Manual and Investigator's Brochure.

4.3.2 Atezolizumab Dosage, Administration, and Compliance

The dose of Atezolizumab in this study will be 1200 mg administered by intravenous infusion every 3 weeks (21 [± 3] days).

Administration of Atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

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

The initial dose of Atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes.

For first infusion of study treatment, the patient's vital signs must be determined within 60 minutes before the infusion; during, and after the infusion if clinically indicated. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and at the end of the infusion, if clinically indicated.

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

No premedication will be allowed for the first dose of Atezolizumab. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The management of infusion-related reactions will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) infusion-related event, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate
- In the event that a patient experiences a moderate infusion-related event (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the patient should have his or her infusion immediately interrupted and should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the infusion-related event
- For severe or life-threatening infusion-related events (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-

threatening infusion-related events will not receive further infusion and will be further managed as clinically indicated until the event resolves

For anaphylaxis precautions, see Appendix 4.

Guidelines for dosage modification, treatment interruption or discontinuation, and the management of specific adverse events are provided in Section 5.1.3 and the Atezolizumab Investigator's Brochure.

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

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

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (Atezolizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

4.3.4 Post-Trial Access to Atezolizumab

The Sponsor will offer post-trial access to the study drug (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 study drug after the end of the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug 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 study drug after the end of the study if any of the following conditions are met:

- The study drug 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 study drug or data suggest that the study drug is not effective for the cohort of advanced solid tumor into which the patient had enrolled
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for the cohort of advanced solid tumor into which the patient had enrolled
- Provision of study drug 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

Patients may also take part in an extension study if the patient is still benefiting from treatment (defined as no registered PD) at the time of planned Last Patient Last Visit date. If the extension study is not set-up in time for the patient to roll over by the planned protocol LPLV date, nor is there a Post-Trial Access Program available, the patient can continue treatment in the study until the extension study is opened at the patient's site. During the interim period between LPLV and a patient rolling over to the extension study, only safety data (AE including SAE and AESI) will continue to be collected in the eCRF. Other assessments (e.g. tumor assessment) can be performed as per standard of care.

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit.

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine and/or famotidine or another H2 receptor antagonist, as per standard practice (for sites outside the United States, equivalent medications may be substituted per local 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 β2-adrenergic agonists).

Systemic corticosteroids and tumor necrosis factor−α inhibitors may attenuate potential beneficial immunologic effects of treatment with Atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician after consultation with the Medical Monitor. The use of inhaled corticosteroids for COPD and mineralocorticoids (e.g., fludrocortisone) and low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as an appetite stimulant is acceptable while the patient is enrolled in the study.

Colony-stimulating factors, such as granulocyte colony-stimulating factor and erythropoietin, should only be used according to the ASCO and ASCO/ASH guidelines, respectively (Smith et al. 2006; Rizzo et al. 2010). Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study treatment, or within 5 months after the last dose of Atezolizumab, but may receive inactivated vaccine.

Patients who use hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer, oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy (see Section 4.1.2) should continue their use.

Females of reproductive potential should use a highly effective means of contraception.

All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

4.4.2 Prohibited Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents or herbal therapy (except for maintenance therapies outlined in Section 4.1.1, and 4.1.2)
  - After Cycle 2, certain forms of radiotherapy may be considered for pain palliation if patients are deriving benefit (e.g., treatment of known bone metastases). Please contact the Medical Monitor prior to initiating radiotherapy.
  - Patients experiencing a mixed response requiring local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue study treatment. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression. Such cases must be discussed with and approved by the Sponsor

- 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 on study is allowed at the discretion of the investigator, provided that there are no known interactions with any study treatment. As noted above, herbal therapies intended for the treatment of cancer are prohibited
- Patients who are receiving a receptor activator of nuclear factor kappa B ligand inhibitor (denosumab) prior to enrollment must be willing and eligible to receive a bisphosphonate instead while on study; denosumab could potentially alter the activity and the safety of Atezolizumab

Patients should not receive any live, attenuated vaccine (e.g., FluMist®) at any time during the study while the patient is receiving Atezolizumab and for a period of 5 months after the discontinuation of Atezolizumab.

Patients are not allowed to receive immunostimulatory agents, including but not limited to interferon (IFN)-α, IFN-γ, or IL-2, during the entire study. These agents, in combination with Atezolizumab, could potentially increase the risk for autoimmune conditions.

Patients should also not receive immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of Atezolizumab. Systemic corticosteroids and anti−TNF-α agents may attenuate potential beneficial immunologic effects of treatment with Atezolizumab, but may be administered at the discretion of the treating physician. If feasible, alternatives to these agents should be considered.

In addition, all patients should not receive other immunostimulatory agents for 10 weeks after the last dose of Atezolizumab.

The above list of medications is not necessarily comprehensive. The investigator should consult the prescribing information for any concomitant medication and contact the Medical Monitor if questions arise regarding medications not listed above.

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the Schedule of Assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before Cycle 1 Day 1. 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, Disease History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including but not limited to cancer histology, grade, stage, prior cancer therapies and procedures, smoking history, asbestos exposure). The following must be reported: results of HPV determination on tumor tissue using in situ hybridization (ISH) or a polymerase chain reaction (PCR)-based test (results from existing tests must be available at baseline for patients who are candidates for the HPV induced tumors cohort), results of determination of microsatellite instability (MSI) or MMR deficiency on tumor tissue and corresponding normal tissue per institution's standard practice (results from existing tests must be available at baseline for patients who are candidates for the MSI-high or MMR deficient tumor cohorts), results of BRCA mutations (results from existing tests must be provided at baseline for patients candidates for the BRCA positive breast or ovarian cancer cohort), results of ER and HER2 status and documentation of number of mutations detected by local test (results from existing tests are mandatory at baseline for patients who are candidates for the breast cancer with > 100 mutations cohort), results of EBV determination on tumor tissue per local institutional practice (nasopharyngeal and gastric cancer cohorts). Associated syndromes, *Helicobacter pylori* infection, and relevant mutations (such as RET/PTC, PTEN, BRAF, RAS, PI3KCA, TP53, etc.), reproductive status, 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 must also be reported. A history of pleural or pericardial effusion or of ascites requiring intervention should be entered in the medical history.

An anonymized copy or transcript of screening test results or medical history may be collected by the Sponsor for data interpretation, either for a specific cohort or for specific cases. A review of histopathology may be performed by the Sponsor or their delegates for individual cases or for specific cohorts to ascertain cancer histology - this will be performed using tissue/slides collected for biomarkers.

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

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Height and weight should be measured and recorded in the 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 respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position and temperature.

For first infusion of study treatment, the patient's vital signs must be determined within 60 minutes before the infusion; during, and after the infusion if clinically indicated. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and at the end of the infusion, if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Blood oxygen saturation will be measured at time points specified in the Schedule of Assessments (see Appendix 1) by pulse oximetry.

4.5.5 Tumor and Response Evaluations

Screening assessments must include CT scans (with oral/IV contrast unless contraindicated) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement.

A CT (with contrast) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan (see Section 4.1.2 for CNS-related exclusions).

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 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7) may be used.

