MULTI 29

A Phase II study of atezolizumab and tiragolumab in patients with NSCLC or advanced solid tumors who have had prior treatment with a PD-1 inhibitor

SARAH CANNON DEVELOPMENT INNOVATIONS STUDY IDENTIFIER (ID):	MULTI 29
STUDY DRUGS:	Atezolizumab and tiragolumab
SPONSOR:	Sarah Cannon Development Innovations, LLC 1100 Dr. Martin L. King Jr. Blvd. Suite 800 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
STUDY CHAIR:	Melissa Johnson, MD Sarah Cannon Research Institute 1100 Dr. Martin L. King Jr. Blvd. Suite 800 Nashville, TN 37203 1-877-MY-1-SCRI
DATE FINAL:	17 August 2018
AMENDMENT 1	28 August 2020
AMENDMENT 2	15 December 2021
AMENDMENT 3	11 July 2022
AMENDMENT 4	25 August 2022
AMENDMENT 5	19 December 2022

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Clinical Study Statement of Compliance

A Phase II study of atezolizumab and tiragolumab in patients with NSCLC or advanced solid tumors who have had prior treatment with a PD-1 inhibitor

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

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Clinical Study Signature Approval Page

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Study Chair Melissa Johnson, MD Sarah Cannon Research Institute	**Study Chair Signature**	**Date**
Marcy Vallone **Sarah Cannon Development Innovations, LLC**	**Sarah Cannon Development Innovations, LLC Representative Signature**	**Date**

SARAH CANNON
Development Innovations

Clinical Study Principal Investigator Signature Form

A Phase II study of atezolizumab and tiragolumab in patients with NSCLC or advanced solid tumors who have had prior treatment with a PD-1 inhibitor

SARAH CANNON DEVELOPMENT INNOVATIONS STUDY ID:	MULTI 29
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By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

_____	_____	_____
Principal Investigator Name (Please Print)	**Principal Investigator Signature**	**Date**

Please retain a copy of this page for your study files and return the original signed and dated form to:

Sarah Cannon Development Innovations, LLC
1100 Dr. Martin L. King Jr. Blvd. Suite 800
Attn: MULTI 29 IIT Study Team
Nashville, TN 37203

MULTI 29 Summary of Changes

AMENDMENT NUMBER:	5	AMENDMENT DATE:	19 DECEMBER 2022

Additions are noted by **bolding**. Deletions are noted by ~~cross outs~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Table of Contents was corrected to reflect the list of appendices.

6.1 Management of Tiragolumab/Atezolizumab-Related Adverse Events

Management of the following tiragolumab/atezolizumab-related AEs is located in Appendix F: Management of Tiragolumab/Atezolizumab-Specific Adverse Events: immune-mediated pericardial disorders, pulmonary (including pneumonitis), hepatic, gastrointestinal, endocrine, immune-mediated myocarditis, ocular, infusion-related reactions (IRRs), pancreatic (including pancreatitis), dermatologic, neurologic, ~~and~~ meningoencephalitis**, immune-mediated myelitis, and immune-mediated facial paresis.**

7.2.1 Day 1 of each cycle (± 3 days)

- Physical examination, including measurement of weight and vital signs **(including signs and symptoms of immune-mediated myelitis)**

8.1.3 Risks Associated With Atezolizumab

Immune-mediated myelitis, immune-mediated facial paresis, and immune-mediated pericardial disorders, including pericarditis, pericardial effusion, and cardiac tamponade, are ~~an~~ identified risk**s** for atezolizumab.

11.4 Adverse Events of Special Interest (AESIs)

- **Immune-mediated facial paresis**
- **Immune-mediated myelitis**

Appendix C Schedule of Assessments

Footnote c: Physical examination will include measurements of height (pretreatment visit only), weight, and vital signs. **Include monitoring for signs and symptoms of immune-mediated myelitis.**

Appendix F: Management of Tiragolumab/Atezolizumab-Specific Adverse Events

Table 11 Management Guidance for Immune-Mediated ~~Myocarditis~~**Cardiac Events**

Event	Management
Immune-mediated myocarditis, Grades 2-4 **Immune-mediated pericardial disorders Grade 2-4**	• Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator.[a] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, ~~or~~ VAD, **or pericardiocentesis** as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

[a] ~~Resumption of atezolizumab and tiragolumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab and/or tiragolumab should be based on the investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate).~~

Immune-Mediated Myelitis

Immune-mediated myelitis is an identified risk with atezolizumab

- **Patients should be monitored for clinical signs and symptoms that are suggestive of myeltis. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies.**
- **Refer patient to neurologist.**
- **For Grade 1 myelitis, continue immunotherapy unless symptoms worsen or do not improve.**
- **Initiate treatment as per institutional guidelines.**
- **Atezolizumab should be permanently withdrawn for ≥Grade 2 immune-mediated myelitis.**

Immune-Mediated Facial Paresis

Immune-mediated facial paresis is an identified risk with 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.**
- **Refer patient to neurologist.**
- **Initiate treatment as per institutional guidelines.**
- **Atezolizumab should be withheld for patients with Grade 1 or 2 immune-mediated facial paresis and permanently withdrawn for ≥Grade 3 immune-mediated facial paresis.**

AMENDMENT NUMBER: 4	AMENDMENT DATE: 25 August 2022

Additions are noted by **bolding**. Deletions are noted by ~~cross outs~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Synopsis

Updated Exclusion criteria numbering and text in the synopsis to match the numbering and text in Section 3.2 Exclusion criteria.

Section 1.2 Atezolizumab

Atezolizumab has been generally well tolerated. Adverse events (AEs) with potentially immune-mediated causes consistent with an immunotherapeutic agent, **including pericardial disorders (pericarditis, pericardial effusion, and cardiac tamponade),** rash, influenza-like illness endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, myocarditis, myositis, neurological issues (including Guillain-Barré Syndrome), and severe cutaneous adverse reactions have been observed (see atezolizumab Investigator's Brochure [IB] for detailed safety results). To date, **the majority of** these events have been manageable with treatment.

