PROTOCOL

TITLE:	**A PHASE III/IV, SINGLE ARM, MULTICENTER STUDY OF ATEZOLIZUMAB (TECENTRIQ) TO INVESTIGATE LONG-TERM SAFETY AND EFFICACY IN PREVIOUSLY-TREATED PATIENTS WITH LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER (TAIL)**
PROTOCOL NUMBER:	MO39171
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EUDRACT NUMBER:	2017-001409-34
IND NUMBER:	Not applicable
NCT NUMBER:	NCT03285763
TEST PRODUCT:	Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], MD
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 16 May 2017

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
23-Mar-2021 08:43:25	Company Signatory	[redacted]
23-Mar-2021 14:59:11	Deputy EU QPPV	

CONFIDENTIAL

DATE AMENDED	Version 2: 04 September 2017
	Version 3: 16 January 2018
	Version 4: 14 January 2019
	Version 5: 17 December 2019
	Version 6: See electronic stamp above

PROTOCOL AMENDMENT, VERSION 6: RATIONALE

The rationales for specific changes in Version 6 of this protocol are listed below:

- Approved indications for atezolizumab have been added (Section 1.2).
- Text describing the current knowledge and risks of COVID-19 infection while receiving anti-programmed death-ligand 1 (PD-L1) immunotherapy are highlighted in the benefit-risk assessment as well as other relevant sections of the protocol (Section 1.3, Section 5.1, Section 10, Appendix 9).
- Language has been added to indicate that sites should confirm that appropriate temperature conditions were maintained during IMP transit and that the sites are responsible for maintaining records of IMP accountability during the study (Section 4.3.3).
- Immunosuppressive medications have been removed from the prohibited therapy section (Section 4.4.2) and added to the permitted therapy section (Section 4.4.1) to align with atezolizumab management guidelines in Appendix 9 that permit use of immunosuppressive medications for the treatment of corticosteroid-refractory immune-mediated adverse events.
- List of identified risks for atezolizumab have been revised to include severe cutaneous adverse reactions (Section 5.1.1).
- Text has been added to clarify that hemophagocytic lymphohisiocytosis (HLH) and macrophage activation syndrome (MAS) are considered potential risks for atezolizumab (Section 5.1.1, Appendix 9).
- To address a request by the French National Agency for the Safety of Medicines and Health Products (ANSM), HLH and MAS have replaced systemic inflammatory response syndrome on the list of atezolizumab-associated adverse events of special interest (Section 5.2.3).
- Influenza-like illness was removed from the list of immediately reportable adverse events of special interest as enough information regarding such events has been collected, in general is infrequently reported, and is a known adverse event of atezolizumab (Section 5.2.3).
- Text has been added to clarify that adverse events associated with special situations that also qualify as adverse events of special interest should be reported within 24 hours (Section 5.3.5.12).
- Text has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1).
- The name of a Roche policy on data sharing has been corrected (Section 9.5).
- Appendix 5 was revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent.
- To address a request by the French ANSM, the management guidelines for infusion-related reactions associated with atezolizumab have been updated to

include guidelines for cytokine-release syndrome (CRS) to align with the definition, grading, and management of CRS reflected in a recent publication (Lee et al. 2019) (Appendix 9).

- Guidelines for management of atezolizumab-associated dermatological adverse events have been revised to provide guidance on severe cutaneous adverse reactions of Stevens-Johnson syndrome and toxic epidermal necrolysis (Appendix 9).
- The management guidelines for Grade 4 myositis have been removed because Version 4.0 of the Common Terminology Criteria for Adverse Events does not have a Grade 4 category for myositis (Appendix 9).
- To address a request by the French ANSM, the management guidelines for HLH and MAS have been modified to indicate that HLH should be considered when CRS presentation is atypical or prolonged, to add anticytokine therapy as an option for treating HLH or MAS, and to suggest that published guidelines should be followed for HLH or MAS events that do not respond to treatment within 24 hours (Appendix 9).

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

PROTOCOL AMENDMENT, VERSION 6.0: SUMMARY OF CHANGES

Section 1.2: Background on Atezolizumab

[…]

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

Section 1.3: Study Rationale and Benefit-Risk Assessment

[…]

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

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

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (85). However, there are insufficient and inconsistent clinical data to assess if outcome from COVID-19 is altered by cancer immunotherapy.

Severe COVID-19 appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-γ (86). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from COVID-19.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for COVID-19–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

Section 4.3.3: Investigational Medicinal Product Accountability

[…] *The study site is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.*

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

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

[…]

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

Section 4.4.1: Permitted Therapy

[…]

- Systemic corticosteroids, *immunosuppressive medications,* 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 after consultation with the Medical Monitor (see Exclusion Criterion 21 [Section 4.1.2] and Prohibited Therapy [Section 4.4.2]). […]

Section 4.4.2: Prohibited Therapy

[…]

~~With the exception of autoimmune disease patients, patients should 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, *immunosuppressive medications,* 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 after consultation with the Medical Monitor.

Section 5.1: Safety Plan

[…]

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

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (86). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Section 5.1.1: Risks Associated with Atezolizumab

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

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

[…]

- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, *HLH, and MAS* ~~influenza-like illness, and systemic inflammatory response syndrome~~

[…]

Section 5.3.5.12: Cases of Overdose or Medication Error

[…] If the associated adverse event fulfills seriousness criteria *or qualifies as an adverse event of special interest*, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). […]

Section 5.4.3.1: Pregnancies in Female Patients

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

Section 9.5: Dissemination of Data and Protection of Trade Secrets

[…] For more information, refer to the Roche Global Policy on Sharing of Clinical ~~Trials Data~~*Study Information* at the following website:

[…]

Section 10: References

[…]

85. *Frebel H, Nindl V, Schuepbach RA, et al. Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice. J Exp Med 2012;209:2485–99.*

86. *Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355–62.*

[…]

Appendix 5*:* Preexisting Autoimmune (Chronic Inflammatory) Diseases *and Immune Deficiencies*

[…]

Caution should be used when considering atezolizumab for patients who have previously expereinced a servere or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent. […]

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

[…]

INFUSION-RELATED REACTIONS *AND CYTOKINE-RELEASE SYNDROME*

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

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

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

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated ~~G~~*g*uidelines for medical management of IRRs *and CRS*~~during Cycle 1~~ are provided in Table 7. ~~For subsequent cycles, IRRs should be managed according to institutional guidelines.~~

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

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

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

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

Event	• *Management*
Grade 3 [a] *Fever* [b] *with hypotension requiring a vasopressor (with or without vasopressin)* ***and/or*** *Hypoxia requiring high-flow oxygen* [d] *by nasal cannula, face mask, non-rebreather mask, or Venturi mask*	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [e] • *Administer symptomatic treatment.* [c] • *For hypotension, administer IV fluid bolus and vasopressor as needed.* • *Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.* • *Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.* • *Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).* • *Consider anti-cytokine therapy.* • *Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.*
Grade 4 [a] *Fever* [b] *with hypotension requiring multiple vasopressors (excluding vasopressin)* ***and/or*** *Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)*	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [e] • *Administer symptomatic treatment.* [c] • *Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice.* • *Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.* • *Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).* • *Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments* [f] *may be considered at the discretion of the investigator and in consultation with the Medical Monitor.* • *Hospitalize patient until complete resolution of symptoms.*

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

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

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

[a] *Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.*

[b] *Fever is defined as temperature ≥38 ℃ not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.*

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

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

[e] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the 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. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit–risk ratio.*

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

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, IV fluids). • 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 medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • 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.

DERMATOLOGIC EVENTS

[…] *Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab.* […]

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist *for evaluation and, if indicated, biopsy*. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist *for evaluation and, if indicated, biopsy*. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	*Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:* • *Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.* • *Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy.* • *Follow the applicable treatment and management guidelines above.* • *If Stevens-Johnson syndrome or toxic epidermal necrolysis, permanently discontinue atezolizumab.*

[…]

IMMUNE-MEDIATED MYOSITIS

[…]

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.~~

[…]

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to HLH and MAS*, which are considered to be potential risks for atezolizumab.*

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

[…]

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*, and/or anti-cytokine therapy*. • *If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019)*~~If event 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.

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PROTOCOL ACCEPTANCE FORM

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MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

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

PROTOCOL SYNOPSIS

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PHASE:	Phase III/IV
INDICATION:	Non-small cell lung cancer (NSCLC)
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the long-term safety and efficacy of atezolizumab in patients with locally advanced or metastatic NSCLC who have progressed following standard systemic chemotherapy (including if given in combination with anti-PD-1 therapy, after anti-PD-1 as monotherapy, or after tyrosine kinase inhibitor [TKI] therapy). Patients with a previously detected sensitizing EGFR mutation or ALK fusion oncogene must have received targeted therapy (TKI) followed by at least one line of standard systemic chemotherapy prior to receiving atezolizumab. Overall, patients should not have received more than two lines of standard systemic chemotherapy. Patients will also be eligible if they discontinued first-line or second-line therapy due to intolerance.

Table 1 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoints
• To evaluate the long-term safety of atezolizumab in previously treated patients with advanced NSCLC	• Incidence of serious adverse events (SAEs) related to atezolizumab treatment • Incidence of immune-related adverse events (irAEs) related to atezolizumab treatment
Main Secondary Objective	**Corresponding Endpoint**
• To evaluate the efficacy of atezolizumab in previously treated patients with advanced NSCLC	• Overall survival (OS) rate at 2 years, defined as the proportion of patients remaining alive 2 years after initiation of study treatment

Other Secondary Objectives	Corresponding Endpoints
• To further evaluate the efficacy of atezolizumab in previously treated patients with advanced NSCLC	• OS, defined as the time from initiation of study treatment to death from any cause • Progression-free survival (PFS), defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause, whichever occurs first. PFS will be calculated based on disease status evaluated by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) and also by disease status evaluated by the investigator according to modified RECIST • OS rate at 3 years, defined as the proportion of patients remaining alive 3 years after initiation of study treatment • Objective response rate (ORR), defined as the percentage of patients who attain complete response (CR) or partial response (PR) according to RECIST v1.1 and also by disease status evaluated by the investigator according to modified RECIST • Duration of response (DOR), defined as the time from initial response to disease progression or death among patients who have experienced a CR or PR (unconfirmed) during the study. Duration of response will be calculated based on disease status evaluated by the investigator according to RECIST v1.1 and also by disease status evaluated by the investigator according to modified RECIST

Exploratory Objectives	Corresponding Endpoints
• To further evaluate the long-term safety and efficacy of atezolizumab in previously treated patients with advanced NSCLC	• Safety and efficacy of atezolizumab in subgroups of the study population differentiated according to: Presence of CNS metastases at baseline (yes vs. no) ECOG performance status (0 or 1 vs. 2) Histologic subtype (squamous vs. non-squamous) History of or current autoimmune disease (yes vs. no) Prior anticancer treatment • Progression-free survival from start of new anti-cancer therapy, defined as the time from initiation of new anti-cancer therapy to objective tumor progression on next-line treatment or death from any cause • Objective response rate from start of new anti-cancer therapy, defined as the percentage of patients who attain complete response (CR) or partial response (PR) • Progression-free survival 2 (PFS2), defined as the time from initiation of study treatment to objective tumor progression on next-line treatment or death from any cause
Exploratory Biomarker Objectives	**Corresponding Endpoints**
• To assess the role of PD-L1 and other biomarkers in the progression and fundamental biology of advanced NSCLC • To evaluate PD-L1 and other biomarkers (e.g., cancer-related genes) as prognostic biomarkers	• Safety and efficacy of atezolizumab in subgroups of the study population differentiated according to: Expression of PD-L1 protein in tumor tissue Presence/absence of other biomarkers in tumor tissue • Correlations between PD-L1 expression and other biomarkers
Patient-Reported Outcome Objectives	**Corresponding Endpoint**
• To evaluate health status utility and HR QoL of atezolizumab in previously treated patients with advanced NSCLC	• EQ-5D-5L index-based and VAS scores • EORTC QLQ-LC13 score

EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire—Supplemental Lung Cancer Module; EQ-5D, EuroQol 5-Dimension Questionnaire; HR QoL, health-related quality of life; VAS, visual analog scale.

Study Design

Description of Study

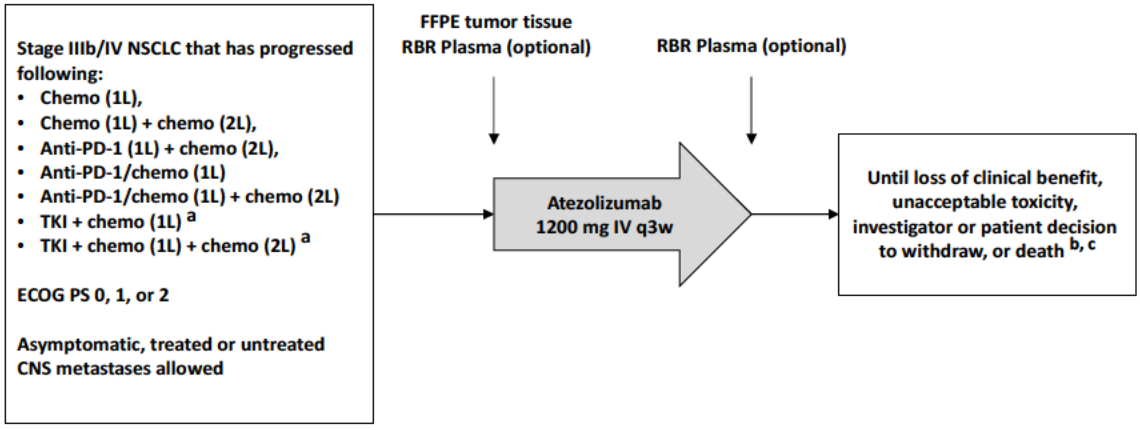
Study MO39171 is a phase III/IV, single-arm, multicenter study of the long-term safety and efficacy of atezolizumab treatment in patients with Stage IIIb or Stage IV NSCLC who have progressed following standard systemic chemotherapy (including if given in combination with

anti-PD-1 therapy, after anti-PD-1 as monotherapy, or after TKI therapy). Patients with a previously detected sensitizing EGFR mutation or ALK fusion oncogene must have received targeted therapy (TKI) followed by at least one line of standard systemic chemotherapy prior to receiving atezolizumab. Overall, patients should not have received more than two lines of standard systemic chemotherapy. Patients will also be eligible if they discontinued first-line or second-line therapy due to intolerance.

The study will consist of a Screening Period (Day –28 to Day –1), a Treatment Period, a Treatment Discontinuation Visit occurring ≤ 30 days after the last dose of study medication, and a Follow-Up Period. Day 1 (baseline) will be defined as the first day the patient receives atezolizumab. It is anticipated that the trial will enroll 600 patients at 140 sites globally.

Enrolled patients will receive atezolizumab at a fixed dose of 1200 mg administered intravenously on the first day of each cycle (Figure 1). One cycle of therapy will be defined as 21 days (± 5 days). Atezolizumab treatment will continue until investigator-assessed loss of clinical benefit, unacceptable toxicity, investigator or patient decision to withdraw from therapy, or death (whichever occurs first).

Figure 1 Study Schema



Chemo, standard systemic chemotherapy; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; FFPE, formalin-fixed paraffin-embedded; IV, intravenous; L, line; NSCLC, non-small cell lung cancer; RBR, Research Biosample Repository; TKI, tyrosine kinase inhibitor.

a. Patients with a previously detected sensitizing EGFR mutation or ALK fusion oncogene must have received targeted TKI therapy (no restrictions on number or sequence) followed by at least one line of standard systemic chemotherapy prior to receiving atezolizumab. Patients will also be eligible if they discontinued first-line or second-line therapy due to intolerance.
b. Response will be assessed by the investigator using RECIST v1.1 (see Appendix 2) and modified RECIST (see Appendix 3). Patients who continue atezolizumab treatment beyond radiographic disease progression assessed per RECIST v1.1 will be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 6 weeks, and will be assessed by modified RECIST criteria (see Appendix 3) until treatment discontinuation. If the scan frequency is every 9 weeks (see Appendix 1), a follow-up scan is recommended at 9 weeks or earlier if clinically indicated.
c. In those patients for whom tumor assessments are performed as part of local clinical practice and are available for report after PD or atezolizumab treatment discontinuation, best overall response (BOR) and PFS will be assessed from the first date of the new anticancer therapy to the end of the study per RECIST v1.1 and modified RECIST.

The primary objective of the study is to evaluate the long-term safety of atezolizumab. Long-term safety will be assessed by monitoring the nature, severity, duration, frequency and timing

of atezolizumab-related SAEs and atezolizumab-related irAEs. An irAE is defined as any adverse event of special interest (AESI) associated with systemic corticosteroid use within 30 days of the onset date. All-causality AEs, all-causality SAEs, AEs and SAEs leading to atezolizumab interruption or discontinuation, and AESIs will also be reported, as well as causes of death, vital signs, physical findings and clinical laboratory results.