For subsequent tumor assessments, procedures should be performed as indicated in Appendix 1. 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). All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation. Response will be assessed by the investigator using RECIST v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7), and modified RECIST criteria (see Appendix 3). The same evaluator should perform assessments if possible to ensure internal consistency across visits.

Computed tomography (CT) scans and other data supporting efficacy measurements may be collected by the Sponsor in case an independent review is required, either for a specific cohort or for specific cases (e.g. to validate responses).

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Local laboratory assessments will include the following:

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count). A manual differential can be done if clinically indicated.
- Serum chemistries (includes BUN, creatinine/creatinine clearance, sodium, potassium, magnesium, chloride, bicarbonate ([if routinely performed on venous blood samples]), calcium, phosphorus, glucose, total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study), ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein and albumin)
- Coagulation (aPTT and INR)
- Serum pregnancy test for women of childbearing potential, including women who have had a tubal ligation; 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 T3, free T4)
- HBV serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen) HBV DNA must be obtained prior to Cycle 1, Day 1 if patient has positive serology for anti-HBc Ab
- C-reactive protein (CRP)
- HCV serology – prior to inclusion only. Patients positive for hepatitis C virus (HCV) antibody must be tested for HCV using RNA polymerase chain reaction
- All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical trial
- Patients with ovarian cancer: CA125 level
- Patients with colon cancer: CEA level
- Patients with prostate cancer: PSA level
- Patients with breast cancer: CA153 level
- Patients with pancreatic cancer: CA 19.9 levels
- Other tumor biomarkers as clinically indicated

- Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:
    - Serum sample for ATA assessment using validated immunoassays (see Appendix 1 and 2 for details)
    - Serum sample for PK assessments using validated immunoassays (see Appendix 1 and 2 for details)
- Plasma samples for biomarkers (see Appendix 1 and 2 for details)

Any remaining samples collected for PK, biomarker assays, and ATAs may be used for exploratory biomarker profiling, identification, and pharmacodynamic assay development purposes and additional safety assessments (e.g., ATA assay), as appropriate.

- Archival or fresh biopsy samples for eligibility:
    - Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (preferred) or, in exceptional cases, 15 freshly cut and unstained slides, with an associated pathology report (in local language), for central testing. Detection of tumor in the provided block (or slide) needs to be confirmed by the central pathology laboratory prior to study enrollment.
    - Only tissue from core needle, punch or excisional biopsy sample collection will be accepted. For core-needle biopsy specimens, at least three cores should be submitted for evaluation. Fine-needle aspiration, brushing, bone tissue, and lavage samples are not acceptable
    - Patients who do not have tissue specimens meeting eligibility requirements must undergo a biopsy during the screening period. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions
- Optional biopsies
    - For patients who have agreed to provide optional tumor tissue samples and have signed the Consent for Optional Biopsies Form.
    - Tumor tissue will be freshly obtained by core needle or excisional/punch biopsy. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.
    - The pre-treatment specimen will be obtained after eligibility criteria have been fulfilled. Alternatively, the pre-treatment biopsy can be replaced by a biopsy which was taken no more than 12 months before Cycle 1, Day 1.

- A subsequent biopsy will then be performed approximately 3 weeks (Cycle 2, Day 1) after the first Atezolizumab administration. (For logistical reasons, the subsequent biopsy may be performed with a time window of 1 week.)

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

Biopsies shall be performed with discernment as this traumatic surgical gesture will not in all cases benefit intrinsically the individual patient, but hypothetically medical research.

4.5.7 Electrocardiograms

Twelve-lead ECG is required at screening and as indicated in Appendix 1. ECGs should be obtained on the same machine whenever possible. Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine position for at least 10 minutes.

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

4.5.8 Samples for Roche Clinical Repository

4.5.8.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) 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 and analysis of RCR 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.

RCR specimens will be used to achieve the following objectives:

- To further 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

4.5.8.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC)

and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.8) will not be applicable at that site.

4.5.8.3 Sample Collection

All blood and tissue samples collected in this study and derivatives thereof will be destroyed no later than 5 years after the date of final closure of the clinical study database. However, patients who enroll in this study will have the option, at the time of enrolment, to consent to RCR sampling to allow the remainder of these samples and derivatives thereof to be stored and used for exploratory research. If the patient provides consent for this optional exploratory research, these samples will be sent to and stored in the RCR and will be destroyed no later than 15 years after the date of final closure of the clinical study database.

These specimens will be used for research purposes to identify biomarkers that are predictive of response to study treatment (in terms of dose, safety, and tolerability) and will help to better understand the pathogenesis, course, and outcome of advanced solid tumors. Specimens for non-inherited biomarker discovery will be single coded like any other clinical sample (labeled and tracked using the patient's study identification number (see Section 8.4 and 4.5.8.4). Genetic specimens will undergo additional processes to maintain confidentiality upon receipt by the RCR (Section 4.5.8.4)

Tumor tissue, plasma samples and derivatives thereof are collected throughout the study for purposes of biomarker assessment (Section 2.4 and Schedule of Assessments [Appendix 1 and 2]). Residual samples will be collected and stored for research purposes, including tumor samples (archival material and freshly obtained biopsies) and plasma samples. Archival tumor tissue blocks from the initial diagnosis will be returned to the site.

The specimens in the RCR will be made available for future biomarker research toward further understanding of study treatment, solid tumors and related diseases, adverse events and toward development of potential associated diagnostic assays. The implementation and use of the RCR specimens is governed by the RCR policy to ensure the appropriate use of the RCR specimens.

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

4.5.8.4 Confidentiality

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described in the section below.

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

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

Patient medical information associated with RCR 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.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study Investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

4.5.8.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form administered at study enrolment will contain a separate section that addresses participation in the RCR. The Investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. 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 participate in the optional RCR research. 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 by completing the RCR Research Sample Informed Consent eCRF.

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

4.5.8.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to RCR research have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the Investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study MO29518 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study MO29518.

4.5.8.7 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice 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. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. 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 RCR samples.

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 must 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 prior to receiving study drug will 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, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment
- Use of another non-protocol anti-cancer therapy (see Section 4.4.2)
- Pregnancy

Atezolizumab treatment may be continued as long as patients are experiencing clinical benefit as assessed by an investigator in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

Patients will be permitted to continue Atezolizumab treatment after RECIST v1.1 (or disease-specific criteria for patients with prostate cancer [see Appendix 6] and malignant pleural mesothelioma [see Appendix 7]) criteria for progressive disease are met if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the Investigator
- Absence of symptoms and signs (including worsening of laboratory values, e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease
- 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 treated with Atezolizumab in whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the Investigator if they continue to meet the above criteria.

If an individual patient continues to experience clinical benefit beyond 2 years of radiologic progressive disease, it lies within the discretion of each investigator to continue study treatment based on a positive risk benefit assessment by the investigator.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Anticancer therapies received after Atezolizumab discontinuation will be collected.

Patients who withdraw from the study prior to receiving study drug will be replaced.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study or any cohort 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 – Recruitment in each cohort will be monitored regularly. After a cohort has been opened for at least 4 months, it may be closed early if the recruitment is less than 2 patients per month on average from the opening of the cohort.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study or close a cohort.