Section 6 Dose Modifications, Table 3

A new row for pericardial disorders was added to Table 3 as follows:

Pericardial events	• **Guidelines for management of pericardial events are provided in the atezolizumab IB for atezolizumab and Table 5.**

Section 6.1 Management of Tiragolumab/Atezolizumab-related Adverse Events

Management of the following tiragolumab/atezolizumab-related AEs is located in Appendix F: Management of Tiragolumab/Atezolizumab-Specific Adverse Events: **immune-mediated pericardial disorders**, pulmonary (including pneumonitis), hepatic, gastrointestinal, endocrine, immune-mediated myocarditis, ocular, infusion-related reactions (IRRs), pancreatic (including pancreatitis), dermatologic, neurologic, and meningoencephalitis.

Section 8.1.3 Risks Associated with Atezolizumab

Immune-mediated pericardial disorders, including pericarditis, pericardial effusion, and cardiac tamponade are an identified risk for atezolizumab. Atezolizumab has **also** been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis,…

Appendix F Management of Tiragolumab/Atezolizumab-Specific Adverse Events

Pericardial Events

Immune-mediated pericardial disorders, including pericarditis, pericardial effusion, and cardiac tamponade are an identified risk with atezolizumab.

Pericardial disorders encompass a range of diseases of the pericardium. Underlying causes include infection (particularly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders. Pericardial disorders are also known to be associated with drugs including immune-checkpoint inhibitors.

Pericarditis may be associated with pericardial effusion, which if significant in volume, may result in hemodynamic instability and progress to cardiac tamponade. Cardiac tamponade is a life-threatening condition and should be treated as a medical emergency.

The diagnosis of immune-mediated pericarditis should be considered in all patients presenting with chest pain.

The diagnosis of immune-mediated pericardial effusion and cardiac tamponade should be considered in all patients presenting with chest pain associated with dyspnea or hemodynamic instability.

Cardiac tamponade should be treated as a medical emergency and consultation with a cardiologist should be sought for further management.

Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a pericardial disorder on prior treatment with other immune-stimulatory anticancer agents.

Management guidelines for pericardial events are presented in Table 5.

Table 5 Management Guidelines for Pericardial Events, Including Pericarditis, Pericardial Effusion, and Cardiac Tamponade

Event	Management
Immune-mediated pericardial disorders, including pericarditis, pericardial effusion, and cardiac tamponade, any grade	• **Withhold atezolizumab for any patient with suspected immune-mediated pericardial disorders and contact the principal investigator.** • **Permanently discontinue atezolizumab for any grade confirmed immune-mediated pericardial disorders.** • **Refer patient to cardiologist.** • **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.**
AMENDMENT NUMBER: 3	**AMENDMENT DATE:** 11 July 2022

Additions are noted by **bolding**. Deletions are noted by ~~cross outs~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

The following changes were in response to FDA comments received on Wednesday, 06 July 2022:

Section 1.4 Rationale for the Study:

In Arm A, patients will be receiving an anti-PD-L1 inhibitor in combination with chemotherapy (or chemotherapy alone) after previously receiving an anti-PD-1 inhibitor. While we assume anti-PD-1 and anti-PD-L1 antibodies are synonymous in clinical practice, in truth this has not been (and will never be) tested. There are several reasons these two classes of antibodies may be at least slightly different. Anti-PD-1 antibodies and anti-PD-L1 antibodies target opposing sides the same the PD-1/PD-L1 interaction, and thereby have distinct downstream effectors (PD-1's ligands are most commonly PD-L1 and PD-L2 while PD-L1 most commonly binds to PD-1and B7-1 (CD80). PD-1 is largely expressed on immune cells, while PD-L1 is expressed on tumor cells. Finally, the impact of tumor heterogeneity on a tumor's predilection to respond to a PD-1 inhibitor vs. PD-L1 is not well understood. It is common in clinical practice for patients to be treated with serial PD-1 inhibitors or PD-1 followed by PD-L1 inhibitors, because these agents are well tolerated and because it is assumed that some portion of cells may remain sensitive to PD-1 blockade even as the therapy has been deemed over all to have lost its usefulness. . We see this in the treatment of renal cell carcinoma and melanoma, for example, where options beyond

immunotherapy are minimal. Arm A of this study aims to test the effect of continued CPI blockade with the addition of chemotherapy in NSCLC.

Section 2.2 Secondary Objectives and Synopsis

- Estimate the 6-month disease control rate (DCR)~~, progression-free survival (PFS), overall survival (OS)~~ in patients with NSCLC and other advanced solid tumors.

Section 2.3 Exploratory Objectives and Synopsis

- **Estimate the 6-month progression-free survival (PFS) and overall survival (OS) in patients with NSCLC and other advanced solid tumors.**

Section 3.1 General Inclusion Criteria and Synopsis

1. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 – ~~1~~ **2**

Section 3.1.1 Inclusion Criteria for Arm A and Synopsis

17. PD-L1 Tumor Proportion Score ≥1%

Section 3.2 Exclusion Criteria and Synopsis

6. Treatment with chemotherapy in the first line setting.

Section 5.1.4: Stopping Rules in Dose Expansion

Arm A will enroll 20 patients and each of the four Arm B cohorts will enroll 15 patients. Should the first 7 patients in Arm A or the first 5 patients consecutively enrolled in any single Arm B cohort develop PD in 2 cycles, that cohort will be stopped and no additional patient enrollment will be allowed.

All other changes as follows:

Section 3.1.2 **Crossover from Arm A to Arm B** and Synopsis

18. Last dose of atezolizumab is ≥21 days

Section 5.4.2 Tumor Tissue Samples

An optional tissue biopsy will be requested for crossover patients. This sample should be collected prior to the start of treatment on Arm B.