Secondary objectives will assess the efficacy of atezolizumab. The main efficacy objective will be to evaluate the OS rate 2 years after the first dose of atezolizumab. Other efficacy objectives will include evaluation of OS, OS rate at 3 years, PFS, ORR, and DOR (additional efficacy assessments may occur on an exploratory basis). All antitumor response assessments will be based on RECIST v1.1 and modified RECIST.

Exploratory objectives will include evaluation of the safety and efficacy of atezolizumab in patient subgroups differentiated by: presence or absence of CNS metastases at baseline; ECOG performance status; histological subtype; history of or current autoimmune disease; and prior anticancer treatment. Other exploratory and PRO outcomes will include objective response rate and progression-free survival (PFS2) following start of new anticancer therapy, HR QoL as measured on the EORTC LQ-LC13, health utility score as measured on the EQ-5D-5L instrument, and expression of PD-L1 protein and cancer-related genes in tumor samples obtained before treatment. Finally, exploratory biomarkers may be assessed in tissue to assist in the potential development of new diagnostic assays and to assess biomarkers in terms of prognosis, response/resistance and safety.

Following discontinuation of study treatment, safety assessments will be conducted for 30 days after the last study drug administration or until initiation of other anti-cancer therapy (whichever occurs first). Thereafter, follow-up information on disease progression (unless this has already occurred), anti-cancer therapy and survival will be collected via telephone contact, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, end of study (30 months after last patient in), patient withdrawal or study termination by the Sponsor, whichever occurs first. In addition, irAEs, SAEs and AESIs will be collected as described in Section 5.4.2.

In those patients for whom tumor assessments are performed as part of local clinical practice and are available for report after PD or atezolizumab treatment discontinuation, overall response rate (ORR) and progression-free survival (PFS) will be assessed from the first date of the new anticancer therapy to the end of the study. These data will be used in an exploratory fashion to assess whether prior atezolizumab treatment positively influences response to subsequent anticancer therapies.

An Independent Data Monitoring Committee (iDMC) will be established to review all AEs, irAEs, SAEs, AESIs and other cumulative safety data.

A Schedule of Assessments for this study is provided in Appendix 1.

Number of Patients

This study will enroll approximately 600 patients with Stage IIIb or Stage IV NSCLC who have progressed following standard systemic chemotherapy (including if given in combination with anti-PD-1 therapy or after anti-PD-1 as monotherapy). Patients with a previously detected sensitizing EGFR mutation or ALK fusion oncogene must have received targeted therapy followed by one line of standard systemic chemotherapy prior to receiving atezolizumab. Overall, patients should not have received more than two lines of standard systemic chemotherapy. Patients will also be eligible if they discontinued first-line or second-line therapy due to intolerance. The recruitment of 600 patients is expected to take place over approximately 18 months. Patients who discontinue the study prior to study treatment initiation will not be replaced.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Age ≥ 18 years

3. Able to comply with the study protocol, in the investigator's judgment
4. Histologically or cytologically documented Stage IIIb or Stage IV NSCLC that has progressed following standard systemic chemotherapy (including if given in combination with anti-PD-1 therapy, after anti-PD-1 as monotherapy, or after TKI therapy). Patients with a previously detected sensitizing EGFR mutation or ALK fusion oncogene must have received targeted therapy (TKI), followed by at least one line of standard systemic chemotherapy, prior to receiving atezolizumab. Overall, patients should not have received more than two lines of standard systemic chemotherapy. Patients who have discontinued first-line or second-line therapy due to intolerance are also eligible

– Staging must be according to the UICC/AJCC system, 7th edition (Detterbeck et al. 2009) (see Appendix 8)
– Pathological characterization may be conducted on tumor specimens from earlier stage disease, but the tumor samples must be sufficient to distinguish squamous or non-squamous histology
– Chemotherapy regimens will be counted based on interval disease progression, and not on the number of agents or the number of switches in agents (e.g., a first-line or second-line therapy that consists of several cycles of a platinum doublet and subsequent maintenance therapy that introduces or switches to a new chemotherapy agent without interval disease progression will all be considered one chemotherapy regimen)
– Patients with a previously-detected sensitizing EGFR mutation must have experienced disease progression (during or after treatment) on an EGFR TKI (erlotinib, gefitinib, osimertinib, etc.)
– Patients with a previously detected ALK fusion oncogene must have experienced disease progression (during or after treatment) with crizotinib, alectinib, or another ALK inhibitor
– Prior radiation therapy is allowed, provided that the patient has recovered from any toxic effects thereof. Combined radiation/chemotherapy treatment constitutes a single regimen
– Combined radiation/chemotherapy treatment (chemoradiation) counts as one prior chemotherapy regimen if < 6 months have elapsed between the last dose and the date of recurrence
– Adjuvant/neoadjuvant chemotherapy is not counted as a line of treatment
– Debulking surgery and anticancer agents used for pleurodesis are not counted as lines of therapy

5. The last dose of prior systemic anticancer therapy must have been administered ≥ 21 days prior to study treatment initiation
6. The last dose of prior anti-PD-1 therapy must have been administered

– Nivolumab must have been discontinued ≥ 14 days and pembrolizumab ≥ 21 days prior to study treatment initiation, providing that these treatments were not administered in a clinical trial setting

7. Measurable disease, as defined by Response Evaluation Criteria for Solid Tumors, Version 1.1 (RECIST v1.1)
8. Patients with asymptomatic CNS metastases (treated or untreated), as determined by CT or MRI evaluation during screening and prior radiographic evaluation, are eligible
9. ECOG performance status 0, 1, or 2 [Appendix 7]
10. Life expectancy ≥ 12 weeks
11. Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 2 weeks prior to the first study treatment:

– Absolute neutrophil count ≥ 1500 cells/μL (without granulocyte colony-stimulating factor support within 2 weeks prior to the first study treatment)
– White blood cell count > 2500/μL
– Lymphocyte count ≥ 500/μL
– Platelet count ≥ 100,000/μL (without transfusion within 2 weeks prior to the first study treatment)

- Hemoglobin ≥ 9.0 g/dL (patients may be transfused or receive erythropoietic treatment to meet this criterion)
- Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase ≤ 2.5 times the upper limit of normal (ULN), with the following exceptions:

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

  Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN

- Serum bilirubin ≤ 1.5 ×ULN. Patients with known Gilbert's Syndrome who have serum bilirubin level ≤ 3 × ULN may be enrolled.
- Calculated creatinine clearance ≥ 15 mL/min (Cockcroft-Gault formula)
- International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 ×ULN. This applies only to patients who are not receiving therapeutic anticoagulation agents
- Patients receiving therapeutic anticoagulation agents must be on a stable dose
- HIV-positive patients are allowed, so long as they are on stable anti-retroviral therapy, have a CD4 count ≥ 200 cells/μL, and have an undetectable viral load at the time of screening

12. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab

- A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)
- Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception

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

Exclusion Criteria

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

1. Symptomatic CNS metastases
2. 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 study treatment initiation
3. Leptomeningeal disease
4. Uncontrolled pericardial effusion or ascites requiring recurrent drainage procedures
5. Pregnant or lactating, or intending to become pregnant during the study

- Women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non-drug-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 2 weeks prior to initiation of study drug

6. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)
7. Significant cardiovascular disease, such as New York Heart Association cardiac disease ≥ Class III, myocardial infarction within 3 months, unstable arrhythmias, or unstable angina

– Patients with known coronary artery disease or left ventricular ejection fraction < 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

8. Significant renal disorder requiring dialysis or indication for renal transplant
9. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to study treatment initiation
10. Major surgical procedure within 4 weeks prior to study treatment initiation or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis
11. Inability to understand the local language(s) for which the EORTC QLQ-LC13 and EuroQol EQ-5D-5L questionnaires are available (see Appendix 4 for English versions)
12. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
13. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
14. History of autoimmune disease (Appendix 5) are allowed if controlled and on stable treatment (i.e., same treatment, same dose) for the last 12 weeks, with the exception of:

– Patients taking concurrent abatacept or belatacept treatment, unless therapy has been withdrawn for > 8 weeks
– Patients with a history of serious or life threatening immune-related events
– No more than 1 concomitant autoimmune disease at the time of study entry is allowed unless one of them is:

    Autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone

    Controlled Type I diabetes mellitus on a stable dose of insulin regimen

    A medical history of such entities as atopic disease or childhood arthralgias, where the clinical suspicion of autoimmune disease is low. 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)

15. Prior allogeneic stem cell or solid organ transplantation
16. 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 computed tomography (CT) scan

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

17. Active tuberculosis

– In patients who have a potentially high likelihood of latent tuberculosis (e.g., recent contact with an infectious carrier, residence in a locale with high TB burden), absence of *Mycobacterium tuberculosis* infection must be confirmed before enrollment according to local practice standards

18. Administration of a live, attenuated vaccine within 4 weeks prior to study treatment initiation

– Influenza vaccination should be given during influenza season only (e.g., approximately October to March in the Northern Hemisphere).
– Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to study treatment initiation or at any time during the study

19. Prior treatment with CD137 agonists or immune checkpoint blockade therapies other than anti-PD-1 therapy, including anti−PD-L1 therapeutic antibodies
20. Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to initiation of study treatment

– Prior cancer vaccines and cellular immunotherapy are permitted

21. Specifically for patients without autoimmune disease: 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 study treatment initiation, or anticipated requirement for systemic immunosuppressive medications during the trial

– For patients with CNS metastases, use of prednisone at a stable dose (or dose equivalent) of ≤ 20 mg/day is acceptable
– The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency and topical steroids for cutaneous diseases are allowed

End of Study and Length of Study

The end of study and final analysis will occur when all enrolled patients have either died, withdrawn consent, are lost to follow up, or have been followed for 30 months since the last study patient is enrolled, whichever occurs first.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4 years.

The primary analysis will occur approximately 6 months after the last patient has been enrolled.

Investigational Medicinal Products

Test Product (Investigational Drug)

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

The dose of atezolizumab in this study will be 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by intravenous infusion every 3 weeks (21 [± 5] 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. For detailed information on drug preparation, storage and administration, refer to the Atezolizumab Investigator's Brochure.

The initial dose of atezolizumab will be administered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated AEs, 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 the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before, during (every 15 [± 5] minutes) if clinically indicated, and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated, and 30 minutes (± 10 minutes) after the infusion if clinically indicated or patient experienced symptoms during previous infusions.

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 (Grade 1) National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 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 6.

Guidelines for dosage modification, treatment interruption or discontinuation, and the management of specific adverse events are provided in Section 5.1.2.

Each AE associated with a special situation should be recorded on the Adverse Event eCRF.

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

Non-Investigational Medicinal Products

Permitted Therapy

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

- 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 (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; see Appendix 6).
- 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 after consultation with the Medical Monitor (see Exclusion Criterion 21 [Section 4.1.2] and Prohibited Therapy [Section 4.4.2]). 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 manufacturers' labels and the ASCO and ASCO/ASH guidelines.
- Influenza vaccination should be given during influenza season only (approximately October to March in the Northern Hemisphere). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to study treatment initiation or at any time during the study.
- Patients who use 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.

- Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

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

Prohibited Therapy

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

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, or investigational agents (except for maintenance therapies outlined in Section 4.1.1 and 4.1.2)

– After completion of Cycle 1, certain forms of radiotherapy may be considered for palliation if patients are deriving benefit (e.g., treatment of known bone metastases)

– 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

- Patients should not receive abatacept or belatacept treatment (those who were receiving it must stop it > 8 weeks before study entry)

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.

With the exception of autoimmune disease patients, patients should 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 after consultation with the Medical Monitor. If feasible, alternatives to these agents should be considered.

Patients with CNS metastases are allowed to receive anticonvulsants and steroid treatments if the dose of prednisone is stable and ≤ 20 mg/day (or equivalent).

In addition, all patients (including those who discontinue the study early) 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.

Statistical Methods

Primary Analysis

All safety analyses will be run on the Safety Analysis set, defined as all enrolled patients who had at least one administration of atezolizumab.

The incidence of SAEs related to atezolizumab and the incidence of irAEs related to atezolizumab will be summarized by incidence rates and 95% Pearson-Clopper confidence intervals.

Determination of Sample Size

No formal sample size calculation linked to hypothesis testing is done for this descriptive study. The sample size considerations are based upon estimation precision for the incidence of AEs.

With 600 patients, the following 95% CIs (Table 2) could be provided for the different incidences of AEs, which is deemed appropriate for the purposes of the study.

Table 2. Adverse Event Incidence and Corresponding 95% Confidence Intervals

Sample Size	AE Incidence	95% Clopper-Pearson Exact CI
600 patients	1%	1% [0.2% ; 1.8%]
	2%	2% [0.9% ; 3.1%]
	3%	3% [1.6% ; 4.4%]
	5%	5% [3.3% ; 6.7%]
	10%	10% [7.6% ; 12.4%]

CI, confidence interval.

Interim Analyses

This study will have no formal interim analyses. However, regular safety reviews of data will be performed by an Independent Data Monitoring Committee (iDMC). The frequency of these reviews will be stated in the iDMC charter.

In addition, to adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim analysis for reporting and publication of safety and efficacy results.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
1L	first line
2L	second line
3L	third line
AE	adverse event
AESI	adverse event of special interest
ALK	echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransaminase
ATA	anti-therapeutic antibodies
BCG	bacillus Clamette-Guerin
BOR	best overall response
BSC	best supportive care
Chemo-RT	chemoradiotherapy
CBC	complete blood count
CI	confidence interval
CNS	central nervous system
CR	complete response
CRO	contract research organization
CRS	cytokine-release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
DFS	disease-free survival
DLT	dose-limiting toxicity
DoR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EGFR	epidermal growth factor receptor
eGFR	estimated glomerular filtration rate
EDC	electronic data capture
EMA	European Medicines Agency

Abbreviation	Definition
EORTC	European Organisation for the Research and Treatment of Cancer
Fc	crystallizable fragment
FDA	Food and Drug Administration
FDG	fludeoxyglucose (^{18}F)
FFPE	formalin-fixed, paraffin-embedded
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	health-related quality of life
IC	tumor-infiltrating immune cells
ICH	International Conference on Harmonisation
iDMC	Independent Data Monitoring Committee
IFN	interferon
IgG1	immunoglobulin G, subclass 1
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (application)
irAE	immune-related adverse event
IRB	Institutional Review Board
IRF	independent review facility
ITT	intent-to-treat
IV	intravenous
IxRS	interactive response system
LDH	lactate dehydrogenase
MAS	macrophage activation syndrome
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography

Abbreviation	Definition
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
PT	prothrombin time
PTT	partial thromboplastin time
q3w	every 3 weeks
QLQ-LC13	Quality-of-Life Questionnaire – Supplemental Lung Cancer Module
QTcF	QT interval corrected using Fridericia's formula
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SABR	stereotactic ablative radiation therapy
SD	stable disease
SAE	serious adverse event
TC	tumor cells
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON NON-SMALL CELL LUNG CANCER

Nearly 1.6 million people die from lung cancer every year, making it the leading cause of cancer-related mortality worldwide (1). In the European Union, 313,000 new cases of lung cancer were diagnosed in 2012 (214,000 men and 99,000 women) and 268,000 people died of the disease (186,000 men and 82,000 women). An estimated 158,080 US citizens were expected to die from lung cancer in 2016, accounting for approximately 27 percent of all cancer deaths (2). Active and passive cigarette smoking is the main risk factor for lung cancer (2), but the disease can also develop in those who have never smoked. Additional risk factors include age, exposure to radon or other environmental carcinogens, radiation therapy to the chest, personal or family history, and air pollution (3-6).

The primary form of lung cancer is non-small cell lung cancer (NSCLC), which occurs in approximately 85% of all lung cancer cases (the other forms include small cell lung cancer [10%–15%] and lung carcinoid tumor [5%]) (7). The two most predominant histologic types of NSCLC are adenocarcinoma (more than half of cases) and squamous cell carcinoma (approximately 25% of cases) (8, 9).

Survival rates are lower for NSCLC than for other common cancers. Thus, the expected 5-year survival rate in NSCLC is 17.1%, compared with 65.2% for colon cancer, 90.0% for breast cancer and 99.9% for prostate cancer (10). More than half of patients with NSCLC present with distant metastatic disease at the time of initial diagnosis, which directly contributes to poor survival prospects. The overall 5-year survival rate for advanced NSCLC is 2% to 4% depending on geographic location (11).