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 and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Atezolizumab (TECENTRIQ®) is approved for the treatment of urothelial carcinoma, NSCLC, small cell lung cancer (SCLC) and triple-negative breast cancer (TNBC). Human experience is currently ongoing and the entire safety profile is not known at this time. The following information is based on results from nonclinical and clinical studies and published data on similar molecules.

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 4.1.2) and close monitoring (as indicated below and in Section 4.5).

Administration of Atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. All adverse events and serious adverse events will be recorded during the trial and for up to 90 days after the last dose of study drug or until the initiation of another anti-cancer therapy, whichever occurs first. To mitigate potential unknown risks, at least in part,

dosing beyond Cycle 1 will be limited to patients who have not developed unacceptable toxicity or disease progression or who have evidence of potential pseudoprogression/tumor immune infiltration. 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.

5.1.1 Risks Associated With Atezolizumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events, specifically the induction or enhancement of autoimmune conditions.

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, and myositis. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome.

Refer to Appendix 8 and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 General Plan to Manage Safety Concerns

5.1.2.1 Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this trial. Results from the nonclinical toxicology studies with Atezolizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were taken into account. Specifically, patients at risk for study-emergent autoimmune conditions or with a prior diagnosis of autoimmune disease, patients with evidence of acute infections, and patients who have received a live-attenuated viral vaccine within 4 weeks of Cycle 1 Day 1 are excluded from the study (see Section 4.1.2 for additional details).

5.1.2.2 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 of Assessments (Appendix 1). Laboratory values must be reviewed prior to each infusion.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Appendix 1 and Appendix 2 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 Sections 5.2.2 and 5.2.3) will be reported in an expedited fashion (see Section 5.4.2).

Patients will be followed for safety for 90 days following their last dose of study drug or until they receive another anti-cancer therapy, whichever comes first.

Patients who have an ongoing study drug−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 Atezolizumab Dose Modification

There will be no dose reduction for Atezolizumab in this study. Patients may temporarily suspend study treatment if they experience adverse events that require a dose to be held. If Atezolizumab is held because of adverse events for > 105 days beyond when the next dose would have been given, then the patient will be discontinued from Atezolizumab treatment and will be followed for safety and efficacy as specified in the Schedule of Assessments (Appendix 1).

If a patient must be tapered off steroids used to treat adverse events, Atezolizumab may be held for additional time beyond 105 days. The acceptable length of interruption will depend on an agreement between the investigator and the Medical Monitor.

Dose interruptions for reason(s) other than adverse events, 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.

5.1.4 Management of Specific Adverse Events

Refer to Appendix 8 and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.8
- 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 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

Non-serious 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 the following:

- The following are confirmed treatment-emergent autoimmune conditions:
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency or hyperthyroidism
- Hepatitis
- Transaminitis: Grade ≥ 2 (AST or ALT > 3 × ULN and bilirubin > 2 × ULN) or

  AST/ALT > 10 × ULN
  - Systemic lupus erythematosus
  - Neurological: Guillain-Barré syndrome, Myasthenia Gravis, Meningoencephalitis
- Events suggestive of hypersensitivity, cytokine release,SIRS (influenza-like illness, systemic inflammatory response syndrome), SIA (systemic inflammatory activation) or infusion-reaction syndromes"
- 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 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected."

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 Section 5.4-5.6.

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events will be reported until 90 days after the last dose of study drug or until they receive another anti-cancer therapy, whichever comes first. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

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

Table 6. Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

[d] Grade 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 or not 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, considering especially 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 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions, 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.

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.3 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.

5.3.5.4 Abnormal Laboratory Values

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

- Change from baseline and one of the following:

- 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 if 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).

5.3.5.5 Abnormal Vital Sign Values

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

- Change from baseline and one of the following:
- 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 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 x baseline value) in combination with either an elevated total bilirubin (> 2xULN) 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 x baseline value in combination with total bilirubin > 2 xULN (of which ≥ 35% is direct bilirubin)
- Treatment-emergent ALT or AST > 3 x 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 a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 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 one of the advanced solid tumors included in this study should be recorded only on the Study Completion/Early Discontinuation 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),

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. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. 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.

During survival follow-up, deaths attributed to progression of one of the advanced solid tumors included in this study should be recorded only on the Survival eCRF.

5.3.5.8 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").

5.3.5.9 Lack of Efficacy or Worsening of the Advanced Solid Tumors Included in This Study

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 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7) and modified RECIST (see Appendix 3). 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.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient 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.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or to perform an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer (including symptoms)

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

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

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events

associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.12 Adverse Events in Individuals Not Enrolled in the Study

If an adverse event inadvertently occurs in an individual not enrolled in the study (e.g., during administration of study drug), the Adverse Event Form provided to investigators should be completed and submitted to the Sponsor or its designee, either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.3.5.13 Infusion related reactions

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (see Section 5.4.2 for further details)
- Non-serious adverse events of special interest (see Section 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

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

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious 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 Serious Adverse Event / Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur After Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until 90 days after the last dose of study drug or until they receive another anti-cancer therapy, whichever comes 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 Drug Safety by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event / Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered 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 to immediately inform the investigator if they become pregnant during the study or within 5 months after the last

dose of study drug. 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 eCRFA pregnancy report will automatically be generated and sent to Roche Drug Safety. 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 the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), 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.

5.4.3.2 Abortions

Any 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).

5.4.3.3 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, the patient withdraws consent or until the patient receives another anti-cancer therapy, whichever comes first. 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. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious 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 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 90 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event / Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators. During survival follow-up, deaths attributed to progression of the advanced solid tumor should be recorded on the Survival eCRF and details should be recorded on the Study Completion/Early Termination eCRF.

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

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

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

- Atezolizumab Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Statistical analyses will be based on patients with the same individual tumor type and may be based on pre-defined cohorts or on sub-cohorts. Furthermore, if during the conduct of the study, a specific subgroup of patients in a cohort/sub-cohort is identified (e.g. a biomarker positive subgroup) then statistical analysis may be performed based on this subgroup of patients. In general, within section 6, the term cohort is used to refer to a group of patients to be analyzed together (whether this is a cohort, a sub-cohort or a subgroup).

The safety population will be the main population for all analyses (demographics, efficacy and safety) unless otherwise stated. For each cohort, the safety population will include all patients who have received at least one dose of study medication.

For each cohort, the intent-to-treat (ITT) population will include all patients enrolled in the study irrespective of whether they have received study medication or not. The ITT population will be used to summarize disposition data.

The evaluation of each cohort at the end of Stage I and Stage II will be based only on data from fully evaluable patients, defined as patients receiving at least one dose of Atezolizumab and having at least one tumor assessment post-baseline (per protocol mandated timelines).

The per-protocol (PP) population will not be defined due to the small number of patients per cohort, but major protocol deviations will be listed.