Section 7.3 Response Assessment Every 2 Cycles **(± 7days)**

Appendix C: Schedule of Assessments

Response every 2 cycles (± ~~3~~ **7 days**)

Optional tumor sample has been added to baseline studies.

Footnote t: Optional tissue biopsy for crossover patients only; sample should be collected prior to start of treatment on Arm B.

AMENDMENT NUMBER: 2	AMENDMENT DATE: 15 December 2021

Additions are noted by **bolding**. Deletions are noted by ~~cross outs~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Global Changes

- Arm A has been revised; the solid tumor cohorts in place prior to Amendment #2 have been deleted and replaced with one NSCLC + standard of care chemotherapy cohort. Approximately 20 NSCLC patients will receive atezolizumab in combination with chemotherapy.
- The following Arm B cohorts have been removed from the Protocol:
  - ~~Advanced SCLC, SCCHN, melanoma, urothelial tumors, or esophageal tumors progressing on anti-PD-1 monotherapy.~~
  - ~~Melanoma progressing on nivolumab plus ipilimumab~~
  - ~~NSCLC progressing on anti-PD-1 monotherapy in ≥ second-line setting~~
  - ~~NSCLC progressing on nivolumab plus ipilimumab in the first-line setting~~
  - ~~NSCLC progressing on nivolumab plus ipilimumab in combination with 2 cycles of chemotherapy in the first-line setting~~
- **Tiragolumab** has been added to Arm B; patients enrolling will receive atezolizumab in combination with tiragolumab. Approximately 60 patients total will be enrolled among the various disease types.
- The number of patients to be enrolled on the study has been updated to ~~258~~ **80**.
- Immune-related events has been changed to immune-**mediated** events.

Section 1.3 Tiragolumab

Tiragolumab is a fully human IgG1/κ monoclonal antibody that binds TIGIT (T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains), an inhibitory immunoreceptor. TIGIT is highly expressed on the surface of activated T-cell and natural killer (NK)-cell subsets and interacts with high affinity with CD155 (also known as poliovirus receptor [PVR]) (Yu et al. 2009). Genetic ablation in T cells in mice results in exacerbated T cell responses, demonstrating the role of TIGIT in inhibiting T cell responses (Joller et al. 2014, Johnston et al. 2014). Activation of TIGIT on T cells and NK cells was demonstrated to limit proliferation, effector cytokine production, and killing of target tumor cells (Stanietsky et al. 2009, Yu et al. 2009, Johnston et al. 2014).

Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of tumor specific T cell responses, which may result in improved meaningful anti-tumor activity when tiragolumab is combined with other cancer immunotherapy (CIT) and chemotherapy (Tiragolumab IB 2020). The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in patients with cancer. Refer to the tiragolumab IB for details on nonclinical and clinical studies of tiragolumab.

Section 1.4 Rationale for the Study

Tiragolumab binds to the inhibitory immunoreceptor TIGIT, which has been shown to limit the effector function of tumor associated lymphocytes. Activation of TIGIT on T cells and NK cells limits proliferation, effector cytokine production, and killing of target T cells. Therefore, in the context of the tumor microenvironment, TIGIT acts to limit anti-tumor immune responses. Interference with TIGIT - PVR interaction may enhance the magnitude and quality of tumor specific T cell responses through increased expansion of T cells as well as improved T cell priming and/or effector function. Because TIGIT and PD-1 are co-expressed by infiltrating T cells in several human tumors, inhibition of the TIGIT/PVR pathway may complement and potentiate the anti-tumor activity of a PD-L1 pathway inhibitor such as atezolizumab

(Tiragolumab IB 2020). Tiragolumab and atezolizumab have been studied in a phase I clinical trial, and have been shown to be safe and tolerable in combination with signals of anti-tumor efficacy (Bendell et al. 2020). Tiragolumab and atezolizumab have also been combined in treatment-naïve NSCLC patient populations with responses and survival outcomes greater than with atezolizumab and placebo combinations, especially in PDL1-high expressing tumors (Rodriguez-Abreu et al. 2020).

This study will investigate the use of atezolizumab **and tiragolumab** in patients with acquired resistance following prior treatment with anti-PD-1 therapy. The main NSCLC cohort, Arm A, will determine whether adding atezolizumab to standard of care (SOC) chemotherapy **will be efficacious.** ~~(group 1) results in a greater benefit when compared to SOC chemotherapy alone (group 2), measured by overall response rate (ORR), in patients with advanced NSCLC with acquired resistance to anti-PD-1 monotherapy.~~ Efficacy of atezolizumab **in combination with tiragolumab** will be explored in a signal-finding cohort of anti-PD-1-treated tumor types and disease settings (Arm B) including RCC **progressing on prior anti-PD therapy**, triple-negative breast cancer (TNBC) tumors progressing on anti-PD-1 therapy**,** NSCLC progressing on **check-point inhibitors** plus chemotherapy in the first-line setting and microsatellite-high (MSI-high) solid tumors [as determined by local testing for MSI/mismatch repair (MMR)] progressing on anti-PD-1 ~~monotherapy~~ therapy.

Section 2.1 Primary Objectives~~

- ~~Assess the efficacy of combining atezolizumab with **SOC** chemotherapy compared to standard of care only in NSCLC patients who have progressed after prior exposure to anti-PD-1.~~
- ~~Assess the efficacy (ORR) of atezolizumab compared to standard of care, in patients with advanced solid tumors who have progressed after prior exposure to anti-PD-1 monotherapy.~~
- **Assess the efficacy (Overall Response Rate [ORR]) of atezolizumab combined with SOC therapy in NSCLC, and atezolizumab combined with tiragolumab in patients with advanced solid tumors who have progressed after prior exposure to anti-PD- treatment.**

Section 2.2 Secondary Objectives

- Determine the safety of atezolizumab **combined with SOC chemotherapy, and atezolizumab combined with tiragolumab,** in patients with NSCLC and other advanced solid tumors.