1.1.1 Treatment of NSCLC

Treatment options for NSCLC are based primarily on the stage of the cancer (5, 12).

1.1.1.1 Stage I–III NSCLC

Surgery provides the best chance of cure for patients with early-stage NSCLC. Adjuvant chemotherapy is of unproven benefit in Stage I NSCLC, but is recommended for Stage II and Stage III disease (4, 5). Key surgical outcome trials in patients with Stage III NSCLC are summarized in Table 1.

Table 1 Summary of Key Surgical Outcome Trials in NSCLC

Treatment	Study Phase	Disease Stage	Median DFS (months)	Median OS (months)	5-year DFS (%)	5-year OS (%)
Surgery + adjuvant vinorelbine + cisplatin (13)	III	Ib/II	Not reported	94	61	69
Surgery + adjuvant cisplatin-based chemotherapy (14)	III	I–III	Not reported	Not reported	39.4	44.5
Surgery + adjuvant vinorelbine + cisplatin (15)	III	Ib–IIIa	36.3	65.7	Not reported	62 (stage Ib) 52 (stage II) 42 (stage IIIa)
Surgery + adjuvant paclitaxel + carboplatin (16)	III	Ib	89	95	52	60
Neoadjuvant cisplatin + etoposide + radiotherapy + surgery (17)	III	IIIa	12.8	23.6	22	27

DFS, disease-free survival; OS, overall survival

The type of surgery performed and survival rates depend on the stage of disease and the health of the patient (18). Typical surgical modalities include sleeve resection, segmentectomy, wedge resection, lobectomy, or pneumonectomy (18). In patients with medically inoperable Stage I–III NSCLC, stereotactic ablative radiation therapy, also known as stereotactic body radiation therapy, is recommended, with or without chemotherapy (Table 2).

Table 2 Summary of Radiotherapy Trials in Patients With Medically Inoperable Stage I–III NSCLC

Treatment	Study Phase	ORR (%)	3-year DFS (%)	Median OS (months)	Survival Rate (%)
Stage I					
SABR (19)	II	Not reported	48.3–86	40.6	1-year: 86 2-year: 65–70 3-year: 32–60 5-year: 42–72
Three-dimensional conformal radiotherapy (20, 21)	I	77	Not reported	24.6–38.5	5-year: 15.3
Stage II–III					
Chemo-RT (22-24)	I/II, III	52–84	29	14.6–26	1-year: 71 2-year: 34.6–52 3-year: 22.3–40 5-year: 10.0–15.8

Chemo-RT, chemoradiotherapy; DFS, disease-free survival; OS, overall survival; SABR, stereotactic ablative radiation therapy

1.1.1.2 Metastatic NSCLC

The treatment landscape in metastatic NSCLC has evolved in recent decades. Optimal treatment decisions are now based on two key features of the underlying disease: presence or absence of an actionable mutation; and histological subtype (5).

Patients without actionable mutations

In patients with metastatic non-squamous NSCLC who lack an actionable mutation, platinum-doublet chemotherapy with or without bevacizumab is recommended (Table 3) (5). Following relapse, options for second-line therapy include chemotherapy, targeted therapies and cancer immunotherapies (Table 3).

Table 3 Summary of Trials Assessing First- and Second-line Treatment of Metastatic Non-Squamous NSCLC Patients Lacking an Actionable Mutation

Treatment Regimen	Study Phase	Response Rate (%)	Median PFS (months)	Median OS (months)
First-line treatment				
Bevacizumab + paclitaxel/carboplatin (25, 26)	III	33–35	5.6–6.2	12.3–13.4
Bevacizumab + pemetrexed/carboplatin (26)	III	34.1	6.0	12.6
Cetuximab [a] + cisplatin/vinorelbine, with cetuximab maintenance (27)	III	Not reported	Not reported	12.0 [b]
Carboplatin/paclitaxel (25)	III	15	4.5	10.3
Cisplatin/docetaxel (28)	III	31.6	5.1‖	11.3
Cisplatin/vinorelbine (28)	III	24.5	5.3‖	10.1
Cisplatin/paclitaxel (29) [c]	III	31.8	4.2	8.1
Cisplatin/gemcitabine (29, 30) [c]	III	36.6	4.7	8.9–10.4
Cisplatin/pemetrexed (30)	III	Not reported	5.3	11.8
Second-line treatment				
Nivolumab (31)	III	19	2.3	12.2
Pembrolizumab (32)	II/III	18.0 [d] / 18.5 [e]	3.9 [d] / 4.0 [e]	10.4 [d] / 12.7 [e]
Ramucirumab + docetaxel (33)	III	23	4.5	10.5
Docetaxel (31, 33, 34)	III	8.8–14	2.9–4.2	7.9–9.4
Pemetrexed (34, 35)	III	9.1–11	2.9	8.3–10.1
Erlotinib (35-37)	III	7.9–9	2.2–3.6	5.3–8.2
Gemcitabine (38)	II	18.5	2.3 [f]	8.8 [f]

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

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

b Patients with adenocarcinoma subtype;

c Patients with non-squamous and squamous histology;

d 2 mg/kg dose;

e 10 mg/kg dose;

f Estimated from original time in weeks.

In patients with metastatic squamous NSCLC who lack an actionable mutation, chemotherapy and best standard of care are recommended (5) (Table 4).

Table 4 Summary of Trials Assessing First- and Second-line Treatment of Metastatic Squamous NSCLC Patients Lacking an Actionable Mutation

Treatment	Study Phase	ORR (%)	Median PFS (months)	Median OS (months)
First-line				
Gemcitabine/cisplatin (30)	III	Not reported	5.5	10.8
First-line continuation maintenance therapy (combined squamous and non-squamous NSCLC population)				
Gemcitabine (39)	III	Not reported	3.8	15.2
First-line switch therapy (combined squamous and non-squamous NSCLC population)				
Docetaxel (40)	III	35.9	5.7	12.3
Second-line (combined squamous and non-squamous NSCLC population unless noted otherwise)				
Docetaxel (34, 41, 42)	III	6.7–8.8	2.0[a]–2.9	5.7–7.9
Gemcitabine (43)	II	13	Not reported	6*
Nivolumab (44, 45) [b]	III	20	3.5	7.2
Pembrolizumab (46)	I	18.7	3.0	11.3
Ramucirumab + docetaxel (33)	III	23	4.5	10.5

a Estimated from original time in weeks;

b Patients with squamous disease.

Patients with actionable mutations

Approximately 10% to 30% of patients with NSCLC harbor mutations in the epidermal growth factor receptor (EGFR) (47). Four tyrosine kinase inhibitors (TKIs)—erlotinib, afatinib, gefitinib, and osimertinib—have been approved for treatment of EGFR mutation-positive disease (48-50). These agents are recommended for first-line use (5). If the EFGR mutation is discovered after first-line chemotherapy has already been initiated, then the clinician has two options at his or her discretion: to interrupt chemotherapy immediately and switch to TKI therapy; or complete the ongoing chemotherapy before switching to TKI therapy (5). Across multiple clinical trials, patients with EGFR mutation-positive disease who were treated with one of these TKIs had median progression-free survival (PFS) of 8.0–16.0 months, compared with 4.6–6.9 months following treatment with platinum-doublet chemotherapy (51-56).

Another approximately 5% of patients with NSCLC harbor the echinoderm microtubule-associated protein-like 4 (EML4)–anaplastic lymphoma kinase (ALK) fusion gene as a result of a chromosomal inversion at 2p21 and 2p23 (57-60). Three specific ALK-targeting agents have been approved for the treatment of patients with ALK-positive NSCLC, including crizotinib, ceritinib and alectinib (61-63). Crizotinib is recommended for first-line use, as well as second-line use in asymptomatic patients who have relapsed on first-line crizotinib (5). If the ALK mutation is discovered after first-line chemotherapy is already underway, then the chemotherapy can be either interrupted to start crizotinib therapy immediately or completed before starting crizotinib. Alectinib and ceritinib are recommended in symptomatic and asymptomatic patients who have relapsed on crizotinib (5). Results of pivotal phase 3 studies have shown that ALK-positive NSCLC is highly sensitive to ALK-targeting agents (Table 5).

Table 5 Summary of Clinical Trials Assessing ALK-targeted Therapy in Patients with NSCLC Carrying ALK-positive Mutations

Treatment	Study phase	ORR (%)	Median PFS (months)	Median OS (months)	Study phase	ORR (%)	Median PFS (months)	Median OS (months)
	First-line treatment outcomes				*Second-line treatment outcomes*			
Crizotinib (64, 65)	III	74	10.9	Not reached	III	65	7.7	20.3
	Crizotinib-naïve				*Crizotinib-refractory*			
Ceritinib (48, 49, 66)	I, II	64–72	11.1–18.4	Not reached	I, II	39–56	5.7–6.9	14.9–16.7
Alectinib (67-70)	I, III	93.5	Not reached	Not reached	II	50.8–52.2	8.1–8.9	Not reached

Immunotherapy in metastatic NSCLC

Immunotherapeutic targeting of programmed death-ligand 1 (PD-L1) or programmed cell death protein 1 (PD-1) is revolutionizing the treatment of metastatic NSCLC (see next section for mechanism). Currently, two anti-PD-1 therapeutic antibodies (pembrolizumab and nivolumab) (71, 72) and one anti-PD-L1 antibody (atezolizumab) (73) have been approved for treatment of NSCLC as monotherapy. Atezolizumab and nivolumab are recommended as second-line agents in advanced NSCLC after prior progression on platinum-containing chemotherapy. Pembrolizumab is approved as a first- and second-line agent in advanced NSCLC.

As the current clinical study focuses exclusively on atezolizumab, a detailed summary of the efficacy and safety profiles of atezolizumab is provided in subsequent sections. A brief summary of the activities of the two approved anti-PD-1 agents is provided in Table 6.

Table 6 Nivolumab and Pembrolizumab Immunotherapy in Advanced NSCLC

Trial	Checkmate 017 (44, 45)	Checkmate 057 (31)	Keynote 010 (32)
Therapy	2L nivo vs. doc	2/3L nivo vs. doc	≥2L pembro vs. doc
n	272	582	1033
Histology	Squamous	Non-squamous	All comers
PD-L1 selected	No	No	Yes (TPS ≥ 1) [a]
Median OS (months)	9.2 vs. 6.0	12.2 vs. 9.4	10.4 [b] vs. 8.5
Median PFS (months)	3.5 vs. 2.8	2.3 vs. 4.2	3.9 [b] vs. 4.0
ORR (%)	20% vs. 9%	19% vs. 12%	18% [b] vs. 9%

doc, docetaxel; L, line; nivo, nivolumab; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival

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

b 2 mg/kg Q3W dose.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin G, subclass 1 (IgG1) monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids). Atezolizumab was engineered to eliminate the crystallizable fragment (Fc)-effector function via a single amino acid substitution that results in a non-glycosylated heavy chain that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human PD-L1 and inhibits the interaction with its receptor, PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells (74). Please refer to the Atezolizumab Investigator's Brochure for further details on nonclinical studies with atezolizumab.

Therapeutic blockade of PD-L1 by atezolizumab enhances the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved atezolizumab (TECENTRIQ®) for two indications: 1) treatment of patients with locally advanced metastatic urothelial carcinoma who have progressed during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; and 2) patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. NSCLC patients with EGFR activating mutations or ALK-positive tumor mutations should also have received targeted therapy before receiving atezolizumab (73, 75).

An increasing number of clinical studies have examined or are examining the use of atezolizumab in NSCLC. A summary of key clinical trials in NSCLC is presented in Section 1.2.1. Please refer to the Atezolizumab Investigator's Brochure for further details on the nonclinical and clinical development program for atezolizumab.

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

1.2.1 Clinical Trials in NSCLC

1.2.1.1 FIR

FIR is a single-arm, phase II study of atezolizumab monotherapy in patients with stage IIIB/IV NSCLC (76, 77). To be eligible, patients had to have PD-L1 expression levels of IC2/3 or TC2/3 at baseline, as determined in the SP142 PD-L1 IHC assay. Cohort 1 included chemotherapy-naive patients without brain metastases, Cohort 2 included patients without brain metastases who had 2 or more prior lines of chemotherapy (2L+), and Cohort 3 included 2L+ patients with treated asymptomatic brain metastases.

Immune-modified objective response rate (ORR), the primary endpoint in the trial, was 29% in Cohort 1 (n=31), 17% in Cohort 2 (n=92), and 23% in Cohort 3 (n=13). There was some evidence that higher PD-L1 expression (TC3 or IC3) was associated with higher ORR (29% in Cohort 1 [n=7]; 26% in Cohort 2 [n=38]; and 25% in Cohort 3 [n=8]). Higher PD-L1 expression may also have been associated with longer PFS and higher landmark PFS and landmark overall survival (OS) rates in previously treated NSCLC patients.

In exploratory studies, results from FIR demonstrated that PD-L1 expression scored consistently across different types of tissue samples, indicating that tissue from primary or metastatic sites, as well as fresh or archival tissue, can be used for PD-L1 testing. In addition, baseline metabolic tumor burden, as defined by FDG-positron emission tomography (PET), was a significant predictor of OS.

1.2.1.2 BIRCH

BIRCH is a phase II study of atezolizumab monotherapy in patients with PD-L1-selected (TC2/3 or IC2/3) advanced NSCLC (78). BIRCH enrolled 3 cohorts of patients based on the number of previous lines of therapy: Cohort 1 included first line (1L) patients; Cohort 2 included 2L patients; and Cohort 3 contained patients who had received third line (3L) therapy or greater. BIRCH met its primary endpoint of achieving ORRs superior to historical controls in all subgroups. ORRs were 19% in Cohort 1 (n=139), 17% in Cohort 2 (n=267), and 17% in Cohort 3 (n=253). Higher PD-L1 expression correlated with higher response. Thus, in the TC3 or IC3 subgroup, ORRs were 26% in Cohort 1 (n=65); 24% in Cohort 2 (n=122); and 27% in Cohort 3 (n=115).

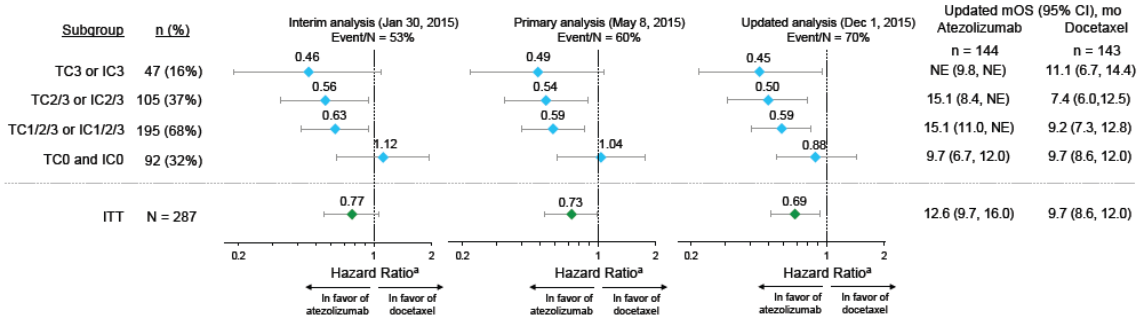
1.2.1.3 POPLAR

POPLAR is a randomized phase II study comparing atezolizumab versus docetaxel in patients with locally advanced or metastatic NSCLC who progressed during or following a platinum regimen (79-82). The co-primary endpoints were OS in the ITT population and OS in the PD-L1-expressing subgroups. To date, three analyses have been conducted on the study population: an interim analysis (data cutoff: Jan 30, 2015) that included 153 events (53% event/patient ratio; 10 months minimum follow-up); the primary analysis (data cutoff: May 8, 2015) that included 173 events (60% event/patient ratio; 13 months minimum follow-up); and an updated analysis (data cutoff: Dec 1, 2015) that included 200 events (70% event/patient ratio; 20 months minimum follow-up).

At baseline, the atezolizumab (n=144) and docetaxel (n=143) treatment groups had well balanced demographics and baseline characteristics. In the ITT population, median OS in the atezolizumab and docetaxel groups were 11.4 months (95% CI, 9.7–NE months) and 9.5 months (95% CI, 8.6–11.9 months) at the interim analysis, 12.6 months (95% CI, 9.7–16.4 months) and 9.7 months (95% CI, 8.6–12.0 months) at the primary analysis, and 12.6 months (95% CI, 9.7–16.0 months) and 9.7 months (95% CI, 8.6–12.0 months) at the updated analysis. The hazard ratios (HR) were 0.77 (p=0.107), 0.73 (p=0.040) and 0.69 (p=0.011) at the three cutoff dates, indicating the clinical benefit of atezolizumab became more apparent with increasing data maturity.