The study will be analyzed for the primary efficacy variable at the end of Stage I and Stage II. All cohorts will also be analyzed at Week 24 (6months) and at the end of cohort. In case a cohort is closed before reaching 12 patients (e.g., due to accrual problems), data for that cohort will be listed only or pooled with cohort 10. The end of cohort analysis for each cohort will take place when all patients in that cohort have been followed for survival for a minimum of 24 months after the last patient has been enrolled in the cohort or until all patients have died, withdrawn consent or are lost to follow up, or if the cohort is stopped due to safety or efficacy reasons, or the Sponsor decides to end the cohort, whichever occurs first.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size for this phase II study is based on Simon's optimal two-stage design (Simon 1989).

In this Phase II study, an NPR of 20% is a level of activity that is not of interest for further clinical development, whereas an NPR of 40% is of clinical interest. The type I error will be 10% and the study will have 80% power to reject the null hypothesis when the true NPR is 40%.

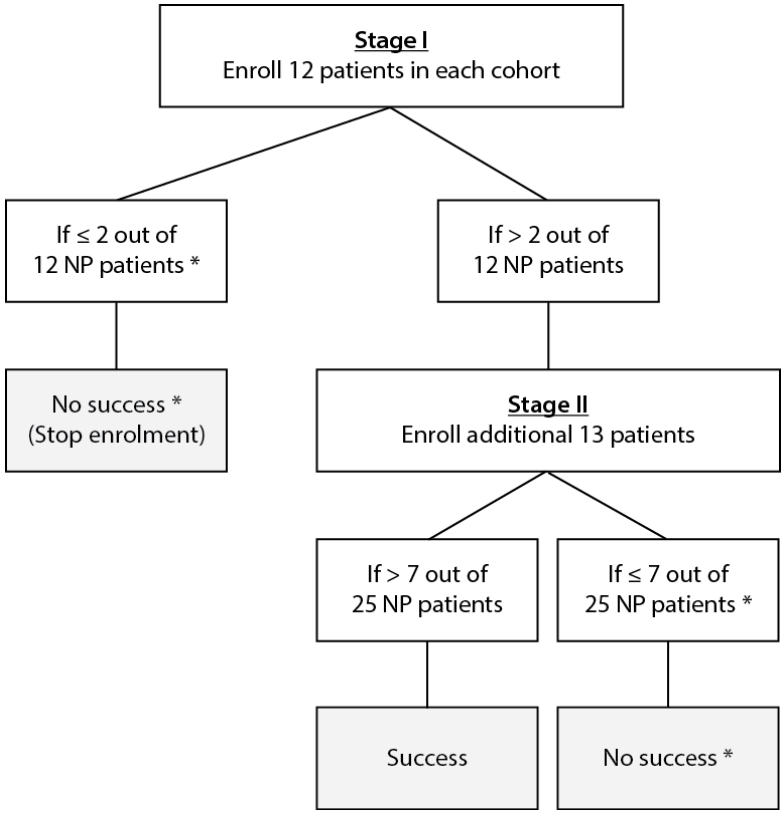
The Simon design in this study requires 12 fully evaluable patients for the first stage. If at the end of the first stage there are 0, 1 or 2 patients with non-progressive disease at Week 18, the enrollment into this cohort will be terminated (or the cohort may be expanded as described below). Otherwise, if more than 2 patients with non-progressive disease are observed at the end of Stage I, an additional 13 fully-evaluable patients may be enrolled into Stage II. The study drug will be considered of clinical interest in this cohort if, at the end of the second stage, there are 8 or more patients with non-progressive disease out of 25 total fully-evaluable patients.

It can be assumed that some patients will not be evaluable for NPR. A patient will be considered evaluable for NPR if they received study drug, have a baseline tumor assessment and at least one tumor assessment post-baseline (per protocol mandated timelines). Thus, more than 25 patients may be needed to be enrolled per cohort to obtain 25 fully-evaluable patients.

The hypotheses and clinical assumptions will be applied to all cohorts individually. Statistical analyses will be based on patients with the same individual tumor type and may be based on pre-defined cohorts or on sub-cohorts

If a clear clinical benefit has been observed for a defined subgroup of patients at the end of Stage I within a cohort that did not meet the criteria for continuation (as described in Section 6.2.1), then enrolment into Stage II might still be allowed in this cohort for this specific subgroup after discussion with the Sponsor and the study Steering Committee. Similarly, if a clear clinical benefit has been observed for a defined subgroup of patients at the end of Stage II within a cohort that did not meet the criteria for success (as described in Section 6.2.2), then enrolment into Stage II might continue in this cohort for this specific subgroup after discussion with the Sponsor and the study Steering Committee.

Figure 2. Sample Size for Each Cohort in Stage I/II



NP = non-progressors; NPR = non-progression rate.
Assumptions: H_0 = NPR 20%; H_1 = NPR 40%; power = 80%; alpha = 10%.
The sample size was estimated using Simon's optimal two-stage design (Simon 1989).
* And no additional clinical benefit in a subgroup.

6.2 STOPPING RULES FOR EACH COHORT

6.2.1 Rules for Stage I

- Enrolment into the cohort may continue into Stage II if more than 2 patients (out of 12) with non-progressive disease at Week 18 are observed at the end of Stage I.

- Enrolment into the cohort will stop at the end of Stage I if the number of patients with non-progressive disease (confirmed or unconfirmed) is 2, 1 or 0 out of 12 patients. However, if the overall patient population does not meet requirements at Stage I, but a clinical benefit is observed in a specific subgroup (e.g. biomarker positive subgroup) of patients, then only this subgroup may be added for Stage I and Stage II to reach numbers as explained in the Sample Size Estimation.

All decisions above will be made by the Sponsor in discussion with the study Steering Committee members.

6.2.2 Rules for Stage II

A study treatment will be considered to be promising for a given cohort in Stage II if:

- there is no unacceptable toxicity, and
- at 18 weeks, there are 8 or more patients with non-progressive disease out of 25 fully-evaluable patients.

If the overall patient population does not meet the Stage II criteria, but a clinical benefit is observed in a specific subgroup (e.g. biomarker positive subgroup) of patients, then Stage II may be expanded to include additional patients from this specific subgroup in order to re-evaluate the Stage II criteria in this patient subgroup.

Additionally, other efficacy endpoints and safety may also be evaluated for a final decision at the end of Stage II.

6.3 SUMMARIES OF CONDUCT OF STUDY

Enrollment criteria exceptions, study treatment administration, reasons for patient discontinuations from the study and duration of follow-up will be described and summarized. Major protocol violations will be listed.

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

This is an open-label phase 2 study that will assess Atezolizumab administered at a single dosage (1200 mg q3w). Consequently, no formal treatment group comparability analyses will be conducted. Demographics and medical history will be summarized for each cohort.

6.5 EFFICACY ANALYSES

6.5.1 Primary Efficacy Endpoint

The primary analysis will be based on NPR at 18 Weeks for each cohort, as assessed by the Investigator using RECIST, v1.1 (except for prostate cancer and malignant pleural mesothelioma) and disease-specific criteria for patients with prostate cancer (see Appendix 6) and malignant pleural mesothelioma (see Appendix 7). This endpoint will be assessed at Stage I and Stage II. The number and percentage of progression-free patients will be presented along with the corresponding Clopper-Pearson 95% confidence interval.