Section 2.3 Exploratory Objectives

- In selected patients with paired biopsy samples (pre-anti-PD1-treated and pre-atezolizumab/**tiragolumab**-treated; or pre- and post-atezolizumab/**tiragolumab**-treated tissue):

Section 3.1 Inclusion Criteria

2. Adequate hematologic function defined as:
    - Absolute neutrophil count (ANC) ≥1500/µL **with one exception:**

      Patients with benign ethnic neutropenia (BEN): ANC >1300/µL

      BEN (also known as constitutional neutropenia) is an inherited cause of mild or moderate neutropenia that is not associated with any increased risk for infections or other clinical manifestation (Atallah-Yunes et al., 2019). BEN is referred to as ethnic neutropenia because of its increased prevalence in people of African descent and other specific ethnic groups.
    - Hemoglobin (Hgb) ≥9 g/dL **(Patients may be transfused to meet this criterion.)**
    - Platelets ≥100,000/µL **(without transfusion, within 7 days of enrollment).**
4. Adequate renal function defined as serum creatinine ≤1.5 mg/dL (133 µmol/L) OR calculated creatinine clearance ≥**3**~~5~~0 mL/min as calculated by the Cockcroft-Gault formula. ~~(for the solid tumor cohort receiving atezolizumab monotherapy, the threshold can be reduced to a creatinine clearance of ≥30 mL/min.)~~
5. For patients not receiving therapeutic anticoagulation: INR or aPTT ≤1.5 × ULN. For patients receiving therapeutic anticoagulant regimen
6. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of <1% per year, during their participation in the study and for 5

months following last dose of study drug(s). Women must refrain from donating eggs during the study and for 5 months following last dose of study drug(s)

- 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). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.
- Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods), and withdrawal are not adequate methods of contraception.

7. Male patients with a female partner of childbearing potential or a pregnant female partner must remain abstinent (refrain from heterosexual intercourse) or use a condom during the treatment period and for 5 months after the last dose of study drug. 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 post-ovulation methods) and withdrawal are not adequate methods of contraception. Men must also agree to refrain from donating sperm during their participation in the study and for 5 months after the last dose of study drug.

14. Asymptomatic patients with treated or untreated CNS lesions are eligible, provided that all of the following criteria are met:
    - Measurable disease, per RECIST v1.1, must be present outside the CNS.
    - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
    - The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment.
    - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.
    - If the patient is receiving anti-convulsant therapy, the dose is considered stable.

Section 3.1.1 Inclusion Arm A – Non-small cell lung cancer

- **Previously received and tolerated nivolumab or pembrolizumab monotherapy or immunotherapy doublets such as nivolumab/ipilimumab therapy (and was the last therapy prior to enrollment).**

Section 3.1.2 Inclusion Arm B – Advanced Solid Tumors

- Patients with:
    - Advanced RCC **progressing on anti-PD-1 therapy**
    - **Advanced** TNBC progressing on anti-PD-1 therapy
    - NSCLC progressing on **check-point inhibitors** plus chemotherapy in the first-line setting
    - MSI-high solid tumors, as defined by local testing for MSI/MMR, progressing on anti-PD-1 therapy. (Only MSI-high tumors will require MSI/MMR testing results).

~~Previously received and tolerated nivolumab or pembrolizumab monotherapy or immunotherapy doublets such as nivolumab/ipilimumab (and was the last therapy prior to enrollment).~~

- Evidence of **PD** after receiving clinical benefit, defined as having at least one scan demonstrating at least SD during most recent **PD-1 inhibitor** treatment

Section 3.2 Exclusion Criteria

3. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab **or tiragolumab** formulation**s**
5. Use of systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) ≤28 days or 5 half-lives (whichever is longer) prior to the first dose of **study drugs**.
6. Treatment with investigational therapy within 28 days prior to initiation of study treatment.

7. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-**tumor necrosis factor** ~~atezolizumab~~ **[**TNF**]**-α agents
8. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study or within 5 months after the last dose of atezolizumab or **tiragolumab**
9. **Uncontrolled tumor-related pain**
    - **Patients requiring pain medication must be on a stable regimen at study entry.**
    - **Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.**
    - **Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.**
10. Treatment with therapeutic oral or **intravenous (**IV**)** antibiotics within 2 weeks prior to initiation of study treatment.

16. Pregnant or lactating **females**

23. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix E:Pre-existing Autoimmune Diseases and Immune Deficiencies for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
    - Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
    - **Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.**

27. Positive Epstein-Barr virus (EBV) viral capsid antigen (VCA) immunoglobulin M (IgM) test at screening

    An EBV PCR test should be performed as clinically indicated to screen for acute infection or suspected chronic active infection. Patients with a positive EBV PCR test are excluded.

29. **In the opinion of the Investigator** any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications

30. Has had malignancies other than NSCLC, **RCC, TNBC, or MSI-high solid tumors** within 5 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year overall survival [OS] >90%) treated with an expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal- or squamous-cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent).

32. Prior treatment with anti-T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains (TIGIT) therapeutic antibodies.

33. Major surgical procedure within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study.

<u>Section 3.2.1 Exclusion Arm A – Non-small cell lung cancer</u>

34. NSCLC with an activating *EGFR* mutation or *ALK* fusion oncogene

- **For patients with non-squamous NSCLC histology: unknown *EGFR* and/or *ALK* status requires testing**

- **For patients with squamous NSCLC histology: unknown *EGFR* and/or *ALK* status does not require test results at screening. However, exclusion is applied if the status of either driver oncogene is known to be positive.**
- **For patients with NSCLC of mixed histology: unknown *EGFR* and/or *ALK* status requires testing at screening**

Note: *ALK* and/or *EGFR* status may be assessed locally or submitted for central laboratory testing. If *ALK* and/or *EGFR* status is assessed locally, testing must be performed on tissue or cytology using a validated FDA-approved test. If samples are submitted for central laboratory testing, five additional slides are required.