Improvements in OS correlated with increasing PD-L1 expression (Figure 1). There was some evidence of a further separation between the atezolizumab and docetaxel survival curves as the data matured in all PD-L1 expression categories, but it was particularly evident in the TC0 and IC0 subgroup. Further survival improvement with increasing data maturity was also observed in patients with squamous NSCLC who received atezolizumab (HR for primary analysis vs. updated analysis, 0.66 vs. 0.80).

Figure 1 OS Hazard Ratios Over Time and Updated Median OS



In the ITT population, efficacy as measured by PFS and ORR did not reflect the favorable treatment effect of atezolizumab on OS. These data imply that atezolizumab

has benefits on survival that extend beyond disease progression by RECIST v1.1. in patients with locally advanced or metastatic NSCLC.

1.2.1.4 OAK

OAK is a phase III study of atezolizumab monotherapy versus docetaxel in 1225 patients with locally-advanced or metastatic NSCLC. Eligible patients had relapsed disease that was progressing after 1–2 prior lines of chemotherapy (including at least 1 platinum-based regimen) and were allowed to have any PD-L1 expression status. OAK has two co-primary endpoints: OS in the ITT population; and OS in the TC1/2/3 or IC1/2/3 subgroup (≥ 1% PD-L1 expression). The primary outcome analysis (n=850 patients), which was sufficiently powered to test both co-primary endpoints, was presented at the 2016 meeting of the European Society for Medical Oncology (83).

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

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

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

In other analyses, patients with nonsquamous histology, squamous histology, CNS metastases, and no CNS metastases all had significantly longer median survival rates in the atezolizumab group, while patients in the TC3 or IC3 subgroup and in the TC2/3 or IC2/3 subgroup also had longer PFS times in the atezolizumab group. In atezolizumab-treated and docetaxel-treated patients, the ORR rates were 14% and 13%, respectively, in the ITT population and 31% and 11%, respectively, in the TC3 or IC3 subgroup.

1.2.2 Safety

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-related adverse events (irAEs) have been closely monitored during the

atezolizumab clinical program. These include potential dermatologic, hepatic, endocrine, gastrointestinal and respiratory events. Refer to the Atezolizumab Investigator's Brochure for details on irAEs that were observed in patients treated with atezolizumab.

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

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

Currently, no MTD, no DLTs, and no clear dose-related trends in the incidence of adverse events have been determined.

The safety profile of atezolizumab as a single agent is observed to be consistent across different indications, including small cell lung cancer, NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, gastric cancer, colorectal cancer, head and neck cancer, breast cancer, and sarcoma.

Of the 629 patients across all cancer types in Study PCD4989g, 619 patients (98.4%) experienced at least one adverse event (AE), including 444 patients (70.6%) who experienced one treatment-related AE. Commonly reported events (reported in ≥ 10% of all patients) included fatigue, nausea, decreased appetite, diarrhea, constipation, dyspnea, pyrexia, and cough (see Table 7).

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

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

Table 7 Adverse Events Reported in ≥ 10% of Patients in Study PCD4989g

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

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

As of the 1 December 2015 data cutoff date, 142 patients with NSCLC were treated with atezolizumab as a fixed dose of 1200 mg IV every 3 weeks and 135 patients were treated with docetaxel 75 mg/m2 IV q21d in Study GO28753. The frequency of patients with any reported AE regardless of attribution was 96% in both arms. Fewer patients in the atezolizumab arm (41%) experienced Grade 3–4 AEs compared with the docetaxel arm (53%). For Grade 3–4 AEs that were assessed as treatment-related, the difference was greater between the two arms (12% vs. 39%, respectively). The most common atezolizumab-related Grade 3 AEs were pneumonia (2%) and increased aspartate aminotransferase (AST; 2%). No atezolizumab-related Grade 4 events have been reported. Treatment-related AEs reported in at least 10% of patients in either treatment arm are listed in Table 8.

Table 8 Treatment-Related Adverse Events Reported in at Least 10% of Patients in Either Treatment Arm in Study GO28753 (POPLAR)

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

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

As of the 1 December 2015 data cutoff date, 659 patients with NSCLC have been treated with atezolizumab as a fixed dose of 1200 mg IV q21d. In Study GO28754, 93.8% of patients experienced at least one AE, 65% of patients experienced one treatment-related AE, and 12% of patients experienced a Grade ≥ 3 treatment-related AE.

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

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

As described Section 1.2.1, therapy with atezolizumab has been associated with significant survival benefits in patients with locally advanced or metastatic NSCLC in multiple clinical trial settings. The improvement in OS was observed in all patients, as well as in patients with differing histologies (squamous and non-squamous), PD-L1 expression statuses, CNS involvement (with or without CNS metastases at baseline), and anticancer response or PFS. Increasing amounts of evidence also indicate that the atezolizumab treatment effect on OS correlated with the PD-L1 expression status as determined by the VENTANA SP142 PD-L1 assay. Furthermore, across the NSCLC clinical developmental program, atezolizumab has been well tolerated, demonstrating a manageable toxicity profile characterized by a low frequency of mild to moderate AEs. Considering the data as a whole, atezolizumab represents an important new treatment modality for patients with locally advanced or metastatic NSCLC.

Appropriate to their early stages in the clinical development plan, prior clinical trials assessing atezolizumab safety and efficacy in NSCLC had relatively stringent enrollment criteria. This was done in part to ensure optimal safety conditions for the participants, i.e., to screen out participants with greater morbidity who might have been less tolerant of atezolizumab or docetaxel, or more susceptible to AEs arising during the course of the study. The restrictions also helped to ensure a less heterogeneous study population, which in turn limited factors that could complicate the final analyses. Specific examples of such constraints in earlier NSCLC clinical trials are as follows:

- Participants were typically required to have an ECOG performance status of 0 or 1, meaning their disease at baseline imparted relatively limited impact on daily living abilities
- Participants were prohibited from having an autoimmune disease. Treatment of autoimmune diseases typically requires immunosuppressive therapies. It remains unknown how checkpoint inhibition with atezolizumab may impact symptoms and progression of autoimmune diseases. For similar reasons, participants in prior studies were required to have disease that did not require treatment with systemic corticosteroids and/or other systemic immunosuppressive medications
- Participants who had received prior anti-PD-1 therapy were excluded from earlier NSCLC studies. This was appropriate, as anti-PD-1 therapies were relatively new, and few patients in the clinic would have been expected to be eligible to receive multiple lines of PD-1/PD-L1 immunotherapy. However, as these agents become more widely used, it becomes of interest to assess the efficacy and safety profiles of atezolizumab therapy following prior anti-PD-1 therapy
- Finally, in earlier clinical trials, potential enrollees were screened out if they had symptomatic CNS metastases at baseline, or if they had asymptomatic central nervous system (CNS) metastases that were at risk of converting into symptomatic ones (i.e., CNS metastases that had not yet been treated). Patients who had CNS metastases that were effectively managed (i.e., CNS metastases that had received treatment and were asymptomatic) were allowed entry into some studies. Since

CNS metastases are common among patients with lung cancer and have been associated with significant morbidity and mortality (84), a significant impetus exists to assess the effects of atezolizumab in a broader population of patients with brain metastases. Furthermore, participants who had received prophylactic radiotherapy were excluded from earlier NSCLC trials, since radiotherapy delays commencement of systemic therapy and is associated with neurocognitive sequelae as early as 3 months. However, this constraint may not be necessary (to be proven in this study)

Given the high unmet need for new therapies for advanced NSCLC, it is of considerable interest to evaluate atezolizumab in a population of advanced patients that mimics more closely a standard clinical practice population. As a first step in this process, the primary objective of Study MO39171 will be to analyze the long-term safety of atezolizumab in a population of advanced NSCLC patients that includes patients who would have been screened out of many of the previous studies. The large majority of eligibility criteria in Study MO39171 remain unchanged from earlier trials and the safety of participants remains the highest priority. However, a reasonable number of criteria have been broadened:

- Patients with a baseline ECOG performance status of 2 will now be eligible for enrollment, in addition to patients with ECOG performance statuses of 0 and 1
- Patients who had received prior anti-PD-1 therapy will be eligible for enrollment
- Patients with untreated asymptomatic CNS metastases will be eligible, provided they meet the other criteria outlined in Inclusion Criterion # 6
- Patients with CNS metastases will be allowed to receive steroid treatments if the dose of prednisone is ≤ 20 mg/day (or equivalent)
- Patients with underlying controlled and stable autoimmune diseases will be allowed

In addition to assessing safety, the current study will have secondary objectives to assess OS, response, and patient-reported outcomes (PROs), which will further advance the understanding of atezolizumab therapy in patients with NSCLC. Finally, in exploratory analyses, the study will assess ORR prior to the next subsequent line of therapy, evaluate PD-L1 and other biomarkers in tumor tissue, and correlate results with efficacy and safety outcomes. These studies will continue to expand our understanding of atezolizumab and lay the groundwork for future clinical trials.

For additional rationale statements explaining the current study design, please refer to Section 3.3.

Several steps will be taken to ensure the safety of participants in MO39171. First, 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 (Section 4.3). Second, identified and potential risks associated with atezolizumab treatment will continue to be closely monitored throughout this study (Section 5.1.1).

Third, the study will have an independent data monitoring committee (iDMC) to assess safety signals on an ongoing basis. Finally, the study contains protocol-specified drug interruption criteria designed to ensure safety (Section 5.1.2).

Overall, the efficacy and safety data in ongoing studies have shown a favorable benefit/risk ratio for atezolizumab treatment in patients with NSCLC. With the above safety precautions in place, the estimated benefits of atezolizumab treatment outweigh the risks in this study, especially given the potential of atezolizumab in patients with advanced NSCLC.

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

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

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (85). However, there are insufficient and inconsistent clinical data to assess if outcome from COVID-19 is altered by cancer immunotherapy.

Severe COVID-19 appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-γ (86). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from COVID-19.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for COVID-19–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the long-term safety and efficacy of atezolizumab in patients with locally advanced or metastatic NSCLC who have progressed following standard systemic chemotherapy (including if given in combination with anti-PD-1 therapy, after anti-PD-1 as monotherapy, or after tyrosine kinase inhibitor [TKI] therapy). Patients with a previously detected sensitizing EGFR mutation or ALK fusion oncogene must have received targeted therapy (TKI) followed by at least one line of standard systemic chemotherapy prior to receiving atezolizumab. Overall, patients should not have received more than two lines of standard systemic chemotherapy. Patients will also be eligible if they discontinued first-line or second-line therapy due to intolerance.

Specific objectives and corresponding endpoints for the study are outlined below.

Table 9 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoints
• To evaluate the long-term safety of atezolizumab in previously treated patients with advanced NSCLC	• Incidence of serious adverse events (SAEs) related to atezolizumab treatment • Incidence of immune-related adverse events (irAEs) related to atezolizumab treatment
Main Secondary Objective	**Corresponding Endpoint**
• To evaluate the efficacy of atezolizumab in previously treated patients with advanced NSCLC	• Overall survival (OS) rate at 2 years, defined as the proportion of patients remaining alive 2 years after initiation of study treatment

Other Secondary Objectives	Corresponding Endpoints
• To further evaluate the efficacy of atezolizumab in previously treated patients with advanced NSCLC	• OS, defined as the time from initiation of study treatment to death from any cause • PFS, defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause, whichever occurs first. PFS will be calculated based on disease status evaluated by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) and also by disease status evaluated by the investigator according to modified RECIST • OS rate at 3 years, defined as the proportion of patients remaining alive 3 years after initiation of study treatment • ORR, defined as the percentage of patients who attain complete response (CR) or partial response (PR) according to RECIST v1.1 and also by disease status evaluated by the investigator according to modified RECIST • Duration of response (DOR), defined as the time from initial response to disease progression or death among patients who have experienced a CR or PR (unconfirmed) during the study. Duration of response will be calculated based on disease status evaluated by the investigator according to RECIST v1.1, and also by disease status evaluated by the investigator according to modified RECIST

Exploratory Objectives	Corresponding Endpoints
• To further evaluate the long-term safety and efficacy of atezolizumab in previously treated patients with advanced NSCLC	• Safety and efficacy of atezolizumab in subgroups of the study population differentiated according to: Presence of CNS metastases at baseline (yes vs. no) ECOG performance status (0 or 1 vs. 2) Histologic subtype (squamous vs. non-squamous) History of or current autoimmune disease (yes vs. no) Prior anticancer treatment • Progression-free survival from start of new anti-cancer therapy, defined as the time from initiation of new anti-cancer therapy to objective tumor progression on next-line treatment or death from any cause • Objective response rate from start of new anti-cancer therapy, defined as the percentage of patients who attain complete response (CR) or partial response (PR) • Progression-free survival 2 (PFS2), defined as the time from initiation of study treatment to objective tumor progression on next-line treatment or death from any cause
Exploratory Biomarker Objectives	**Corresponding Endpoints**
• To assess the role of PD-L1 and other biomarkers in the progression and fundamental biology of advanced NSCLC • To evaluate PD-L1 and other biomarkers (e.g., cancer-related genes) as prognostic biomarkers	• Safety and efficacy of atezolizumab in subgroups of the study population differentiated according to: Expression of PD-L1 protein in tumor tissue Presence/absence of other biomarkers in tumor tissue • Correlations between PD-L1 expression and other biomarkers
Patient-Reported Outcome Objectives	**Corresponding Endpoints**
• To evaluate health status utility and HR QoL of atezolizumab in previously treated patients with advanced NSCLC	• EQ-5D-5L index-based and VAS scores • EORTC QLQ-LC13

EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire—Supplemental Lung Cancer Module; EQ-5D, EuroQol 5-Dimension Questionnaire; HR QoL, health-related quality of life; VAS, visual analog scale.

3. STUDY DESIGN

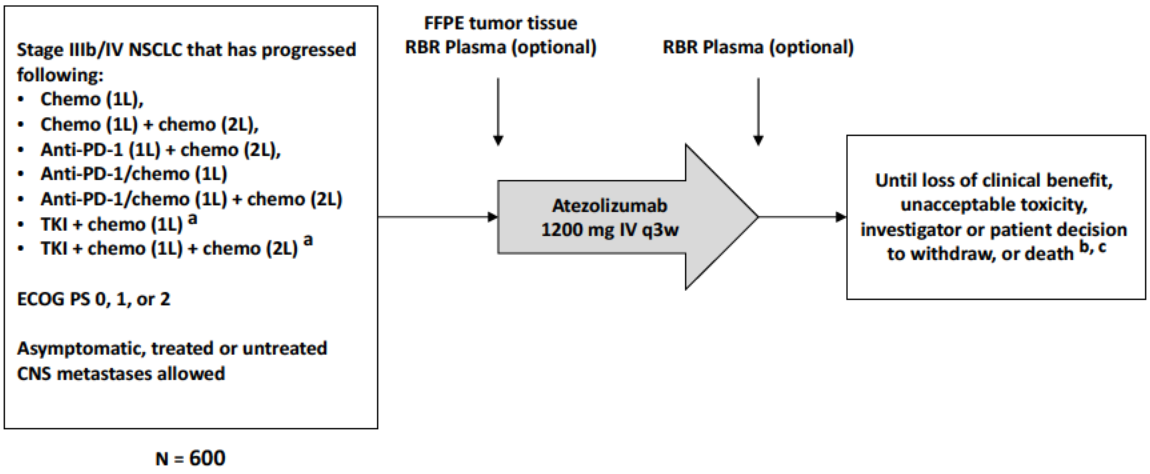
3.1 DESCRIPTION OF THE STUDY

Study MO39171 is a phase III/IV, single-arm, multicenter study of the long-term safety and efficacy of atezolizumab treatment in patients with Stage IIIb or Stage IV NSCLC who have progressed following standard systemic chemotherapy (including if given in combination with anti-PD-1 therapy, after anti-PD-1 as monotherapy, or after TKI therapy). Patients with a previously detected sensitizing EGFR mutation or ALK fusion oncogene must have received targeted therapy (TKI) followed by at least one line of standard systemic chemotherapy prior to receiving atezolizumab. Overall, patients should not have received more than two lines of standard systemic chemotherapy. Patients will also be eligible if they discontinued first-line or second-line therapy due to intolerance.

The study will consist of a Screening Period (Day –28 to Day –1), a Treatment Period, a Treatment Discontinuation Visit occurring ≤ 30 days after the last dose of study medication, and a Follow-Up Period. Day 1 (baseline) will be defined as the first day the patient receives atezolizumab. It is anticipated that the trial will enroll 600 patients at 140 sites globally.

Enrolled patients will receive atezolizumab at a fixed dose of 1200 mg administered intravenously on the first day of each cycle (Figure 2). One cycle of therapy will be defined as 21 days (± 5 days). Atezolizumab treatment will continue until investigator-assessed loss of clinical benefit, unacceptable toxicity, investigator or patient decision to withdraw from therapy, or death (whichever occurs first).