Hypothesis Testing

A Simon optimal two-stage design will be used to test whether Atezolizumab yields a NPR that is of clinical interest. In this Phase II study, an NPR of 20% is a level of activity that is not of interest for further clinical development, whereas an NPR of 40% is of clinical interest.

The study hypotheses are:

- H_0: $\pi \leq \pi_0$
- H_1: $\pi > \pi_1$

Where $\pi_0 = 20\%$ and the assumed NPR under the alternative is $\pi_1 = 40\%$.

The type I error will be 10% and the study will have 80% power to reject the null hypothesis when the true NPR is 40%.

The hypothesis and clinical assumptions will be applied to all cohorts separately. This is an early phase II study and cohorts are independent, hence there will be no adjustment for multiplicity.

6.5.2 Secondary Efficacy Endpoints

The number and percentage of progression-free patients at 24 weeks will be presented along with the corresponding Clopper-Pearson 95% confidence interval. The ORR, BOR and CBR will be analyzed in a similar way.

The time-to-event variables, DOR, PFS, TTP and OS, will be presented graphically using the Kaplan-Meier (KM) approach. Estimates together with the associated 95% confidence interval will be reported for the median and for the 1-year and 2-year survival rates. Duration of response will be summarized only for responders.

NPR, ORR, BOR, DOR, CBR, PFS and TTP as assessed by the by the Investigator using modified RECIST (see Appendix 3) will also be analyzed as described above.

6.6 SAFETY ANALYSES

The safety variables will be summarized for the safety population. All safety variables will be summarized for each cohort.

Safety will be assessed through summaries of AEs, changes in laboratory test results, changes in vital signs and ECGs, and exposure to Atezolizumab.

Verbatim descriptions of AEs will be mapped to thesaurus terms. Adverse event data will be listed by cohort, study site, patient number and study day. Events occurring on or after treatment on Day 1 will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4.0 grade. In addition, SAEs, deaths, and AESIs will be listed separately and summarized. AEs leading to treatment discontinuation will be listed.

Relevant laboratory and vital signs data will be displayed by time, with NCI CTCAE Grade 3 and 4 values identified, where appropriate. Additionally, all laboratory data will be summarized by grade with use of NCI CTCAE v4.0.

Number of cycles and duration on study medication will be summarized by means of frequency tables and descriptive statistics for continuous variable (N, median, inter-quartile range, mean, SD, minimum, maximum).

6.7 PHARMACOKINETIC ANALYSES

Atezolizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized for each cycle at which pharmacokinetics are measured (C_{max} will be reported for Cycle 1 only; C_{min} will be evaluated at Cycles 1, 2, 3, 4, 8, every eight cycles thereafter and at treatment discontinuation). Descriptive statistics will include means, medians, ranges and SDs, as appropriate.

6.8 EXPLORATORY ANALYSES

Exploratory biomarker analyses (e.g. but not limited to protein and genetic markers) in tumor and plasma samples (both baseline and on treatment) will be performed in an effort to understand the association of these markers with study drug response. Biomarkers will be summarized using descriptive statistics: N, medians, inter-quartile range, mean, standard deviation, minimum and maximum for continuous variables and frequency counts and percentages for categorical variables. The relationship between biomarkers and efficacy variables will be assessed using appropriate models. More details will be provided in the Statistical Analysis Plan.

6.9 INTERIM ANALYSES

The study will be analyzed for efficacy at Stage I and Stage II. All cohorts will also be analyzed at Week 24 (6 months) and at the end of cohort for each cohort. No additional interim analysis for efficacy will be performed in this study.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's

standard procedures will be used to handle and process the electronic transfer of these data.

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

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

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. 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 allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

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

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

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

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a

separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

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.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann-La Roche Ltd. Approximately 50 sites globally will participate in the study, and approximately 725 patients will be enrolled.

Enrollment will occur through an IxRS. Central facilities will be used for study assessments throughout the study (e.g., PDL1 testing, ATA and PK analyses). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

A Steering Committee will be the advisory committee, and study status will be discussed at an ongoing basis.

Global CRO will support coordination and medical monitoring activities.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

https://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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APPENDICES

Appendix 1 Schedule of Assessments

	Screening[1]	Treatment (All cycles, unless otherwise indicated) [2]	Treatment discontinuation visit	Follow-Up	End of Study Visit
Day (Window)	Days -35 to -1	Day 1 (± 3 days for cycles ≥ 2)	≤ 30days after last dose	Every 3 months from study treatment discontinuation (+/- 30 days)	24 months
Informed consent [1]	X				
Review of eligibility criteria	X				
Medical history and demographics [3]	X				
Cancer history [4]	X				
Concomitant medications [5]	X	X	X		
Tumor assessment RECIST 1.1 and modified RECIST per Appendix 3 [6]	X	Every 6 weeks, ± 5 days (2 cycles) for the first 24 weeks and every 12 weeks, ± 5 days (4 cycles) thereafter until loss of clinical benefit, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first			
Brain MRI/CT Scan with contrast [6]	X				
Specific tumor markers [7]	X	As clinically indicated, but at least every 6 weeks, ± 5 days (2 cycles) for the first 24 weeks and every 12 weeks , ± 5 days (4 cycles) thereafter until loss of clinical benefit, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first			
Collection of results from specific markers assessed on tumor tissue [8]	X				

Appendix 1
Schedule of Assessments (cont.)

	Screening[1]	Treatment (All cycles, unless otherwise indicated) [2]	Treatment discontinuation visit	Follow-Up	End of Study Visit
Day (Window)	Days –35 to –1	Day 1 (± 3 days for cycles ≥ 2)	≤ 30 days after last dose	Every 3 months from study treatment discontinuation (+/- 30 days)	24 months
Physical examination [9]	X	X	X		
ECOG performance status	X	X(-3 days from treatment start)	X		
Vital signs [10]	X	X	X		
Oxygen saturation (pulse oximetry)	X	X	X		
12-lead electrocardiogram [11]	X	X	X		
Weight	X				
Height	X				

Appendix 1
Schedule of Assessments (cont.)

	Screening[1]	Treatment (All cycles, unless otherwise indicated) [2]	Treatment discontinuation visit	Follow-Up	End of Study Visit
Day (Window)	Days –35 to –1	Day 1 (± 3 days for cycles ≥ 2)	≤ 30days after last dose	Every 3 months from study treatment discontinuation (+/- 30 days)	24 months
Local laboratory assessments					
Hematology [12, 13]	X	X	X		
Serum chemistry [-13]	X	X	X		
Coagulation panel (aPTT, INR)	X		X		
C-reactive protein	X	X	X		
Urinalysis [14]	X	X[15]	X		
Serum pregnancy test [16]	X				
TSH, free T3, free T4	X	Every 3rd cycle (starting at C3, C6, C9 ctd.)	X		
HIV, HBV and HCV serology [17]	X				

Appendix 1
Schedule of Assessments (cont.)