35. **Known c-ros oncogene 1 (*ROS1*) rearrangement: *ROS1* testing at screening is not required for study inclusion; however, patients with known *ROS1* rearrangements are excluded.**

Section 3.2.2 Exclusion Arm B – Advanced Solid Tumors

37. **Prior treatment with anti-TIGIT therapeutic antibodies.**
38. **Known hypersensitivity to any component of the tiragolumab formulation**

Section 4 Study Registration

- Patients enrolling in Arm A will be assigned to atezolizumab and SOC chemotherapy for NSCLC. **Patients enrolling in Arm B will be assigned into a cohort based on disease type to receive atezolizumab and tiragolumab for 4 solid tumor types.**

Section 5 Study Design

- Figure 1 "Study Schema" has been updated.
- Table 1 "Administration of First and Subsequent Atezolizumab Infusions" has been updated.

This is an open-label, multi-center, Phase II study of atezolizumab **and tiragolumab, or atezolizumab in combination with SOC chemotherapy in patients with NSCLC or advanced solid tumors that** have had prior treatment with a PD-1 inhibitor (e.g., nivolumab or pembrolizumab).

Arm A: Arm A will enroll approximately 20 patients.

Arm B: The following solid tumors will be enrolled into Arm B:

- RCC **progressing on prior atni-PD-1 therapy**
- NSCLC progressing on **check-point inhibitors** plus chemotherapy in the first-line setting
- MSI-high solid tumors [as determined by local testing for MSI/MMR] **progressing on prior** anti-PD-1 therapy.

In Arm B, patients with advanced solid tumors will be treated with atezolizumab **at a** flat dose of 1200 mg IV every 3 weeks **and tiragolumab at a flat dose of 600 mg IV every 3 weeks.**

For Arm B the precise sample size cannot be determined. Approximately **60 patients** total **will be enrolled** among the various disease types.

Section 5.1.1 Atezolizumab

On days of scheduled infusions**,** atezolizumab **should be administered first, before** chemotherapy **or tiragolumab**.

Section 5.1.2 Tiragolumab has been added to the protocol

Tiragolumab **600 mg IV every 3 weeks**

On days of scheduled infusions, atezolizumab should be administered first, before chemotherapy or tiragolumab. Administration of tiragolumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Tiragolumab infusions will be administered per the instructions outlined in Table 2.

Table 2 "Administration of First and Subsequent Tiragolumab Infusions" has been added to the protocol.

Section 5.3.1 Permitted Concomitant Medications

- The following criterion has been added: "**Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab and/or tiragolumab infusions only, at the discretion of the Investigator.**"

Section 5.3.3 Prohibited Concomitant Medications

- **Investigational therapy within 42 days prior to initiation of study treatment and during study treatment**
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or five half-lives of the drug (whichever is ~~longer~~ **shorter**) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab **and tiragolumab**.

Section 6 Dose Modifications

- Updated throughout to include dose modification instructions for both atezolizumab and tiragolumab. Including Table 3 "Dose Modifications for Study Drugs."
- **Resume atezolizumab/tiragolumab if event resolves to Grade 1 or better within 21 days. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 21 days. If atezolizumab is discontinued, the Investigator may continue tiragolumab, provided AEs have returned to Grade 1 or better within 21 days. Permanently discontinue both atezolizumab and tiragolumab if event does not resolve to Grade 1 or better within 12 weeks.** ~~Any patient requiring a toxicity-related dose delay of more than 21 days from the intended day of the next scheduled dose must be discontinued from the study.~~"

Section 6.1 Management of Tiragolumab/Atezolizumab-Related Adverse Events

Management of the following **tiragolumab**/atezolizumab-related AEs is located in Appendix F: pulmonary (including pneumonitis), hepatic, gastrointestinal, endocrine, **immune-mediated myocarditis,** ocular, infusion-related reactions (IRRs), pancreatic (including pancreatitis), dermatologic, neurologic, and meningoencephalitis.

Section 8 Drug Formulation, Availability, Administration, and Toxicity Information

- Updated to include Section 8.2.1 Tiragolumab Labeling, Packaging, and Supply, Section 8.2.2 Preparation and Administration of Tiragolumab, and Section 8.2.3 Precautions and Risks Associated with Tiragolumab.

Section 8.1.3 Precautions and Risks Associated with Atezolizumab

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

Section 10 Statistical Considerations

10.2 Sample Size Considerations

No formal statistical power calculations to determine sample size were performed for this study. Hence the numbers of patients have been based on the desire to obtain adequate safety and efficacy data while exposing as few patients as possible to the investigational products and procedures. Approximately 80 patients are planned to be enrolled in this study.

NSCLC Cohort

In Arm A, ~~in group 1 and 54 in group 2 achieve 80.761% power to detect a difference between the group proportions of 0.2500. The proportion in group 1 (the treatment group) is assumed to be 0.2500 under the null hypothesis and 0.5000 under the alternative hypothesis. The proportion in group 2 (the control group) is 0.2500. The test statistic used is the one-sided Fisher's Exact Test. The significance level of the test is 0.0500.~~

~~**Numeric Results for Testing Two Proportions using Fisher's Exact Test**~~

~~H0: P1 – P2 ≤ 0 vs. H1: P1 – P2 = D1 > 0.~~

~~Target Power~~	~~Actual Power*~~	~~N1~~	~~N2~~	~~N~~	~~P1~~	~~P2~~	~~Diff D1~~	~~Alpha~~
~~0.80~~	~~0.80761~~	~~54~~	~~54~~	~~108~~	~~0.5000~~	~~0.2500~~	~~0.2500~~	~~0.0500~~

~~* Power was computed using the normal approximation method~~

~~**Exploratory Cohort:**~~

precise sample size cannot be determined. A sample size of approximately 20 patients will be enrolled to the cohort.