Figure 2 Study Schema



Chemo, standard systemic chemotherapy; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; FFPE, formalin-fixed paraffin-embedded; IV, intravenous; L, line; NSCLC, non-small cell lung cancer; RBR, Research Biosample Repository; TKI, tyrosine kinase inhibitor.

a. Patients with a previously detected sensitizing EGFR mutation or ALK fusion oncogene must have received targeted TKI therapy (no restrictions on number or sequence) followed by at least one line of standard systemic chemotherapy prior to receiving atezolizumab. Patients will also be eligible if they discontinued first-line or second-line therapy due to intolerance.
b. Response will be assessed by the investigator using RECIST v1.1 (see Appendix 2) and modified RECIST (see Appendix 3). Patients who continue atezolizumab treatment beyond radiographic disease progression assessed per RECIST v1.1 will be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 6 weeks, and will be assessed by modified RECIST criteria (see Appendix 3) until treatment discontinuation. If the scan frequency is every 9 weeks (see Appendix 1), a follow-up scan is recommended at 9 weeks or earlier if clinically indicated.
c. In those patients for whom tumor assessments are performed as part of local clinical practice and are available for report after PD or atezolizumab treatment discontinuation, best overall response (BOR) and PFS will be assessed from the first date of the new anticancer therapy to the end of the study per RECIST v1.1 and modified RECIST.

The primary objective of the study is to evaluate the long-term safety of atezolizumab. Long-term safety will be assessed by monitoring the nature, severity, duration, frequency and timing of atezolizumab-related SAEs and atezolizumab-related irAEs. An irAE is defined as any adverse event of special interest (AESI) associated with systemic corticosteroid use within 30 days of the onset date. All-causality AEs, all-causality SAEs, AEs and SAEs leading to atezolizumab interruption or discontinuation, and AESIs will also be reported, as well as causes of death, vital signs, physical findings and clinical laboratory results.

Secondary objectives will assess the efficacy of atezolizumab. The main efficacy objective will be to evaluate the OS rate 2 years after the first dose of atezolizumab.

Other efficacy objectives will include evaluation of OS, OS rate at 3 years, PFS, ORR, and DOR (additional efficacy assessments may occur on an exploratory basis). All antitumor response assessments will be based on RECIST v1.1 and modified RECIST.

Exploratory objectives will include evaluation of the safety and efficacy of atezolizumab in patient subgroups differentiated by: presence or absence of CNS metastases at baseline; ECOG performance status; histological subtype; history of or current autoimmune disease; and prior anticancer treatment. Other exploratory and PRO outcomes will include objective response rate and progression-free survival 2 (PFS2) following start of new anticancer therapy, HR QoL as measured on the EORTC LQ-LC13, health utility score as measured on the EQ-5D-5L instrument, and expression of PD-L1 protein and cancer-related genes in tumor samples obtained before treatment. Finally, exploratory biomarkers may be assessed in tissue to assist in the potential development of new diagnostic assays and to assess biomarkers in terms of prognosis, response/resistance and safety.

Following discontinuation of study treatment, safety assessments will be conducted for 30 days after the last study drug administration or until initiation of other anti-cancer therapy (whichever occurs first). Thereafter, follow-up information on disease progression (unless this has already occurred), anti-cancer therapy and survival will be collected via telephone contact, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, end of study (30 months after last patient in), patient withdrawal or study termination by the Sponsor, whichever occurs first. In addition, irAEs, SAEs and AESIs will be collected as described in Section 5.4.2.

In those patients for whom tumor assessments are performed as part of local clinical practice and are available for report after PD or atezolizumab treatment discontinuation, overall response rate (ORR) and progression-free survival (PFS) will be assessed from the first date of the new anticancer therapy to the end of the study. These data will be used in an exploratory fashion to assess whether prior atezolizumab treatment positively influences response to subsequent anticancer therapies.

An Independent Data Monitoring Committee (iDMC) will be established to review all AEs, irAEs, SAEs, AESIs and other cumulative safety data.

A Schedule of Assessments for this study is provided in Appendix 1.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of study and final analysis will occur when all enrolled patients have either died, withdrawn consent, are lost to follow up, or have been followed for 30 months since the last study patient is enrolled, whichever occurs first.

The primary analysis will occur approximately 6 months after the last patient has been enrolled.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population and Analysis Groups

Please refer to Section 1.3, Study Rationale and Benefit Risk Assessment.

3.3.2 Rationale for an Open-Label Single-Arm Design

The primary objective of this study is to assess the long-term safety profile of atezolizumab in a noncomparative fashion. Thus, as all patients are pre-specified to receive active treatment, the study will have an open-label and non-randomized design.

3.3.3 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 (PK) 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 clinical activity, safety, PK, and immunogenicity data. Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg. The maximum tolerated dose of atezolizumab was not reached, and no dose-limiting toxicities have been observed at any dose in Study PCD4989g. Available preliminary PK data (0.03–20 mg/kg) from Study PCD4989g suggest that for doses ≥ 1 mg/kg, overall atezolizumab exhibits pharmacokinetics that are both linear and consistent with typical IgG1 antibodies.

Detectable anti-therapeutic antibodies (ATAs) were observed in patients at all dose levels but were associated with changes in PK for some patients in only the lower dose cohorts (0.3, 1, and 3 mg/kg). It is unclear from currently available data in these lower dose cohorts if administration of higher doses to patients with both detectable ATAs and reduced exposure would necessarily restore exposure to expected levels. No clear relationship between the development of measurable ATAs and safety or efficacy has been observed. Available data suggest that the development of detectable ATAs does not appear to have a significant impact on the PK for doses from 10 to 20 mg/kg in most

patients. Correspondingly, patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained target trough levels of drug despite the detection of ATAs.

Currently available PK and ATA data suggest that the 15-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent) for Phase II and Phase III studies would be sufficient to both maintain $C_{trough} \geq 6$ µg/mL and further safeguard against both interpatient variability and the potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, moving further to the 20-mg/kg atezolizumab q3w regimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15-mg/kg atezolizumab q3w level.

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

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

3.3.4 Rationale for Biomarker Assessments

PD-L1 expression on tumor cells (TC) and immune cells (IC) varies significantly among patients with NSCLC, and these differing levels of PD-L1 expression have been shown to correlate with atezolizumab response in several studies (76, 79, 80, 87). Further defining the relationship between atezolizumab treatment outcomes in NSCLC and PD-L1 expression continues to be important, as it will advance the understanding of a potential differential benefit from atezolizumab treatment across PD-L1-defined patient subgroups, as well as add to the understanding of the basic biology underlying immune checkpoints and their role in cancer.

Therefore, to address these issues, the current study will collect, if available, tumor tissue obtained at the time of diagnosis (archival tissue) or at any time before the start of atezolizumab therapy and analyze PD-L1 expression by immunohistochemistry (IHC). As PD-L1 IHC is also tested routinely, results from local PD-L1 analysis will be collected instead of central testing or in addition to central testing. Results from the IHC assay will be used to correlate baseline levels of PD-L1 with subsequent safety and efficacy outcomes. If tissue quantity allows, other PD-L1 tests may be conducted to, e.g., assess concordance of methods (the pretreatment sample may also be used for other exploratory biomarker analyses [see next paragraph]).

For patients who received prior PD-1-targeted therapy, results from local PD-L1 testing should be provided, and whenever feasible, archival tissue obtained before the start of PD-1 therapy should be submitted for central IHC analysis. In order to better understand

the effect of anti-PD-1 therapy on PD-L1 expression, as well as its effects on anti-PD-L1 treatment efficacy, a biopsy should be taken prior to receiving atezolizumab therapy (screening biopsy).

NSCLC is a heterogeneous disease involving multiple genetic lesions and alterations in expression patterns (88-90). Therefore, in addition to PD-L1, other biomarkers may be examined in this study on an exploratory basis. This will be accomplished by, e.g., IHC and/or a variety of protein-, DNA- and RNA-based profiling methodologies. These analyses are of significant interest for their potential of revealing molecular mechanisms involved in advanced NSCLC carcinogenesis and susceptibility to atezolizumab treatment.

3.3.5 Rationale for Patient-Reported Outcome Assessments

PRO assessments improve our understanding of a treatment's impact from the patient's perspective, an important consideration in many of today's quality initiatives (91). This study will therefore employ the EORTC QLQ-LC13 instrument to assess self-reported outcomes in all enrolled patients (Appendix 4). The EORTC QLQ-LC13 is a lung-cancer-specific module designed to supplement the more general EORTC QLQ-C30 core measure (92). Developed for use with lung cancer patients undergoing anticancer therapy, the EORTC QLQ-LC13 includes 13 items that address key lung cancer symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related adverse effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication. The dysphagia scale is multi-item, while the rest are single-item scales.

In addition, patients in this trial will complete the EuroQol EQ-5. The EQ-5D-5L is a self-report health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis (93-96). The EuroQol EQ-5D has two components: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort and anxiety/depression, as well as a visual analog scale that measures health state. Published weighting systems allow for creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The EQ-5D will be utilized in this study for economic modeling.

3.3.6 Rationale for Allowing Patients to Continue Atezolizumab Treatment Beyond Initial Progression

Anti-tumor immune responses such as those associated with atezolizumab may result in objective responses that are delayed and that can be preceded by initial apparent radiological progression. This initial apparent progression may occur as a result of either delayed anti-tumor activity and/or robust tumor immune cell infiltration with a concomitant increase in tumor size (pseudo-progression). In addition, lesions that might otherwise be undetectable with conventional imaging may increase in size as a result of these processes and be recorded as new lesions (97).

Furthermore, prior clinical evidence indicates that treatment with atezolizumab beyond apparent PD can have beneficial effects in patients with NSCLC:

- In Study PCD4989g, several patients with NSCLC who progressed by RECIST v1.1 criteria continued on atezolizumab treatment and demonstrated durable anti-tumor activity. In some responding patients, the growth of known lesions or the appearance of new radiographic lesions were shown to contain immune cells and no viable cancer cells on biopsy.
- In POPLAR, 47% of patients who continued atezolizumab after PD had subsequent stable or reduced target lesions relative to baseline (80). Moreover, in the atezolizumab arm of the study, OS from the time of first RECIST v1.1 PD was 11.1 months for patients who continued atezolizumab post PD versus 8.3 months for patients who received a different anti-cancer therapy post PD. These data suggest that continuation of atezolizumab after progression can, in some patients, have a positive benefit-risk profile.

Based on the previous considerations, this study will allow patients to remain on atezolizumab after apparent radiographic progression, provided the benefit-risk ratio is judged to be favorable by the investigator. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status, as described in Section 4.6.2.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll approximately 600 patients with Stage IIIb or Stage IV NSCLC who have progressed following standard systemic chemotherapy (including if given in combination with anti-PD-1 therapy or after anti-PD-1 as monotherapy). Patients with a previously detected sensitizing EGFR mutation or ALK fusion oncogene must have received targeted therapy followed by one line of standard systemic chemotherapy prior to receiving atezolizumab. Overall, patients should not have received more than two lines of systemic chemotherapy. Patients will also be eligible if they discontinued first-line or second-line therapy due to intolerance.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
1. Age ≥ 18 years
2. Able to comply with the study protocol, in the investigator's judgment
3. Histologically or cytologically documented Stage IIIb or Stage IV NSCLC that has progressed following standard systemic chemotherapy (including if given in combination with anti-PD-1 therapy, after anti-PD-1 as monotherapy, or after TKI therapy). Patients with a previously detected sensitizing EGFR mutation or ALK

fusion oncogene must have received targeted therapy (TKI), followed by at least one line of standard systemic chemotherapy, prior to receiving atezolizumab. Overall, patients should not have received more than two lines of standard systemic chemotherapy . Patients who have discontinued first-line or second-line therapy due to intolerance are also eligible

- Staging must be according to the UICC/AJCC system, 7th edition (Detterbeck et al. 2009) (see Appendix 8)
- Pathological characterization may be conducted on tumor specimens from earlier stage disease, but the tumor samples must be sufficient to distinguish squamous or non-squamous histology
- Chemotherapy regimens will be counted based on interval disease progression, and not on the number of agents or the number of switches in agents (e.g., a first-line or second-line therapy that consists of several cycles of a platinum doublet and subsequent maintenance therapy that introduces or switches to a new chemotherapy agent without interval disease progression will all be considered one chemotherapy regimen)
- Patients with a previously-detected sensitizing EGFR mutation must have experienced disease progression (during or after treatment) on an EGFR TKI (erlotinib, gefitinib, osimertinib, etc.)
- Patients with a previously detected ALK fusion oncogene must have experienced disease progression (during or after treatment) with crizotinib, alectinib, or another ALK inhibitor
- Prior radiation therapy is allowed, provided that the patient has recovered from any toxic effects thereof. Combined radiation/chemotherapy treatment constitutes a single regimen
- Combined radiation/chemotherapy treatment (chemoradiation) counts as one prior chemotherapy regimen if < 6 months have elapsed between the last dose and the date of recurrence
- Adjuvant/neoadjuvant chemotherapy is not counted as a line of treatment
- Debulking surgery and anticancer agents used for pleurodesis are not counted as lines of therapy

4. The last dose of prior systemic anticancer therapy or targeted therapy must have been administered ≥ 21 days prior to study treatment initiation
5. The last dose of prior anti-PD-1 therapy must have been administered
   - Nivolumab must have been discontinued ≥ 14 days and pembrolizumab ≥ 21 days prior to study treatment initiation, providing that these treatments were not administered in a clinical trial setting
6. Measurable disease, as defined by Response Evaluation Criteria for Solid Tumors, Version 1.1 (RECIST v1.1)

7. Patients with asymptomatic CNS metastases (treated or untreated), as determined by CT or MRI evaluation during screening and prior radiographic evaluation, are eligible
8. ECOG performance status 0, 1, or 2 [Appendix 7]
9. Life expectancy ≥ 12 weeks
10. Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 2 weeks prior to the first study treatment:
    - Absolute neutrophil count ≥ 1500 cells/μL (without granulocyte colony-stimulating factor support within 2 weeks prior to the first study treatment)
    - White blood cell count > 2500/μL
    - Lymphocyte count ≥ 500/μL
    - Platelet count ≥ 100,000/μL (without transfusion within 2 weeks prior to the first study treatment)
    - Hemoglobin ≥ 9.0 g/dL (patients may be transfused or receive erythropoietic treatment to meet this criterion)
    - Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase ≤ 2.5 times the upper limit of normal (ULN), with the following exceptions:

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

      Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN

    - Serum bilirubin ≤ 1.5 ×ULN. Patients with known Gilbert's Syndrome who have serum bilirubin level ≤ 3 × ULN may be enrolled.
    - Calculated creatinine clearance ≥ 15 mL/min (Cockcroft-Gault formula)
    - International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 ×ULN. This applies only to patients who are not receiving therapeutic anticoagulation agents
    - Patients receiving therapeutic anticoagulation agents must be on a stable dose
    - HIV-positive patients are allowed, so long as they are on stable anti-retroviral therapy, have a CD4 count ≥ 200 cells/μL, and have an undetectable viral load at the time of screening
11. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab
    - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)

- Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception

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

4.1.2 Exclusion Criteria

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

1. Symptomatic CNS metastases
13. 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 study treatment initiation
14. Leptomeningeal disease
15. Uncontrolled pericardial effusion or ascites requiring recurrent drainage procedures
16. Pregnant or lactating, or intending to become pregnant during the study
    - Women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non-drug-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 2 weeks prior to initiation of study drug
17. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)
18. Significant cardiovascular disease, such as New York Heart Association cardiac disease ≥ Class III, myocardial infarction within 3 months, unstable arrhythmias, or unstable angina

– Patients with known coronary artery disease or left ventricular ejection fraction < 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

19. Significant renal disorder requiring dialysis or indication for renal transplant
20. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to study treatment initiation
21. Major surgical procedure within 4 weeks prior to study treatment initiation or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis

22. Inability to understand the local language(s) for which the EORTC QLQ-LC13 and EuroQol EQ-5D-5L questionnaires are available (see Appendix 4 for English versions)
23. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
24. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
25. History of autoimmune disease (Appendix 5) are allowed if controlled and on stable treatment (i.e., same treatment, same dose) for the last 12 weeks, with the exception of:

– Patients taking concurrent abatacept or belatacept treatment, unless therapy has been withdrawn for > 8 weeks

– Patients with a history of serious or life threatening immune-related events

– No more than 1 concomitant autoimmune disease at the time of study entry is allowed unless one of them is:

  Autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone

  Controlled Type I diabetes mellitus on a stable dose of insulin regimen

  A medical history of such entities as atopic disease or childhood arthralgias, where the clinical suspicion of autoimmune disease is low. 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)

26. Prior allogeneic stem cell or solid organ transplantation
27. 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 computed tomography (CT) scan

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

28. Active tuberculosis

– In patients who have a potentially high likelihood of latent tuberculosis (e.g., recent contact with an infectious carrier, residence in a locale with high TB burden), absence of *Mycobacterium tuberculosis* infection must be confirmed before enrollment according to local practice standards

29. Administration of a live, attenuated vaccine within 4 weeks prior to study treatment initiation

– Influenza vaccination should be given during influenza season only (e.g., approximately October to March in the Northern Hemisphere).

– Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to study treatment initiation or at any time during the study

30. Prior treatment with CD137 agonists or immune checkpoint blockade therapies other than anti-PD-1 therapy, including anti−PD-L1 therapeutic antibodies
31. Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to initiation of study treatment

– Prior cancer vaccines and cellular immunotherapy are permitted

32. Specifically for patients without autoimmune disease: 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 study treatment initiation, or anticipated requirement for systemic immunosuppressive medications during the trial

– For patients with CNS metastases, use of prednisone at a stable dose (or dose equivalent) of ≤ 20 mg/day is acceptable
– The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency and topical steroids for cutaneous diseases are allowed

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label (unblinded) study in which all subjects will be assigned to receive the same treatment, i.e., atezolizumab.

4.3 STUDY TREATMENT

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

4.3.1 Formulation, Packaging, and Handling

Atezolizumab will be supplied by the Sponsor as sterile liquid in 20-mL glass vials. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution, but may contain more than the stated volume to enable delivery of the entire 20 mL volume. Atezolizumab will be supplied by the Sponsor as sterile liquid in 20-mL glass vials.

For information on the formulation and handling of atezolizumab, refer to the Atezolizumab Investigator's Brochure and Pharmacy Manual.

4.3.2 Dosage, Administration, and Compliance

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 [± 5] 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. For detailed information on drug preparation, storage and administration, refer to the Atezolizumab Investigator's Brochure.

The initial dose of atezolizumab will be administered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated AEs, 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 the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before, during (every 15 [± 5] minutes if clinically indicated), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated, and 30 minutes (± 10 minutes) after the infusion if clinically indicated or patient experienced symptoms during previous infusions.

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 (Grade 1) National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 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 6.

Guidelines for dosage modification, treatment interruption or discontinuation, and the management of specific adverse events are provided in Section 5.1.2.

Each AE associated with a special situation 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

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

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

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

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

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

4.3.4 Continued Access to Atezolizumab

The Sponsor will offer continued access to Sponsor 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 Sponsor study drug (atezolizumab) after completing the study if all of the following conditions are met:

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

- The Sponsor 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 drug or data suggest that the drug is not effective for non-small cell lung cancer
- The Sponsor has reasonable safety concerns regarding the drug as treatment for non-small cell lung cancer
- Provision of the 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

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any prescription medications or over-the-counter preparations (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days preceding the screening evaluation to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

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

- 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 (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; see Appendix 6).

- Systemic corticosteroids, immunosuppressive medications, 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 after consultation with the Medical Monitor (see Exclusion Criterion 21 [Section 4.1.2] and Prohibited Therapy [Section 4.4.2]). 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 manufacturers' labels and the ASCO and ASCO/ASH guidelines (98, 99).
- Influenza vaccination should be given during influenza season only (approximately October to March in the Northern Hemisphere). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to study treatment initiation or at any time during the study.
- 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.
- Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

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, unless otherwise specified, is prohibited. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, or investigational agents (except for maintenance therapies outlined in Sections 4.1.1 and 4.1.2)

- After completion of Cycle 1, certain forms of radiotherapy may be considered for palliation if patients are deriving benefit (e.g., treatment of known bone metastases)
- 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

- Patients should not receive abatacept or belatacept treatment (those who were receiving it must stop it > 8 weeks before study entry)

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.

Systemic corticosteroids, immunosuppressive medications, 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 after consultation with the Medical Monitor. If feasible, alternatives to these agents should be considered.

Patients with CNS metastases are allowed to receive anticonvulsants and steroid treatments if the dose of prednisone is stable and ≤ 20 mg/day (or equivalent).

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-related procedures. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

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

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases (including autoimmune diseases), surgeries, cancer history (including prior cancer therapies and procedures), reproductive

status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit. A history of pleural or pericardial effusion or of ascites requiring intervention should be entered in the medical history.

Cancer history will also include the histopathologic subtype for all patients and results from molecular analysis (including EGFR mutation and ALK fusion status) for all patients with non-squamous NSCLC. EGFR mutation and ALK testing should be considered for patients with squamous NSCLC who are never smokers, have mixed histology or small biopsy specimen.

If available, PD-L1 immunohistochemistry results, including the name of the assay used, should be documented.

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

4.5.3 Physical Examinations

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

For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before, during (every 15 [± 5] minutes) if clinically indicated, and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated, and 30 minutes (± 10 minutes) after the infusion if clinically indicated or patient experienced symptoms during previous infusions.

4.5.5 Tumor and Response Evaluations

Measurable and non-measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation.

Tumor assessments are to be performed at the timepoints specified in Appendix 1 (± 5 days) regardless of drug delays or interruptions (i.e., independent of treatment cycles).

Screening assessments must include CT scans (with oral/IV contrast unless contraindicated) or MRI of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained, but is not a requirement. MRIs of the chest, abdomen, and pelvis with a noncontrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance).

A CT (with contrast if not contraindicated) or MRI scan of the brain is required at screening for patients with known or suspected CNS metastases, or to confirm or refute a diagnosis of CNS metastases at baseline. Patients with active CNS metastases (treated or untreated) are eligible for this study if they are asymptomatic.

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

Bone scans (Technetium-99m [TC-99m]) or sodium fluoride PET (NaF-PET) should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, or if clinically indicated, TC-99m or NaF-PET bone scans should be repeated when complete response is identified in target disease or when progression in bone is suspected.

CT scans of the neck or extremities should also be performed if clinically indicated and followed throughout the study if there is evidence of disease at screening. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

Results of standard of care tests or examinations performed prior to obtaining Informed Consent and ≤ 28 days prior to study entry may be used for the purposes of Screening rather than repeating such tests.

For subsequent tumor assessments, procedures for tumor assessment should be performed as clinically indicated. 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 (see Appendix 2) and modified RECIST (see Appendix 3). The same evaluator should perform assessments if possible to ensure internal consistency across visits.

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

Patients who continue atezolizumab treatment beyond radiographic disease progression assessed per RECIST v1.1 will be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 6 weeks. If the scan frequency is every 9 weeks (see Appendix 1), a follow-up scan is recommended at 9 weeks or earlier if clinically indicated. Patients will be assessed by modified RECIST criteria (see Appendix 3) until treatment discontinuation.

4.5.6 Ongoing Tumor Assessments

Patients who discontinue study treatment early for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments (See Appendix 1) until the patient dies, experiences confirmed disease progression, withdraws consent, until study termination, or until the study closes, whichever occurs first.

Patients who start a new anti-cancer therapy in the absence of disease progression should continue to be followed for progression according to the protocol schedule of response assessments, unless consent is withdrawn or the patient experiences disease progression or death or until study termination or withdrawal from study, whichever occurs first.

In those patients for whom tumor assessments are performed as part of local clinical practice and are available for report after PD or atezolizumab treatment discontinuation, overall response rate (ORR) and progression-free survival (PFS) will be assessed from the first date of the new anticancer therapy to the end of the study. These data will be used in an exploratory fashion to assess whether prior atezolizumab treatment positively influences response to subsequent anticancer therapies.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology (complete blood count, including red blood cell count, hemoglobin, hematocrit, white blood cell count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)
- Coagulation panel (aPTT and INR)
- Serum pregnancy test (for women of childbearing potential, including premenopausal women who have had a tubal ligation)

- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
- Thyroid function testing (thyroid-stimulating hormone, free triiodothyronine [T3] [or total T3 for sites where free T3 is not performed], free thyroxine [also known as T4])
- HBV serology (HBsAg, antibodies against HBsAg, antibodies against hepatitis B core antigen [anti−HBcAb])
- HBV DNA should be obtained prior to Cycle 1, Day 1 if patient has positive serology for anti-HBc Ab.
- HCV serology (anti-HCV)
- HIV serology

– HIV testing is not required in the absence of clinical symptoms and signs suggestive of HIV infection. HIV-positive patients are allowed, so long as they are stable on anti-retroviral therapy, have a CD4 count ≥ 200 cells/μL, and have an undetectable viral load at the time of screening

- Central EGFR/ALK testing for sites that do not routinely perform testing:

– Patients with non-squamous NSCLC are required to be tested. Patients with squamous NSCLC will not be required to be tested. However, EGFR mutation and ALK testing should be considered for patients with squamous NSCLC who are never-smokers, have mixed histology or small biopsy specimen. At least 7 slides from the most recent FFPE tumor tissue sample (archival material or screening biopsy) must be submitted for central testing during the Screening Period

Samples for exploratory biomarker analyses will be sent to one or several central laboratories for analysis:

- For patients who were not treated with anti-PD1 therapies:

– If available, pre-treatment FFPE tumor tissue (most recent sample) for PD-L1 testing and exploratory biomarkers. Most recent archival sample or a sample obtained during screening should be submitted if available (1 FFPE tissue block or 5–10 slides)

– For patients who have already been tested for PD-L1 by IHC, results and assay name are to be submitted

- For patients who were treated with anti-PD-1 therapy, sites are highly encouraged to submit the following samples if available:

– Archival tissue taken prior to treatment with PD-1 targeting agents (FFPE tissue block or 5–10 slides)

– Screening biopsy taken prior to treatment with atezolizumab (after PD-1 targeting agents (FFPE tissue block or 5–10 slides)

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

Exploratory biomarker research may include, but will not be limited to, the following analyses:

- PD-L1 IHC assessment
- Tumor DNA isolation for detection of gene alterations
- Tumor RNA isolation for gene expression profiling

Unless the patient gives specific consent for his or her leftover or unused samples to be stored for optional exploratory research (see Section 4.5.10.6), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exception:

- Leftover tumor tissue that remains after a maximum of 10 slides have been cut will be returned to the study site

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

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

4.5.8 Electrocardiograms

Single 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the Schedule of Assessments (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

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.

If at a particular postdose timepoint the mean QT interval corrected using Fridericia's formula (QTcF) is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the

investigator. A decision on study drug discontinuation should be made, as described in Section 4.6.2. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.9 Patient-Reported Outcomes

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

One PRO questionnaire will be used in this study:

- EORTC QLQ-LC13: The EORTC QLQ-LC13 is a lung-cancer-specific module designed to supplement the more general EORTC QLQ-C30 core measure (92). Developed for use with lung cancer patients undergoing anticancer therapy, the EORTC QLQ-LC13 includes 13 items that address key lung cancer symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related adverse effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication. The dysphagia scale is multi-item, while the rest are single-item scales.

In addition, subjects in this study will complete the EuroQol 5-Dimension Questionnaire (EQ-5D-5L).

- The EQ-5D-5L is a self-report health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis (93-96). There are two components to the EuroQol EQ-5D: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale (VAS) that measures health state. Published weighting systems allow for creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The EQ-5D will be utilized in this study for economic modeling

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 TAIL Substudy: Stool Sample Collection for the Research Biosample Repository

At selected sites in participating countries, a substudy will be conducted to examine stool samples collected from patients in Study MO39171. Please refer to Appendix 10 for detailed information about the substudy's rationale and sample collection procedures.

4.5.10.2 Overview of the Research Biosample Repository

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

RBR specimens will be used to achieve the following objectives:

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

4.5.10.3 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.4 Sample Collection

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

- Leftover or unused FFPE tissue samples or derivatives thereof after study-related tests have been performed
- Ten milliliters (10 mL) whole blood for plasma preparation will be collected at baseline and at the time of disease progression

The above samples may be sent to one or more laboratories for DNA and RNA extraction to enable analysis of tumor mutations via next-generation sequencing (NGS), or other genetic analysis methods, as well as for gene expression or protein analyses.

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

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

4.5.10.5 Confidentiality

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

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

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

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

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

4.5.10.6 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.10.7 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study MO39171 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study MO39171.

4.5.10.8 Monitoring and Oversight

RBR 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. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

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

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Subjects who discontinue will be asked to provide consent allowing the Study Investigator and/or F. Hoffman-La Roche Ltd to collect follow up information regarding disease progression and survival. Otherwise, without this consent, patients will not be followed for any reason after withdrawal. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment (but will continue to receive tumor assessments) if they experience any of the following:

- Intolerable toxicity related to study treatment
- Myocarditis of any grade
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment
- Use of another systemic anti-cancer therapy (see Section 4.4.2)
- Pregnancy
- Radiographic disease progression per RECIST v1.1

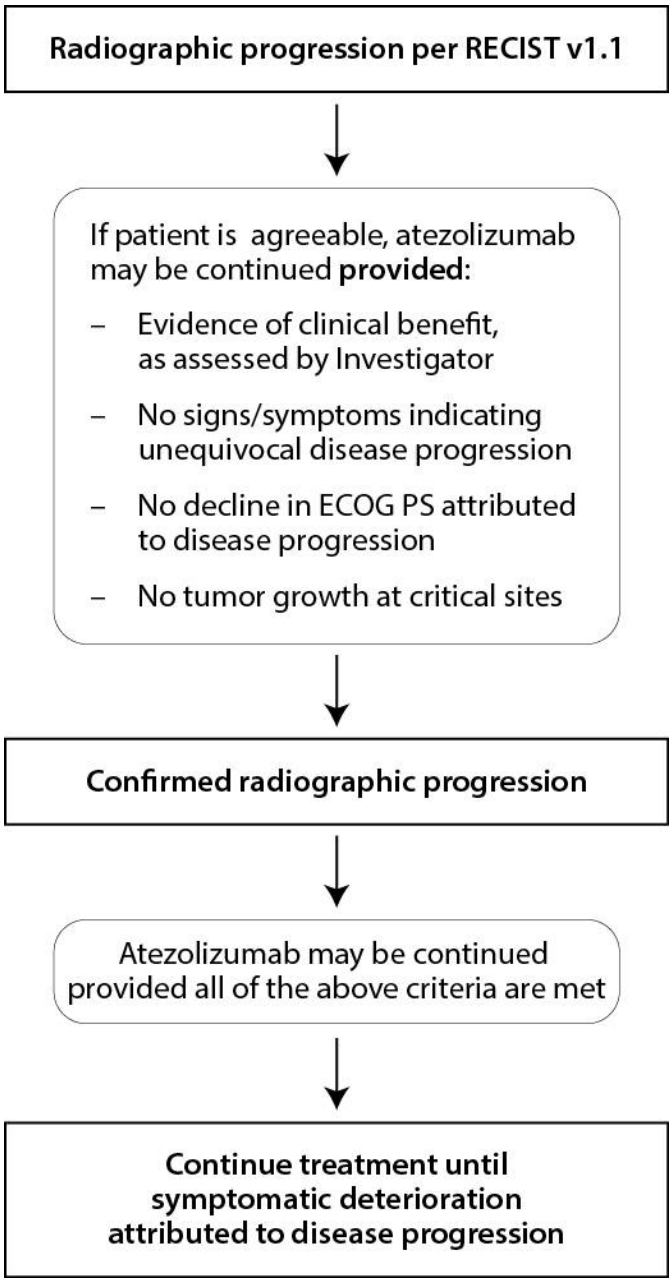
  Exception: Patients will be permitted to continue atezolizumab after RECIST v1.1 criteria for progressive disease are met if they meet all of the following criteria (see Figure 3 for schematic representation):

  - Evidence of clinical benefit (defined as the stabilization or improvement of disease-related symptoms) 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 readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing

  Patients who demonstrate confirmed radiographic disease progression may be considered for continued study treatment at the discretion of the investigator, provided they continue to meet all the criteria above

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

Figure 3 Conditions for Continuing Atezolizumab in the Presence of Increased Radiographic Tumor Size



ECOG PS, Eastern Cooperative Oncology Group performance status; ICF, Informed Consent Form; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, Version 1.1.

4.6.3 Study and Site Discontinuation

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

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

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

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is derived from clinical experience with atezolizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Section 5.1.1).

Measures will be taken to ensure the safety of patients participating in this study, including the use of carefully chosen inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new anti-cancer therapy, whichever occurs first. SAEs and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new anti-cancer therapy, whichever occurs first.

Guidelines for managing anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below (Section 5.1.2), in Appendix 9 and in the Atezolizumab Investigator's Brochure. Refer to Sections 5.2–5.6 for details on safety reporting during the study.