	Screening[1]	Treatment (All cycles, unless otherwise indicated) [2]	Treatment discontinuation visit	Follow-Up	End of Study Visit[24]
Day (Window)	Days –35 to –1	Day 1 (± 3 days for cycles ≥ 2)	≤ 30 days after last dose	Every 3 months from study treatment discontinuation (+/- 30 days)	24 months
Central laboratory assessments [18]					
Serum sample for ATA assessment		X	X	120 (±30) days after last dose	
Serum sample for PK assessments		X	X	120 (±30) days after last dose	
Plasma sample for biomarkers		X	X		
Adverse events[19]	X	X	X	X	X
Atezolizumab infusion [20]		X			
Archival tissue specimen (tumor block preferred) [21]	X				
Freshly obtained tumor specimen (optional) [22]	X	X			
Survival follow-up [-23]				X	X

ATA = anti-therapeutic antibody; ECOG = Eastern Cooperative Oncology Group; FDG =[18]fluorodeoxyglucose; HBV = hepatitis B virus; HCV = hepatitis C virus; PET = positron emission tomography; RECIST = Response Evaluation Criteria in Solid Tumors; TSH = thyroid-stimulating hormone; PSA = prostate-specific antigen.

1. Written informed consent is required for performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 35 days prior to study entry may be used for screening assessments rather than repeating such tests.

Appendix 1
Schedule of Assessments (cont.)

2. Visits during the Treatment Period are to be completed on Day 1 (± 3 days for cycles ≥ 2) of every 3-week cycle until study drug discontinuation.
3. Demographic information includes sex, age, and self-reported race/ethnicity.
4. Cancer history including but not limited to cancer histology, grade, stage, prior cancer therapies and procedures, smoking history, asbestos exposure, HPV infection and HPV subtypes, associated syndromes, Helicobacter Pylori infection, and relevant mutations such as RET/PTC, PTEN, BRAF, RAS, PI3KCA, TP53, etc.
5. Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.
6. Examinations performed as standard of care prior to obtaining informed consent and within 35 days of Cycle 1, Day 1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at this visit, with use of physical examination and image-based evaluation. Screening assessments should include CT scans with oral and intravenous contrast or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis, and a brain scan (CT or MRI). Bone scans and CT scan of neck should also be performed if clinically indicated. If a CT scan for tumor assessment is performed in a PET/CT scanner, the CT acquisition must be consistent with standards of a full-contrast CT scan. CT scans must be used to measure lesions selected for response assessment. The same radiographic procedure used to define measurable lesions at baseline must be used throughout the study for each patient.
7. CA125 level for patients with ovarian cancer, CEA level for patients with colorectal cancer, PSA for patients with prostate cancer, CA153 levels for patients with breast cancer, CA 19.9 levels for patients with pancreatic cancer, or other tumor marker (as appropriate) should be obtained as clinically indicated or with each tumor assessment.
8. Results of local tests performed to meet eligibility criteria must be submitted at baseline and recorded in the eCRF as specified: -1) Known HPV induced tumors: HPV determination on tumor tissue using in situ hybridization (ISH) or a polymerase chain reaction (PCR) must be provided at baseline and recorded in the eCRF (results of HPV determination in cervical cancer cohort must be recorded in the eCRF) -2) MSI-high or MMR deficient cohorts: microsatellite instability or MMR deficiency on tumor tissue and corresponding normal tissue must be provided at baseline and recorded in the eCRF -3) Nasopharyngeal carcinoma or gastric adenocarcinoma / adenocarcinoma of the gastro-esophageal junction: EBV determination on tumor tissue per institution's standard practice (recorded in the eCRF). -4) BRCA positive breast or ovarian cancer cohort – BRCA testing must be provided at baseline and recorded in the eCRF - 5) ER positive, HER2 negative breast cancer with > 100 mutations: ER and HER2 test and determination of mutational load per local test must be provided at baseline and recorded in the eCRF.
9 Complete physical examination at screening and treatment discontinuation visit and limited physical examination during treatment. At baseline, physical examination should be done within 3 days prior to the first drug administration (Day 1) See Section 4.5.3.
10. Vital signs include heart rate, respiratory rate, blood pressures, and temperature. At baseline, vital signs should be done within 3 days prior to the first drug administration (Day 1). For first infusion of study treatment, the patient's vital signs should be determined within 60 minutes before the infusion; during, and after the infusion if clinically indicated. For subsequent infusions, vital signs will be collected within 60 minutes

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

11. ECG recordings will be obtained during screening and as clinically indicated at other time points. ECG should be done during screening period (within 35 day from Day 1), not needed to be repeated at D1. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.
12. Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. See Section 4.1.1 for a list of laboratory results obtained within 3 days prior to the first study treatment.
13. Laboratory tests that should be done within 3 days prior to the first drug administration (Day 1): Absolute neutrophil count (ANC), lymphocyte count, white blood cell counts, platelet count, hemoglobin, serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase, serum albumin, serum creatinine, international normalized ratio (INR) and activated partial thromboplastin time (aPTT). These tests must meet the eligibility criteria.

    The other biochemistry test sodium, potassium, magnesium, chloride, bicarbonate ([if routinely performed on venous blood samples]), calcium, phosphorus, glucose, lactate dehydrogenase and total protein can be done within 35 days from D1.
14. Urinalysis includes specific gravity, pH, glucose, protein, ketones and blood; dipstick permitted. Urinary analysis should be done during screening period (within 35 day from day 1, not needed to be repeated at D1)
15. On Day 1 of Cycle 3 and every two cycles thereafter.
16. Serum pregnancy test for women of childbearing potential must be performed and documented as negative within 14 days prior to Day 1.
17. All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical trial. Hepatitis B surface antigen, anti-HBc antibody, anti-HBs antibody, and anti-HCV antibody should be collected during screening. In patients who have positive serology for the anti-HBc antibody, HBV DNA should be done during screening and the results should be available prior to Cycle 1, Day 1.
18. See Section 4.5.6 and Appendix 2 for details.
19. 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. After initiation of study drug, all adverse events will be reported until 90 days after the last dose of study treatment or until initiation of another 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. 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.
20. The initial dose of study treatment will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes.

Appendix 1
Schedule of Assessments (cont.)

21. Archival tumor tissue specimen may be obtained from any prior tumor excision or biopsy performed at any time during the course of the patient's illness. Tumor blocks are preferred; 15 freshly cut and unstained slides can be provided in exceptional circumstances if tumor blocks are unavailable. Patients with fewer than 15 unstained slides available at baseline (but no fewer than 10) may be eligible following discussion with the Sponsor. Patients who do not have tissue specimens meeting eligibility requirements must undergo a biopsy during the screening period. Alternatively, the biopsy during screening can be replaced by a biopsy which was taken no more than 12 months before Cycle 1, Day 1. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.
22. For patients who have signed the Consent for Optional Biopsies Form. Tumor tissue will be freshly obtained by core needle or excisional/punch biopsy. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. The pre-treatment specimen will be obtained after eligibility criteria have been fulfilled. Alternatively, the pre-treatment biopsy can be replaced by a biopsy which was taken no more than 12 months before Cycle 1, Day 1. A subsequent biopsy will then be performed approximately 3 weeks (Cycle 2, Day 1) after the first Atezolizumab administration (for logistical reasons, the subsequent biopsy may be performed with a time window of 1 week.)
23. Will also include new anticancer drug(s) received after treatment discontinuation, responses and duration of responses to them, and other cancer information. Survival follow-up information will be collected via clinic visits, telephone calls, and/or review of patient medical records approximately every 3 months and this period will last for a minimum of 24 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up or the Sponsor decides to end the study (whichever occurs first).
24. During the interim period between LPLV and a patient rolling over to the extension study, only safety data (AE including SAE and AESI) will continue to be collected in the eCRF. Other assessments (e.g. tumor assessment) can be performed as per standard of care.