Advanced Solid Tumor Cohort

In Arm B, precise sample size cannot be determined. ~~Descriptive statistics will be used.~~ A sample size of approximately **60** ~~20~~ patients will be enrolled to the cohort

Section 10.4.2 Efficacy Analysis

For PFS and OS, Kaplan-Meier curves will be generated and the median time to event and the associated 95% CI **in each treatment group** will be provided. ~~The hazard ratio and the 95% CI for these endpoints between the two treatment groups will be calculated.~~

Section 11 Safety Reporting and Analyses

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs, **adverse events of special interest (AESIs), performing protocol-specified safety laboratory assessments,** measurement of protocol-specified hematology, clinical chemistry, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

Section 11.1.6 Assessment of Adverse Events

Expected AEs are those AEs that are listed or characterized in the US Package Insert (USPI) or current IB.

~~Appendix C Guidelines for Female Patients of Childbearing Potential and Fertile Male Patients~~

Section 11.3 Recording of Adverse Events and Serious Adverse Events

Procedures for Recording Adverse Events

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

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

Infusion-Related Reactions and Cytokine-Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and cytokine-release syndrome (CRS). While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

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

If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF or Cytokine-Release Syndrome eCRF.

NCI CTCAE v4.0 and the American Society for Transplantation and Cellular Therapy (ASTCT) CRS Consensus Grading Scale should be used when reporting severity of CRS on the Adverse Event eCRF. NCI CTCAE v5.0 should be used when reporting severity of organ toxicities associated with CRS on the dedicated Cytokine Release Syndrome eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

Guidelines for medical management of IRRs and CRS are provided in Appendix F.

11.3.9 Lack of Efficacy or Worsening of Cancer

Deterioration that is judged by the Investigator to have unexpectedly worsened in severity or frequency, or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of cancer on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of non-small cell lung cancer" [spell out name of condition, do not use acronym]). 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 v.1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

11.3.10 Atezolizumab and Tiragolumab Overdose

For Information on how to manage an overdose of atezolizumab **and tiragolumab**, see the **IBs**.

Section 11.4 Adverse Events of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to the other parties (e.g., regulatory authorities) may also be warranted.

The following are events of special interest, and **must be reported to Genentech Drug Safety** expeditiously**, irrespective of regulatory seriousness criteria** (see Section 11.2). These **AESIs** ~~adverse events of special interests~~ include the following:

- **Data related to** suspected transmission of an infectious agent **via medicinal product (STIAMP)**, as defined below:

11.5 Sponsor Serious Adverse Event Reporting Requirements

Development Innovations will provide case information on a completed MedWatch form within 1 business day to the Genentech contact information specified above.

Transmission of these reports (initial and follow-up) will be sent either electronically or by fax and within the timelines specified below:

PC Hotline Number: (800) 334-0290 **(M-F: 5 am to 5 pm PST)**

Additional reporting requirements to Genentech include the following:

- **Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported to Genentech as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to atezolizumab should be reported to Genentech as an SAE.**

In addition to SAEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech even in the absence of an AE within **one (1)** ~~thirty (30)~~ calendar day~~s~~.

Reporting to Regulatory Authorities, Ethics Committees and Investigators

The Sponsor of the study (Development Innovations), will be responsible for the expedited reporting of safety reports originating from the study to the regulatory authority (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

The Sponsor (Development Innovations) will be responsible for the expedited reporting of safety reports originating from the study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

The Sponsor (Development Innovations) will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

Section 11.5.2 Sponsor Reporting for Clinical Studies under an Investigational New Drug Application
For investigator-initiated IND studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Compliance with Pharmacovigilance Agreement/Audit

The Parties shall follow their own procedures for adherence to AE reporting timelines.

Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

Section 11.5.3 Signal Management and Risk Management

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own product. However, it is agreed that Development Innovations, as Sponsor of the study, will be primarily responsible for assessment of the benefit-risk balance of the study.

If Development Innovations issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the study and/or triggers any changes to the study) this will be sent to Genentech within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist Development Innovations with signal and risk management activities related to the product within the study.

Genentech will also provide Development Innovations with any new relevant information that may modify or supplement known data regarding the product (e.g., relevant Dear Investigator Letter).

~~Section 11.6 Safety Crisis Management~~

~~In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Products (atezolizumab and tiragolumab) are used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.~~

~~The Parties agree that Genentech shall have the final say and control over safety crisis management issues relating to the Products (atezolizumab and tiragolumab). Development Innovations agrees that it shall not answer such queries from media and other sources relating to the Products but shall redirect such queries to Genentech.~~

Section 13.5 IND Annual Reports

Or emailed to the Genentech Drug Safety CTV mailbox: ctvistsa@gene.com.

Section 13.7 Study Close-out

And to the Genentech Drug Safety CTV oversight mailbox: ctvistsa@gene.com

Appendix C: Guidelines for Female Patients of Childbearing Potential and Fertile Male Patients

Appendix C has been removed as the necessary and consistent information is now within the protocol.

Appendix C: Schedule of Assessment

Footnote p.**:** EOT evaluations must be completed within 30 days after the last dose of study treatment. Patients must be followed for AEs for 30 calendar days after the last dose of study drug and serious adverse events **and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment.**

Thyroid Function Tests have been added for C1D1 and every 4th cycle thereafter.

Footnote s: Thyroid function tests will include TSH, FT4, and T3. TFTs will be collected at C1D1 and every 4th cycle thereafter.

Appendix D: Immune-Modified Response evaluation Criteria in Solid Tumors (immune-Modified RECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab **and tiragolumab**, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions.