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

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (86). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-related reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab. Refer to Appendix 9 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Management of Patients Who Experience Specific Adverse Events

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

Atezolizumab may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from study drug. If the investigator believes the patient is likely to derive clinical benefit and the Medical Monitor is in agreement, atezolizumab can be resumed after being withheld for > 12 weeks after event onset.

If a patient must be tapered off steroids that have been used to treat adverse events, then atezolizumab may be withheld for more than 12 weeks after event onset until the steroids are discontinued or reduced to a prednisone dose (or dose equivalent) of ≤ 10 mg/day. For patients with CNS metastases or autoimmune disease who require chronic steroid therapy, who have been receiving additional steroids to treat adverse events, and who now require a reduction in steroid dosage, atezolizumab may be withheld for more than 12 weeks after event onset until the steroid dosage has returned

to its baseline value. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

Dose interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-related adverse events (irAEs) have been closely monitored during the atezolizumab clinical program. Guidelines for the management of patients who experience specific adverse events associated with atezolizumab (i.e., pulmonary, hepatic, gastrointestinal, endocrine, ocular, infusion-related [IRR], pancreatic, dermatologic, neurologic, or autoimmune events) are provided in Appendix 9 and Section 6 (Guidance for the Investigator) of the Atezolizumab Investigator's Brochure.

For patients developing a new autoimmune disease not listed in the Atezolizumab Investigator's Brochure, or for patients with an autoimmune disease who develop a flare, the following dosing guidance should be applied:

- Grade 1 event: atezolizumab dosage should be maintained
- Grade 2 or 3 event: atezolizumab should be suspended until the subject responds to treatment of the autoimmune disease and the disease becomes stable (see rules above regarding maximum suspended time). The subject should be referred to an appropriate specialist
- Grade 4 event: atezolizumab should be permanently discontinued and the subject should be referred to an appropriate specialist

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a

pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Sections 5.3.5.9 and 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

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:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hypothyroidism, hypophysitis or hyperthyroidism
- Hepatitis, including AST or ALT > 10 x ULN
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenia gravis, meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH, and MAS
- Cardiac disorders – Grade ≥ 2 in severity (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Myositis
- Myopathies, including rhabdomyolysis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is

considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study drug and 90 days for serious adverse events or adverse events of special interest.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 10 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 10 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 11):

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

Table 11 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (>3 x baseline value) in combination with either an elevated total bilirubin (>2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST >3 x baseline value in combination with total bilirubin >2 × ULN (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 an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of locally advanced or metastatic NSCLC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An iDMC will monitor the frequency of deaths from all causes.

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

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

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or to perform an efficacy assessment for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

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

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

5.3.5.12 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as “special situations”) are defined as follows:

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

  In some cases, a medication error may be intercepted prior to administration of the drug.

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

- Accidental overdose: Enter the adverse event term. Check the "Overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Overdose" and "Medication error" boxes.

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

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

- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

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

5.3.5.13 Patient-Reported Outcome Data

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

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

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor/Roche Medical Responsible: [redacted], M.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

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

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial 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, all adverse events will be reported until 30 days after the last dose of study drug and until 90 days for serious adverse events or adverse events of special interest. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial 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 serious adverse events that occur > 30 days after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

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

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 30 days after the last dose of study drug for all AEs and 90 days for serious adverse events and adverse events of special interest), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- **Atezolizumab Investigator's Brochure**

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

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

An IDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is an open-label, single-arm safety study.

Analysis populations

This study will include the following analysis populations:

- Safety population: The primary analysis population for this study will include all enrolled patients who have received at least one dose of atezolizumab. The safety population will be used for all baseline and safety analyses, unless otherwise stated
- Intent-to-treat population: The intent-to-treat (ITT) population will include all enrolled patients

A per-protocol population will not be defined for this study. However all major deviations (at study entry and on study) will be summarized and reported.

6.1 DETERMINATION OF SAMPLE SIZE

No formal sample size calculation linked to hypothesis testing is done for this descriptive study. The sample size considerations are based upon estimation precision for the incidence of AEs. With 600 patients, the following 95% CIs (Table 12) could be provided for the different incidences of AEs, which is deemed appropriate for the purposes of the study.

Table 12 Adverse Event Incidence and Corresponding 95% Confidence Intervals

Sample Size	AE Incidence	95% Clopper-Pearson Exact CI
600 patients	1%	1% [0.2% ; 1.8%]
	2%	2% [0.9% ; 3.1%]
	3%	3% [1.6% ; 4.4%]
	5%	5% [3.3% ; 6.7%]
	10%	10% [7.6% ; 12.4%]

CI, confidence interval.

6.2 ANALYSIS OF THE CONDUCT OF THE STUDY

Enrollment (e.g., by country, by site), screening failures, study treatment administration, and discontinuation (including reasons) from the study will be summarized using descriptive statistics.

6.3 SUMMARIES OF TREATMENT GROUP

Demographic and other baseline characteristics (at patient and disease level), medical history, prior treatments (study and non-study condition related) will be presented descriptively using the overall safety population. These may also be presented using the ITT population if the difference is more than 5 patients compared with the number of patients in the safety population.

6.4 PRIMARY ENDPOINT ANALYSIS

All safety analyses will be run on the Safety Analysis set, defined as all enrolled patients who had at least one administration of atezolizumab. The primary analysis will occur approximately 6 months after the last patient has been enrolled.

The incidence of SAEs related to atezolizumab and the incidence of irAEs related to atezolizumab will be summarized by incidence rates and 95% Pearson-Clopper confidence intervals.

6.5 MAIN SECONDARY ENDPOINT ANALYSES

6.5.1 Landmark Analysis

Estimates of OS rates at 24 and 36 months in the ITT population will be provided using the Kaplan-Meier methodology, along with 95% CIs calculated using Greenwood's formula.

6.6 OTHER SECONDARY ENDPOINT ANALYSES

6.6.1 Other Safety Analyses

Safety analyses include the following:

- All causality AEs
- All causality AEs (Grades 3–5)
- All causality SAEs
- AEs and SAEs leading to atezolizumab interruption or discontinuation
- AESIs
- irAEs
- Causes of deaths
- Changes from baseline in vital signs during and following atezolizumab administration
- Changes from baseline in clinical laboratory results during and following atezolizumab administration
- Concomitant medications

AEs will be displayed in standard frequency tables according to overall frequency and severity. Time to first incidence of AEs, SAEs, AEs (Grades 3–5) and irAEs will be estimated using the Kaplan-Meier approach. AEs and laboratory parameters will be assessed by the investigator according to the National Cancer Institute Common Terminology Criteria, Version 4.0 (NCI CTC v4.0). AEs and/or SAEs will be coded and analyzed by "preferred terms" according to the Medical Dictionary for Regulatory Activities (MedDRA) and evaluated descriptively

6.6.2 Other Efficacy Analyses

Overall Survival

OS is defined as the time from initiation of study treatment to death from any cause. Data for patients who are not reported as having died at the time of analysis will be censored at the date they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of initiation of study treatment plus 1 day.

Progression-Free Survival

PFS is defined as the time (in months) between the date of initiation of study treatment and the date of first documented disease progression or death, whichever occurs first. PFS will be calculated based on disease status evaluated by the investigator according to RECIST v1.1 and also by disease status according to modified RECIST. Patients who are alive and have not experienced disease progression at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the time of initiation of study treatment plus 1 day.

Objective Response Rate

Objective response is defined as a confirmed complete or a partial response per RECIST v1.1 and/or modified RECIST. Patients without any post-baseline tumor assessments will be considered non-responders. An estimate of ORR will be provided along with the corresponding 95% CIs calculated using the Clopper-Pearson method.

Duration of Response

For patients who have experienced an objective response (CR or PR) during the study as assessed by the investigator, DOR is defined as the duration from the first tumor assessment that supports the patient's objective response (CR or PR, whichever is first recorded) to disease progression or death due to any cause, whichever occurs first. Patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the time of the last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a complete or partial response, DOR will be censored at the date of the first occurrence of a complete or partial response plus 1 day. Two separate analyses will be presented for RECIST v1.1 and modified RECIST.

6.6.3 Exploratory Efficacy Analysis

The following efficacy endpoints will be evaluated to further asses the efficacy of atezolizumab after disease progression (no confirmation of response will be required for these analyses)

In those patients who received further anti-cancer therapy:

- Progression-free survival from start of new anti-cancer therapy, defined as the time from initiation of new anti-cancer therapy to objective tumor progression on next-line treatment or death from any cause
- Objective response rate from start of new anti-cancer therapy, defined as the percentage of patients who attain complete response (CR) or partial response (PR)

In the ITT population:

- Progression-free survival 2 (PFS2), defined as the time from initiation of study treatment to objective tumor progression on next-line treatment or death from any cause

The prior analyses might be repeated in the following subgroups, if enough patients are available:

- Presence of CNS metastases at baseline (yes vs. no)
- ECOG performance status (0 or 1 vs. 2)
- Histologic subtype (squamous vs. non-squamous)
- History of or current autoimmune disease (yes vs. no)
- Prior anticancer treatment

6.7 INTERIM ANALYSES

This study will have no formal interim analyses. However, regular safety reviews of data will be performed by an Independent Data Monitoring Committee (iDMC). The frequency of these reviews will be stated in the iDMC charter.

In addition, to adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim analysis for reporting and publication of safety and efficacy results.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the

Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 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 trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. and was designed in collaboration with outside guidance from a Steering Committee. The Sponsor will provide clinical operations management, data management, and medical monitoring. An iDMC will review SAEs and accumulating safety data.

Approximately 140 sites globally will participate to enroll approximately 600 patients.

Enrollment will occur through an IxRS system. Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests and biomarker analyses) as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

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

10. REFERENCES

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Appendix 1
Schedule of Assessments

	Screening Period		Treatment Period	Treatment Discontinuation	Follow-Up Period
	Day –28 to Day –1	Day –14 to –1	Day 1 (± 5 days) of each 3-week treatment cycle	≤ 30 days from last dose or at initiation of new anti-cancer therapy (whichever occurs first)	
Informed consent [a]	x				
Review of eligibility criteria	x				
Medical history and demographics [b]	x				
Weight	x		x	x	
Height	x				
Complete physical examination [c]	x			x	
Limited physical examination [c, d]			x [d]		
ECOG Performance Status [e]	x		x [d]	x	
Vital signs [f]	x		x	x	
12-lead ECG [g]	x		as clinically indicated		
HIV, HBV, HCV serology [h]	x		as clinically indicated		
Hematology [i]		x	x [d]	x	
Coagulation (aPTT, INR)		x		x	
Thyroid function testing [j]		x	Cycle 2, Day 1, then every other cycle		
Serum chemistry [k]		x	x [d]	x	
Urinalysis [l]		x	x [d]	x	

Appendix 1
Schedule of Assessments (cont.)

	Screening Period		Treatment Period	Treatment Discontinuation	Follow-Up Period
	Day –28 to Day –1	Day –14 to –1	Day 1 (± 5 days) of each 3-week treatment cycle	≤ 30 days from last dose or at initiation of new anti-cancer therapy (whichever occurs first)	
Pregnancy test [m]		x	Every 3 cycles		
Tumor assessment [n]	x [o]		Every 6 weeks for 48 weeks, thereafter every 9 weeks until PD (regardless of atezolizumab discontinuation) or until loss of clinical benefit for patients treated beyond progression [p]		
EGFR/ALK testing [q]	x				
Submission of pre-treatment tumor tissue (biomarker) [r, s]		x [u]			
Plasma for RBR (optional) [t]		x [u]		PD	
EORTC QLQ-LC13 & EQ-5D-5L [v]			Day 1 of first 3 cycles, then with tumor assessments		
Concomitant medications [w]	x		x	x	
Adverse events [x]	x		x	x	x
Study drug infusion			x		
Survival and new anti-cancer therapy [y]				x	x

Abbreviations: aPTT: activated partial thromboplastin time; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer; INR: international normalized ratio; PD: progressive disease; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events

Note: Unless otherwise indicated, assessments scheduled on the study treatment days should be performed prior to initiation of study treatment infusion.

a. 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 28 days prior to study entry (except where otherwise specified) may be used for screening assessments rather than repeating such tests.

b. Medical history includes surgical and cancer histories. Cancer history includes stage, date of diagnosis, prior anti-cancer treatment, EGFR/ALK status and, if available, PD-L1 status. Reproductive status and smoking history should also be captured. Demographic information includes age, sex, and self-reported race/ethnicity.
c. A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.
d. Limited physical examination, ECOG performance status (Appendix 7), and local laboratory assessments may be obtained ≤ 96 hours before Day 1 of each cycle. It is not necessary to repeat these assessments again prior to Cycle 1 if they have been conducted for screening within this time period.
e. See Appendix 7.
f. Vital signs include respiratory rate, heart rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Treatment cycle Day 1 vital sign assessments will be done prior to study treatment.
g. ECG recordings will be obtained during screening and when clinically indicated. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG recording.
h. Refer to Section 4.5.7. HIV testing is not required in the absence of clinical symptoms and signs suggestive of HIV infection; patients with a positive serological test may be enrolled so long as they are stable on anti-retroviral therapy, have a CD4 count ≥ 200 cells/μL, and have an undetectable viral load at the time of screening.
i. Hematology consists of CBC (including RBC count), hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. A manual differential may be done if clinically indicated.
j. Includes thyroid-stimulating hormone (TSH), free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), free thyroxine (also known as T4).
k. Serum chemistry includes glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.
l. Urinalysis includes specific gravity, pH, glucose, protein, ketones, and blood.
m. A serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1. On study pregnancy tests performed every 3 treatment cycles can be conducted with serum or urine.
n. The same radiographic procedure should be used throughout the study for each patient. A CT (with contrast) or MRI of the head must be included in screening tumor assessments for patients with known or suspected CNS disease. Results must be reviewed by the investigator before dosing at the next cycle. Patients who continue treatment beyond radiographic disease progression assessed per RECIST v1.1 should be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 6 weeks, and will be assessed

by modified RECIST criteria (see Appendix 3) until treatment discontinuation. If the scan frequency is every 9 weeks, a follow-up scan is recommended at 9 weeks or earlier if clinically indicated. Investigators may perform additional scans or more frequent assessments if clinically indicated.

o. Ideally within 14 days of the start of study treatment.

p. Patients will undergo tumor assessments at baseline, every 6 weeks ± 5 days for the first 48 weeks following treatment initiation, and every 9 weeks thereafter until radiographic disease progression per RECIST v1.1 or (for patients who continue atezolizumab after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 4.6.2 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy.

q. For sites where EGFR/ALK testing is not routinely performed at local laboratories, a minimum of 7 consecutively cut slides from a most recent FFPE tumor tissue block must be submitted for EGFR/ALK testing for all patients with non-squamous NSCLC. Testing is not required for patients who have squamous NSCLC. EGFR mutation and ALK testing should be considered for patients with squamous NSCLC who are never-smokers, have mixed histology or small biopsy specimen.

r. If available, pre-treatment FFPE tumor tissue (most recent sample) for PD-L1 testing and exploratory biomarkers. Most recent archival sample or a sample obtained during screening should be submitted if available (1 FFPE tissue block or 5–10 slides).

s. From patients who received anti-PD-1 therapy, sites are highly encouraged to provide archival FFPE tissue (prior anti-PD1 therapy) and an FFPE tissue biopsy obtained during screening (archival and screening tissue sample).

t. Ten milliliters (10 mL) whole blood for plasma. Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

u. Only to be shipped if the patient is eligible for enrollment.

v. See Appendix 4.

w. 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.

x. After informed consent has been obtained, but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all SAEs and AESIs, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other AEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period, the investigator should report any SAEs or AESIs believed to be related to prior study drug treatment. The investigator should follow each AE 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 SAEs considered to be related to study drug or study-related procedures until a final outcome can be reported.

y. Survival and new anti-cancer therapy follow-up information will be collected via telephone contact, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, end of study (30 months after the last patient in), patient withdrawal or study

termination by the Sponsor, whichever occurs first. In those patients for whom tumor assessments are performed and available for report after PD or treatment discontinuation, best overall response (BOR) will be assessed from the first date of the new anticancer therapy to the end of the study per RECIST v1.1. These data will be used in an exploratory fashion to assess whether prior atezolizumab treatment positively influences response to subsequent anticancer therapies.

Appendix 2
Response Evaluation Criteria in Solid Tumors, Version 1.1: Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 [1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or nonmeasurable as follows:

Measurable Tumor Lesions

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

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

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Nontarget Lesions" for information on lymph node measurement.