Appendix 2
Schedule of Anti-Therapeutic Antibody, Pharmacodynamic and Pharmacokinetic Assessments

Visit	Time	Sample Type
Cycle 1, Day 1	Pre-dose	Atezolizumab PD [1] Serum Atezolizumab PK Serum Atezolizumab ATA
	30 min (± 10 min) after end of Atezolizumab infusion	Serum Atezolizumab PK
Cycle 2, Day 1 (± 1 day)	Pre-dose	Atezolizumab PD [1] Serum Atezolizumab ATA Serum Atezolizumab PK
Cycle 3, Day 1 (± 1 day)	Pre-dose	Serum Atezolizumab ATA Serum Atezolizumab PK
Cycle 4, Day 1 (± 1 day)	Pre-dose	Atezolizumab PD [1] Serum Atezolizumab ATA Serum Atezolizumab PK
Cycle 8 and every 8 cycles thereafter Day 1 (± 1 day)	Pre-dose	Serum Atezolizumab ATA Serum Atezolizumab PK
At progression of disease (RECIST)		Atezolizumab PD [1]
Treatment discontinuation visit (≤ 30 days after last dose) [4]	At visit	Atezolizumab PD [1,3] Serum Atezolizumab ATA Serum Atezolizumab PK
Post-treatment discontinuation visit (120 [± 30 days] after last dose) [4]	At visit	Serum Atezolizumab ATA [2] Serum Atezolizumab PK [2]

PD = plasma PD (pharmacodynamic) biomarkers; PK = pharmacokinetics; ATA = anti-therapeutic antibody

1. Plasma
2. For patients who discontinue the study treatment, ATA and PK samples are to be obtained at 120 days ± 30 days after the last dose of study treatment unless the patient dies or withdraws consent or the study closes (during the interim period between LPLV and a patient rolling over to the extension study, ATA and PK samples do not need to be collected).
3. Plasma sample at treatment discontinuation visit only required if radiologic progression sample is taken outside a ±4 week window of the treatment discontinuation visit.

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors

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. In this protocol, patients will be permitted to continue study treatment even after modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria for progressive disease are met if the risk/benefit ratio is judged to be favorable.

Modified RECIST is derived from RECIST, Version 1.1 conventions [1] and immune-related response criteria [2] (irRC). When not otherwise specified, RECIST v1.1 conventions will apply.

Modified RECIST and RECIST, Version 1.1: 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; must be confirmed by a consecutive assessment ≥ 4 weeks from the date first documented

RECIST = Response Evaluation Criteria in Solid Tumors.

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.

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

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412–20.

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors (cont.)

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:

1. 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
2. 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 $\geq$ 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.

NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with short axis $\geq$ 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.

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.

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.

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors (cont.)

TUMOR RESPONSE EVALUATION

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 $\geq$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. 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 $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but $<$ 15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$ 10 mm are considered non-pathological and should not be recorded or followed. 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.

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 and all new measurable lesions 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.

RESPONSE CRITERIA

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all 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.

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors (cont.)

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 on study.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and all new measurable lesions, taking as reference the smallest sum on study (nadir SlD; this includes the baseline sum if that is the smallest on 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.

EVALUATION OF BEST OVERALL RESPONSE USING MODIFIED RECIST

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.

MISSING ASSESSMENTS AND NOT EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is 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 time point 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 at follow-up only two lesions were assessed but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors (cont.)

Table 1 Modified RECIST Timepoint Response Definitions

% Change in Sum of the Diameters (Including Measurable New Lesions When Present)	Target Lesion Definition	Non-Target Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Overall Modified RECIST Timepoint Response
− 100% [a]	CR	CR	No	No	CR
− 100% [a]	CR	Non-CR or not all evaluated	No	No	PR
≤ − 30%	PR	Any	Yes or no	Yes or no	PR
> − 30% to < + 20%	SD	Any	Yes or no	Yes or no	SD
Not all evaluated	Not evaluated	Any	Yes or no	Yes or no	NE
≥ + 20%	PD	Any	Yes or no	Yes or no	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] 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.

BEST OVERALL RESPONSE: ALL TIMEPOINTS

The best overall response is determined once all the data for the patient are known.

The best overall response according to modified RECIST is interpreted as below:

3. **CR**: Complete disappearance of all tumor lesions (target and non-target) and no new measurable or unmeasurable lesions, confirmed by a consecutive assessment ≥ 4 weeks from the date first documented. All lymph nodes short axes must be < 10 mm.
4. **PR**: Decrease in the sum of the diameters of all target and all new measurable lesions ≥ 30% relative to baseline, in the absence of CR, confirmed by a consecutive assessment ≥ 4 weeks from the date first documented.
5. **SD**: Criteria for CR, PR, and PD are not met.

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors (cont.)

6. **PD**: Increase in the sum of the diameters of all target and all new measurable lesions ≥ 20% relative to the nadir, which mustbe confirmed by a consecutive assessment ≥ 4 weeks from the date first documented as follows:

   The confirmatory assessment shows an additional measurable increase in tumor burden as measured by the sum of the diameters of all target and all new measurable lesions.

Appendix 4
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous and/or intratracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters and tape

PROCEDURES

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

- Stop the study drug infusion
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow to the limb.
- Maintain an adequate airway
- Administer antihistamines, epinephrine or other medications as required by patient status and directed by the physician in charge
- Continue to observe the patient and document observations

Appendix 5
Preexisting Autoimmune Diseases

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease.

Subjects 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 subjects 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). –
Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen are eligible.
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:

1. Rash must cover less than 10% of body surface area (BSA).
2. Disease is well controlled at baseline and only requiring low potency topical steroids.
3. No acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)

Please contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Appendix 5
Preexisting Autoimmune Diseases (cont.)