Appendix E ~~F~~ Pre-existing Autoimmune Disease and Immune Deficiencies

- Include **patients with controlled Type 1 diabetes mellitus who are on an insulin regimen** as an exception to the exclusion criteria
- Include instructions to **contact the Medical Monitor if there is any uncertainty over autoimmune exclusions**

Appendix F ~~G~~ Management of Tiragolumab/Atezolizumab-specific Adverse Events

- The entire appendix has been updated to include management for adverse events specific to the study drugs. Instructions for hypophysitis, immune-mediated myocarditis, and Stevens-Johnson syndrome have been added.
- Table 11, footnote e: ~~There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors, but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.~~
- Table 18, footnote a: **If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab and tiragolumab can be resumed.**

AMENDMENT NUMBER: 1	AMENDMENT DATE: 28 August 2020

Additions are noted by **bolding**. Deletions are noted by ~~cross outs~~.

Synopsis and Section 1.3

Arm B consists of approximately 10-15 patients per disease type (renal cell carcinoma [RCC], triple negative breast cancer [TNBC], small cell lung cancer [SCLC], squamous cell carcinoma of the head and neck [SCCHN], melanoma, **urothelial tumors, or esophageal tumors progressing on anti-PD-1 monotherapy; melanoma progressing on nivolumab plus ipilimumab; NSCLC progressing on anti-PD-1 monotherapy in ≥ second-line setting; NSCLC progressing on pembrolizumab plus chemotherapy in the first-line setting; NSCLC progressing on nivolumab plus ipilimumab in the first-line setting; NSCLC progressing on nivolumab plus ipilimumab in combination with 2 cycles of chemotherapy in the first-line setting; and** microsatellite instability-high [MSI-high] solid tumors {as determined by local testing for MSI/mismatch repair (MMR) **progressing on anti-PD-1 monotherapy**~~}), as well as patients with NSCLC who were treated with a PD-1 antibody in ≥ second-line setting and who have had subsequent disease progression and NSCLC patients who have progressed after pembrolizumab plus chemotherapy in the first-line setting.~~

Synopsis and Section 3.1 General Inclusion Criteria

7. Willingness to provide a **mandatory** new pre-treatment tumor biopsy. **(Archival tumor tissue collected following anti-PD-1 therapy may be used if there have been no subsequent treatment regimens following tissue collection and the tissue meets the criteria in Section 5.4.2).**

10. Measurable disease by RECIST v1.1.

Synopsis and Section 3.1.1 Inclusion Arm A-Non-small cell lung cancer

2. Disease progression after **prior documented clinical benefit, defined as having at least one scan demonstrating at least stable disease (SD), on** first-line **treatment with** anti-PD-1 **monotherapy**~~ therapy, (pembrolizumab) for ≥ months~~.

Synopsis and Section 3.1.2 Inclusion Arm B-Advanced Solid Tumors

1. Patients with~~advanced~~**:**

1. **Advanced** RCC, TNBC, SCLC, SCCHN, melanoma, ~~MSI-high solid tumors, and patients with~~**urothelial tumors, or esophageal tumors progressing on anti-PD-1 monotherapy.**
2. **Melanoma progressing on nivolumab plus ipilimumab**
3. NSCLC ~~who were~~ **progressing on anti-**PD-1 **monotherapy** in the ≥ second-line setting ~~or~~
4. NSCLC **progressing on** pembrolizumab plus chemotherapy in the first-line setting
5. **NSCLC progressing on nivolumab plus ipilimumab in the first-line setting**
6. **NSCLC progressing on nivolumab plus ipilimumab in combination with 2 cycles of chemotherapy in the first-line setting**~~ Additional cohorts may be added~~
7. MSI-high solid tumors, as defined by local testing for MSI/MMR**, progressing on anti-PD-1 monotherapy. (Only MSI-high tumors** will ~~be included.~~**require MSI/MMR testing results).**

2. Previously received and tolerated nivolumab or pembrolizumab **monotherapy or immunotherapy doublets such as nivolumab/ipilimumab** ~~therapy~~ (and was the last therapy prior to enrollment).

3. Evidence of disease progression~~.~~ **after receiving clinical benefit defined as having at least one scan demonstrating at least stable disease (SD) during the most recent treatment.**

Synopsis and Section 3.2 Exclusion Criteria

4. ~~Most recent immunotherapy ≤21 days and ≥ Grade 1 immunotherapy related side effects, with the exception of alopecia~~**Most recent immunotherapy ≤21 days and ≥ Grade 2 immunotherapy-related side effects that are unresolved prior to enrollment on study**~~.~~

23. ~~Diagnosis~~**Known active Hepatitis B or C infection; HBV and HCV testing is not required as part of this study.**

24. **Known history** of human immunodeficiency virus~~, hepatitis B, or hepatitis C.~~ **(HIV1 or 2); HIV testing is not required as part of this study.**

27 ~~Has a second primary malignancy that in the judgment of the investigator and sponsor may affect the interpretation of results.~~**Has had malignancies other than NSCLC within 5 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year overall survival [OS] >90%) treated with an expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal- or squamous-cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent).**

Section 3.3 Discontinue from Study Treatment

- Intercurrent illness (this will be at the Investigator's discretion **and may also include COVID-19**)

Section 5 Study Design

Arm A consists of patients with advanced NSCLC who received first-line anti-PD-1-monotherapy **with prior documented clinical benefit (e.g. ≥ SD) prior to**~~, who have subsequent~~ disease progression. In Arm A, patients with NSCLC will be randomized 1:1 to either chemotherapy plus atezolizumab at a flat dose of 1200 mg IV every 3 weeks or chemotherapy alone. Standard of care chemotherapy is defined as a platinum-doublet therapy (or triplet if bevacizumab is used) of the Investigator's choice.