Nonmeasurable Tumor Lesions

Nonmeasurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

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

Cystic lesions:

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

Lesions with prior local treatment:

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

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of Lesions

All measurements should be recorded in metric notation, with use of calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Appendix 2
Response Evaluation Criteria in Solid Tumors:
Modified Excerpt from Original Publication (cont.)

Method of Assessment

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

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

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

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

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

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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

BASELINE DOCUMENTATION OF TARGET AND NONTARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as nonmeasurable lesions (even if the size is >10 mm by CT scan).

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

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

but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

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

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

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

RESPONSE CRITERIA

Evaluation of Target Lesions

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

- **Complete response (CR)**: disappearance of all target lesions

  Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.

- **Partial response (PR)**: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- **Progressive disease (PD)**: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- **Stable disease (SD)**: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Special Notes on the Assessment of Target Lesions

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

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

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

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

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

Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. Whereas some nontarget lesions may actually be

measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- **CR**: disappearance of all nontarget lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size (< 10 mm short axis).

- **Non-CR/Non-PD**: persistence of one or more nontarget lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- **PD**: unequivocal progression of existing nontarget lesions

  The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Nontarget Disease

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

When the Patient Has Only Nonmeasurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. Whereas it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

When the patient has bone lesions at baseline. When a bone scan is the sole indicator of progression, progression in bone will be defined as when at least two or more new lesions are seen on bone scan compared with screening. In situations where the scan findings are suggestive of a flare reaction, or apparent new lesion(s) which may represent trauma, these results must be confirmed with other imaging modalities such as MRI or fine-cut CT to constitute progression. Only a single new bone lesion on bone scan is required for progression if the lesion can be correlated on CT, MRI or plain film.

New Lesions

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

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

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

New osteoblastic bone lesions identified on plain films, CT, or MRI will not be considered progression in an otherwise stable or responding subject, if, in the opinion of the physician, the osteoblastic lesion appears to be healing or a response to therapy.

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

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

When patients have nonmeasurable (therefore nontarget) disease only, Table 2 is to be used.

Appendix 2
Response Evaluation Criteria in Solid Tumors:
Modified Excerpt from Original Publication (cont.)

Table 1 Timepoint Response: Patients with Target Lesions (with or without Nontarget Lesions)

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

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

Table 2 Timepoint Response: Patients with Nontarget Lesions Only

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

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

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

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely

to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

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

Table 3 Best Overall Response When Confirmation Is Required

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

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

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

NOTE: In this study, stable disease must persist for at least 6 weeks (minimum duration) to be considered a bona fide SD.

Special Notes on Response Assessment

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

Appendix 2
Response Evaluation Criteria in Solid Tumors:
Modified Excerpt from Original Publication (cont.)

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and nontarget disease as shown in Table 1, Table 2, and Table 3.

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

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

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.

Modified RECIST is derived from RECIST, Version 1.1 conventions [3] and immune-related response criteria [4] (irRC).

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; may 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

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[3] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

[4] 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.

performed, as clinically indicated for suspicion of progression. The investigator will evaluate response to treatment using modified RECIST.

MEASURABLE LESIONS

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

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

NON-MEASURABLE LESIONS

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

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.

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.

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.

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.

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 (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 INEVALUABLE 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.

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:

- **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.
- **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.
- **SD**: Criteria for CR, PR, and PD are not met.
- **PD**: Increase in the sum of the diameters of all target and all new measurable lesions ≥ 20% relative to the nadir, which may be 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
EORTC QLQ-LC13 and EQ-5D-5L

ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		**Not at All**		**Quite a Bit**	**Very Much**
31	How much did you cough?	1	2	3	4
32	Did you cough up blood?	1	2	3	4
33	Were you short of breath when you rested?	1	2	3	4
34	Were you short of breath when you walked?	1	2	3	4
35	Were you short of breath when you climbed stairs?	1	2	3	4
36	Have you had a sore mouth or tongue?	1	2	3	4
37	Have you had trouble swallowing?	1	2	3	4
38	Have you had tingling hands or feet?	1	2	3	4
39	Have you had hair loss?	1	2	3	4
40	Have you had pain in your chest?	1	2	3	4
41	Have you had pain in your arm or shoulder?	1	2	3	4
42	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where? _____				
43	Did you take any medicine for pain?				
	1 No **2 Yes**				
	If yes, how much did it help?	1	2	3	4

Figure 1: EQ-5D-5L (UK English sample version)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

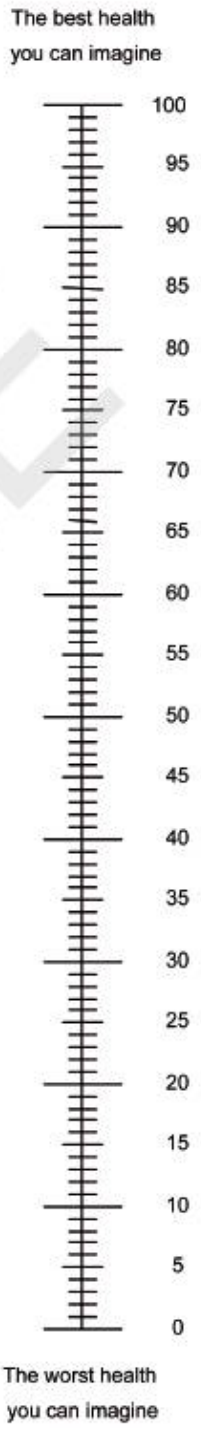
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



Appendix 5
Preexisting Autoimmune (Chronic Inflammatory) Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with an history of immune deficiencies or autoimmune disease (see Table below) are allowed in the study.

Patients with a history of more than one immune deficiency or autoimmune disease are excluded from participating in the study unless one of them is:

- Autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone
- Controlled Type I diabetes mellitus on a stable dose of insulin regimen
- A medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis).

Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life–threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent. Please contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Acute disseminated encephalomyelitis	Epidermolysis bullosa acquista	Ord's thyroiditis
Addison's disease	Gestational pemphigoid	Pemphigus
ANKA positive vasculitis	Giant cell arteritis	Pernicious anemia
Ankylosing spondylitis	Glomerulonephritis	Polyarteritis nodusa
Antiphospholipid antibody syndrome	Goodpasture's syndrome	Polyarthritis
Aplastic anemia	Graves' disease	Polychondritis
Autoimmune hemolytic anemia	Guillain-Barré syndrome	Polyglandular autoimmune syndrome
Autoimmune hepatitis	Hashimoto's disease	Polymyositis
Autoimmune hypoparathyroidism	IgA nephropathy	Primary biliary cirrhosis
Autoimmune hypophysitis	Inflammatory bowel disease	Psoriasis
Autoimmune myocarditis	Interstitial cystitis	Pyoderma gangrenosum
Autoimmune oophoritis	Kawasaki's disease	Reactive arthritis
Autoimmune orchitis	Lambert-Eaton myasthenia syndrome	Rheumatoid arthritis

Appendix 5
Preexisting Autoimmune (Chronic Inflammatory) Diseases (cont'd)

Autoimmune thrombocytopenic purpura	Lupus erythematosus	Sarcoidosis
Behcet's disease	Lyme disease – chronic	Scleroderma
Bullous pemphigold	Mixed connective tissue disease	Sjögren's syndrome
Celiac disease	Mooren's ulcer	Stiff-Person syndrome
Chronic fatigue syndrome	Morphea	Takayasu's arteritis
Chronic inflammatory demyelinating polyneuropathy	Multiple sclerosis	Ulcerative colitis
Chung-Strauss syndrome	Myasthenia gravis	Vitiligo
Crohn's disease	Neuromyotonia	Vogt-Kovanagi-Harada disease
Dermatomyositis	Opsoclonus myoclonus syndrome	Wegener's granulomatosis
Dysautonomia	Optic neuritis	

Appendix 6
Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

1. Stop the study drug infusion.
2. Call for additional medical assistance
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
5. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 7
Eastern Cooperative Oncology Group Performance Status Scale

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

Appendix 8
American Joint Committee on Cancer
Non-Small Cell Lung Cancer Staging, 7th Edition

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS	PATHOLOGIC *Extent of disease through completion of definitive surgery*
☐ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	TUMOR SIZE: _____ LATERALITY: ☐ left ☐ right ☐ bilateral	☐ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)	
☐ TX	Primary tumor cannot be assessed	☐ TX
☐ T0	No evidence of primary tumor	☐ T0
☐ Tis	Tis Carcinoma in situ	☐ Tis
☐ T1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*	☐ T1
☐ T1a	Tumor ≤2 cm in greatest dimension	☐ T1a
☐ T1b	Tumor > 2 cm but ≤3 cm in greatest dimension	☐ T1b
☐ T2	Tumor > 3 cm but ≤7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤ 5 cm) Involves main bronchus, ≥2 cm distal to the carina Invades visceral pleura (PL1 or PL2) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung	☐ T2
☐ T2a	Tumor > 3 cm but ≤5 cm in greatest dimension	☐ T2a
☐ T2b	Tumor > 5 cm but ≤7 cm in greatest dimension	☐ T2b
☐ T3	Tumor > 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (< 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe	☐ T3
☐ T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe	☐ T4
	* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.	
	REGIONAL LYMPH NODES (N)	
☐ NX	Regional lymph nodes cannot be assessed	☐ NX
☐ N0	No regional lymph node metastasis	☐ N0
☐ N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	☐ N1
☐ N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	☐ N2
☐ N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)	☐ N3
	DISTANT METASTASIS (M)	
☐ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
☐ M1	Distant metastasis	☐ M1
☐ M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion**	☐ M1a
☐ M1b	Distant metastasis (in extrathoracic organs)	☐ M1b
	** Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.	

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

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

Although most immune-related 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-related 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 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 the equivalent of $\leq$ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for $>$ 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for $>$ 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for $>$ 12 weeks if the 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 have computed tomography (CT) and/or magnetic resonance imaging (MRI) 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 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] • 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 corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

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

HEPATIC EVENTS

Immune-related 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 or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be 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 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 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 corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function test.

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

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 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]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be 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 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 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 corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

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

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-related hyperthyroidism. [c]

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be 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 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 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 corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be 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 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 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact 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 corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

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

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

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 corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related 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-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

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

Table 6 Management Guidelines for Immune-Related Myocarditis

Event	Management
Immune-related 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 corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-related 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 corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

[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 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.

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

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

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

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

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

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

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

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

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

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

Event	• Management
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

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

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

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

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature $\geq 38°C$ not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

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

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the 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. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit–risk ratio.

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

PANCREATIC EVENTS

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

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be 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 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 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be 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 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. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A

dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and , if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be 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 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 workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-related neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-related 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-related 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 corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

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

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related 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-Related Meningoencephalitis

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

[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.

RENAL EVENTS

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

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

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• 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 ≥ 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 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-RELATED MYOSITIS

Immune-related 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-Related Myositis

Event	Management
Immune-related myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-related 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 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-Related Myositis (cont.)

Immune-related 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.

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

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

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

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

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

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

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 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, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate

Event	Management
	according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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Appendix 10
Stool Sample Collection for the Roche Research BioSample Repository in Association With Protocol MO39171

PROTOCOL

TITLE:	**STOOL SAMPLE COLLECTION FOR THE ROCHE RESEARCH BIOSAMPLE REPOSITORY IN ASSOCIATION WITH PROTOCOL MO39171**
PROTOCOL NUMBER:	MO39171 (Stool Sample Substudy in Selected Countries and Selected Sites)
VERSION NUMBER:	2
EUDRACT NUMBER:	2017-001409-34
IND NUMBER:	Not applicable
TEST PRODUCT:	Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below

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PROTOCOL ACCEPTANCE FORM

TITLE:	**STOOL SAMPLE COLLECTION FOR THE ROCHE RESEARCH BIOSAMPLE REPOSITORY IN ASSOCIATION WITH PROTOCOL MO39171**
PROTOCOL NUMBER:	MO39171 (Stool Sample Substudy in Selected Countries and Selected Sites)
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IND NUMBER:	Not applicable
TEST PRODUCT:	Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form {as instructed by XX ***[e.g., your local study monitor, the CRO]*** } ***[or]*** {to the contact provided below}.

{Name}
{Address}

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
EC	Ethics Committee
eCRF	electronic Case Report Form
IFN–γ	interferon-gamma
IRB	Institutional Review Board
NSCLC	non-small cell lung cancer
PD-1	Programmed cell death protein 1
PD-L1	Programmed-death ligand 1
RBR	Research Biosample Repository
WMS	whole metagenomic sequencing

11. BACKGROUND

Study MO39171 is an ongoing, phase III/IV, single arm, multicenter clinical trial that is investigating the long-term safety and efficacy of atezolizumab (Tecentriq®) in previously-treated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) (TAIL). The study is planned to enroll approximately 600 patients. Exploratory biomarker analyses are being performed on samples collected under the main study protocol.

This protocol describes an optional substudy of MO39171 (MO39171 Stool Sample Substudy), which will collect stool samples for the Research Biosample Repository (RBR) at Roche.

11.1 BACKGROUND

Response to cancer immunotherapy is under intense research, and possible determinants include genetic variations, activation of the immune system, and the bacterial communities living on our mucosal surfaces (referred to as the microbiome), which are shaped by diet, environment, and antibiotic exposure (3). Preclinical studies and clinical data suggest that variability in the microbiome influences response to chemotherapy and immunotherapy (7-8,10-12). Additionally, it has been shown that bacterial communities associate with treatment-induced adverse effects (e.g., colitis) (4). Recent studies show that antibiotic therapy was negatively associated with treatment outcome (10). These findings are intriguing and fit with a growing understanding of how bacteria-derived metabolites influence systemic immune responses.

Roche / Genentech is interested in building a gut microbiome sample repository, which would permit examination of how microbial heterogeneity among patients contributes to the variable response of atezolizumab-based immunotherapy (including monotherapy and combination therapy). Patient donation of a stool sample (prior to treatment and on treatment) will support our ability to define the role of the microbiome as a determinant of treatment response and safety in cancer immunotherapy. Whole metagenomic sequencing (WMS) of microbial communities and identification of bacterial-derived metabolites in plasma, which may affect systemic immune responses, will allow us to understand how the microbiome affects response to treatment. These studies will also establish a foundation for the discovery of new targets.

11.2 STUDY RATIONALE

Checkpoint inhibitors targeting the PD1 / PD-L1 axis have shown efficacy in the treatment of NSCLC (1-2,5-6,13). While the success of immunotherapy has been encouraging, not all patients respond to treatment, suggesting that genetics, tumor microenvironment, stage of disease and other host-related factors may have bearing on this response and determine the “immune set point” (3). For example, the overall survival rate in NSCLC patients treated with atezolizumab was higher in those with increased PD-L1 expression and associated with preexisting T-effector / IFN–γ high

gene signatures (5). Another study showed that high non-synonymous tumor mutation burden in patients treated with pembrolizumab was associated with increased progression-free survival (9). The gut microbiome has been established as another of the key determinants in immune regulation, in part by influencing T-cell-driven anti-tumor responses (7,10-11). Finally, antibiotic treatment has been associated with poor survival outcomes to immunotherapy (10).

In this study, we aim to determine whether an individual's microbiome can determine response to atezolizumab and, conversely, whether atezolizumab alters the microbiome such that on-treatment changes could be early predictors of adverse events, including colitis (5). Analyzing the microbiome in NSCLC may also provide an opportunity to discover systemic effects in gut distal cancers.

12. OBJECTIVES

The objective of this study is to obtain stool samples from patients who participate in Study MO39171 for the Roche RBR in order to assess the micobiome, metabolites and other biomarkers in the stool of patients. The samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to the response to atezolizumab and the development of adverse events in NSCLC.

13. MATERIALS AND METHODS

13.1 OVERVIEW OF THE ROCHE RESEARCH BIOSAMPLE REPOSITORY

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

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

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

13.2 APPROVAL BY THE INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body.

13.3 SAMPLE COLLECTION

The following samples and/or derivatives thereof will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to atezolizumab or diseases:

- Stool sample collected during screening
- Stool sample collected at the Day 1 (± 5 days) of Cycle 3 (i.e., at the time of tumor assessment)
- Plasma samples at baseline
- Plasma samples at disease progression

The above samples may be sent to one or more laboratories for analysis of microbial communities through WMS, bacterial culture, or metabolomics profiling.

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

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

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

13.4 CONFIDENTIALITY

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

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

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or

patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

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

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

13.5 CONSENT TO PARTICIPATE IN THE RESEARCH BIOSAMPLE REPOSITORY

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

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

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

13.6 WITHDRAWAL FROM THE RESEARCH BIOSAMPLE REPOSITORY

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR 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 this substudy of Study MO39171 will not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study MO39171.

13.7 MONITORING AND OVERSIGHT

RBR 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. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

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