Autoimmune Diseases and Immune Deficiencies

Acute disseminated encephalomyelitis	Dermatomyositis	Neuromyotonia
Addison's disease	Dysautonomia	Opsoclonus myoclonus syndrome
ANCA positive vasculitis	Epidermolysis bullosa acquista	Optic neuritis
Ankylosing spondylitis	Gestational pemphigoid	Ord's thyroiditis
Antiphospholipid antibody syndrome	Giant cell arteritis	Pemphigus
Aplastic anemia	Glomerulonephritis	Pernicious anemia
Autoimmune hemolytic anemia	Goodpasture's syndrome	Polyarteritis nodosa
Autoimmune hepatitis	Graves' disease	Polyarthritis
Autoimmune hypoparathyroidism	Guillain-Barré syndrome	Polyglandular autoimmune syndrome
Autoimmune hypophysitis	Hashimoto's disease	Primary biliary cirrhosis
Autoimmune myocarditis	IgA nephropathy	Psoriasis
Autoimmune oophoritis	Inflammatory bowel disease	Reiter's syndrome
Autoimmune orchitis	Interstitial cystitis	Pyoderma gangrenosum
Autoimmune thrombocytopenic purpura	Kawasaki's disease	Reactive arthritis
Behcet's disease	Lambert-Eaton myasthenia syndrome	Rheumatoid arthritis
Bullous pemphigold	Lupus erythematosus	Sarcoidosis
Celiac disease	Lyme disease - chronic	Scleroderma
Chronic fatigue syndrome	Meniere's syndrome	Sjögren's syndrome
Chronic inflammatory demyelinating polyneuropathy	Mooren's ulcer	Stiff-Person syndrome
Chung-Strauss syndrome	Morphea	Takayasu's arteritis
Crohn's disease	Multiple sclerosis	Ulcerative colitis
	Myasthenia gravis	Vogt-Kovanagi-Harada disease
		Wegener's granulomatosis

Appendix 6
Prostate Response Evaluation Criteria

PROSTATE-SPECIFIC ANTIGEN ASSESSMENT

Prostate-specific antigen (PSA) Assessment will be evaluated according to the recommendations of the Prostate Cancer Working Group 2 (PCWG2)[1] with modification

- PSA complete response is defined as a PSA concentration < 0.5 ng/mL for two consecutive measurements separated by at least 3 weeks
- PSA response will be defined as a PSA concentration < 50% of the PSA reference value occurring at any time after treatment is initiated. The PSA reference value will be the PSA concentration measured immediately prior to treatment
- PSA decrease of ≥ 30% from baseline by Week 12 will also be assessed
- PSA progression is defined as follows:
  - In patients where no decrease in PSA from baseline is documented, PSA progression is a ≥ 25% increase from the baseline value along with an increase in absolute value of 2ng/mL or more after 12 weeks of treatment. It should be confirmed by a second value obtained 3 or more weeks later
  - In patients whose PSA nadir is < 100% of the baseline value, PSA progression is≥ 25% increase from the nadir and an absolute increase of 2 ng/mL or more from the nadir, confirmed by a second value obtained 3 or more weeks later

RADIOGRAPHIC ASSESSMENT

- Bone lesions
  - Progression is defined as the appearance of two or more new lesions
  - Progression should be confirmed by a repeat measurement at least 6 weeks later demonstrating additional new lesions
- Soft tissue lesions
  - Soft tissue lesions should be assessed according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria v. 1.1

Patients should be kept on study until no longer experiencing clinical benefit as determined by the investigator and an effort should be made not to discontinue therapy solely on the basis of an increase in PSA in the absence of other indicators of disease progression.

[1] Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the prostate cancer clinical trials working group. J Clin Oncol 2008;26:1148−59.

Appendix 7
Malignant Pleural Mesothelioma Response Evaluation Criteria

RATIONALE

The major problems in applying the RECIST criteria to malignant pleural mesothelioma are in the interpretation of the meaning and placement of the "longest uni-dimensional diameter" of the target tumor mass to be measured.

The longest diameter of a tumor mass is frequently that which follows the inner curve of the chest wall. Defining the limits of such a diameter is often problematical.

When the tumor regresses with treatment, the line may cross an area outside the tumor margin because of the curve of the chest wall. This may produce difficulty with reproducibility of measurement. Furthermore, the longest tumor diameter may be between two fixed structures, such as the thoracic vertebrae and the carina, and measurement in these areas may not fully reflect tumor response.

MODIFIED RECIST FOR MALIGNANT PLEURAL MESOTHELIOMA

Modified RECIST criteria have been published with particular reference to malignant pleural mesothelioma (Byrne and Nowak, 2004)[1]:

- Response to treatment is evaluated by measuring uni-dimensional tumor thickness perpendicular to the chest wall in 2 positions at 3 different levels on CT. The sum of these 6 measurements is defined as the pleural uni-dimensional measure
- Transverse cuts at least 1 cm apart and related to anatomical landmarks in the thorax were chosen to allow reproducible assessment at later time points
- If a measurable tumor was present, transverse cuts in the upper thorax, above the level of the main bronchi division were preferred
- At reassessment, pleural thickness was measured at the same position and at the same level by the same observer. This measurement did not necessarily represent the greatest tumor thickness at the level
- Nodal, subcutaneous, and other bi-dimensionally measurable lesions were measured uni-dimensionally based on the RECIST criteria
- Uni-dimensional measurements were included to obtain the total tumor measurement
- A confirmed response required repeat observation on 2 occasions 4 weeks apart

[1] Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann Oncol. 2004 Feb;15(2):257-60.

Appendix 7
Malignant Pleural Mesothelioma Response Evaluation Criteria (cont.)

The RECIST definition is listed in the table below

Complete response (CR)	Disappearance of all target lesions with no evidence of tumors elsewhere
Partial response (PR)	At least a 30%reduction in the total tumor measurement
Progressive disease (PD)	Increase of at least 20% in the total tumor measurement over the nadir measurement or the appearance of one or more new lesions
Stable disease (SD)	Those who fulfilled the criteria for neither PR and PD

Appendix 8
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 investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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 $\geq$1 month to $\leq$ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for $>$ 105 days after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for $>$ 105 days to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for $>$ 105 days if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for

pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

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

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in 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.
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 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

LFT = liver function tests.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function tests.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

GASTROINTESTINAL EVENTS

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

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

ENDOCRINE EVENTS

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

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

OCULAR EVENTS

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over $\geq$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 $\leq$10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over $\geq$1 month to $\leq$10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. 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.

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 6 Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.[a] • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated myocarditis, Grade 3-4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. [a,b] • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

INFUSION-RELATED REACTIONS

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

Guidelines for medical management of IRRs during Cycle 1 are provided in Table 7. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 7 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. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, 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, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics 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 Medical Monitor. [a]

IRR = infusion-related reaction.

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up 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	• Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
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 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limited, with or without pruritus. 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.

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]

[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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

NEUROLOGIC DISORDERS

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1−2 mg/kg/day oral or IV prednisone or equivalent.

[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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

IMMUNE-MEDIATED MENINGOENCEPHALITIS

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

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

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

Table 11 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

RENAL EVENTS

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

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over $\geq$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 $\leq$10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over $\geq$1 month to the equivalent of $\leq$10 mg/day oral prednisone before atezolizumab can be resumed.

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-MEDIATED MYOSITIS

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

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

Table 13 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

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

- Fever $\geq$38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin $<$90 g/L (9 g/dL) ($<$100 g/L [10 g/dL] for infants $<$4 weeks old)
  - Platelet count $<100\times10^9$/L (100,000/μL)
  - ANC $<1.0\times10^9$/L (1000/μL)
- Fasting triglycerides $>$2.992 mmol/L (265 mg/dL) and/or fibrinogen $<$1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin $>$500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated $\geq$2 standard deviations above age-adjusted laboratory-specific norms

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

- Ferritin $>$684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq181\times10^9$/L (181,000/μL)
  - AST $\geq$48 U/L
  - Triglycerides $>$1.761 mmol/L (156 mg/dL)
  - Fibrinogen $\leq$3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids and/or an immunosuppressive agent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over $\geq$1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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