Arm B consists of approximately 10-15 patients per disease type ~~(~~**which include the following solid tumors**:

- RCC, TNBC, SCLC, SCCHN melanoma, ~~MSI-high solid tumors [as determined by local testing for MSI/MMR]), patients with~~ **urothelial tumors, or esophageal tumors progressing on prior anti-PD-1 monotherapy**
- **Melanoma progressing on nivolumab plus ipilimumab**
- NSCLC **progressing on anti-**PD-1 ~~antibody~~**monotherapy** in ≥ second-line setting
- NSCLC ~~patients who have progressed~~ **progressing on** pembrolizumab plus chemotherapy in the first-line setting
- **NSCLC progressing on nivolumab plus ipilimumab in the first-line setting**
- **NSCLC progressing on nivolumab plus ipilimumab in combination with 2 cycles of chemotherapy in the first-line setting**
- **MSI-high solid tumors [as determined by local testing for MSI/MMR] who progressed following anti-PD-1 monotherapy.**

Figure 1, Arm B has been updated

Section 5.4.2 Tumor Tissue Samples

All patients ~~are required~~**highly encouraged** to provide an archival tissue sample obtained prior to **anti-**PD-1 ~~CPI~~**therapy**, if available (approximately 50% of patients). ~~A paraffin block is preferred or at~~ **At** least 15 slides containing unstained, freshly cut, serial sections not older than **180**~~60~~ days ~~upon submission~~**should be submitted** to the analytical laboratory. Prior PD-L1 ~~molecular profiling~~**expression results** by IHC should be captured on the eCRF.

All patients are required to submit a **mandatory** new pre-treatment tissue sample from a core biopsy prior to initiating **anti-**PD-L1 ~~CPI~~ **therapy**~~treatment~~ (Cycle 1 Day 1) on this study for correlative research (see Section 7.2). **Archival tissue collected following anti-PD-1 therapy may be used if there have been no subsequent treatment**

regimens following tissue collection. Archival tissue must not be older than 180 days and provide at least 15 slides containing unstained, freshly cut, serial sections. One to three core needle biopsies (minimum diameter 18 gauge; however, 16 gauge is desirable) embedded in a single formalin-fixed paraffin-embedded (FFPE) block are required. Alcohol fixation, fine needle aspirates, cell blocks, or cytology specimens are not allowed.

An optional tissue biopsy will be requested upon disease progression with **anti-**PD-L1 **therapy**~~CPI~~ (approximately 25% of patients).

Section 7.2 Baseline Study Assessments

- Pre-PD-1-**treated** archival tumor tissue sample provided as~~ a formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or ideally~~ at least 15 slides (or whatever is available) containing unstained, freshly cut (not older than **180**~~60~~ days) serial sections.
- PD-L1 ~~molecular profiling~~**expression status** by IHC (prior PD-L1 ~~molecular profiling~~**testing results** should be captured in the eCRF ~~and does~~**if available; however, PD-L1 testing is** not ~~need to be repeated).~~**required as part of this study).**
- A **mandatory** new pre-treatment tumor sample after progression on ~~a PD-1 CPI~~**anti-PD-1 therapy** ~~(if available).~~**(Archival tumor tissue collected following anti-PD-1 therapy may be used if there have been no subsequent treatment regimens following tissue collection and the tissue meets the criteria in Section 5.4.2).**

Section 10.1 Statistical Design

This is a multi-center, open-label, Phase II study of atezolizumab in patients with NSCLC or advanced solid tumors that have had prior treatment with a PD-1 inhibitor**.** ~~(either nivolumab or pembrolizumab).~~

Arm A consists of patients with advanced NSCLC who received first-line anti-PD-1-monotherapay with prior documentation of clinical benefit (e.g. ≥ SD) prior to disease progression. ~~Arm A consists of patients with advanced NSCLC who received first-line anti-PD-1 monotherapy, who have subsequent disease progression.~~ In Arm A, patients with NSCLC will be randomized 1:1 to either chemotherapy plus atezolizumab at a flat dose of 1200 mg IV every 3 weeks or chemotherapy alone until progression or unacceptable toxicity. Standard of care chemotherapy is defined as a platinum-doublet therapy of the Investigator's choice.

Arm B consists of approximately 10-15 patients per disease type RCC, TNBC, SCLC, SCCHN, melanoma, ~~and MSI-high solid tumors [as determined by local testing for MSI/MMR]), patients with~~**urothelial tumors, or esophageal tumors progressing on anti-PD-1 monotherapy, melanoma progressing on nivolumab plus ipilimumab;** NSCLC ~~who were~~ **progressing on anti-**PD-1 ~~antibody~~**monotherapy** in ≥ second-line setting; **NSCLC progressing on pembrolizumab plus chemotherapy in the first-line setting; NSCLC progressing on nivolumab plus ipilimumab in the first-line setting; NSCLC progressing on nivolumab plus ipilimumab in combination with 2 cycles of chemotherapy in the first-line setting; and MSI-high solid tumors [as determined by local testing for MSI/MMR]) progressing on anti-PD-1 monotherapy.** In Arm B, patients with advanced solid tumors will be treated with an atezolizumab flat dose of 1200 mg IV every 3 weeks until progression or unacceptable toxicity. Additional cohorts may be added as emerging clinical data becomes available.

Section 11.1.2 Statistical Design

- Death **(i.e., the AE actually causes or leads to death)**
- A life-threatening AE **(i.e., the AE, in the view of the Investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)**

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTAE added.

Section 11.2 Serious Adverse Event Reporting by Investigators

Adverse events of special interest, special situation reports, and product complaints are added events to be reported to the Innovations Safety Department.

Section 11.4 Adverse Events of Special Interest

- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, **macrophage activating syndrome and hemophagocytic lymphohistiocytosis**~~systemic inflammatory response syndrome, and systemic immune~~

Section 11.1.2 Statistical Design
Guidance text for reporting SAEs, AESIs, and product complaints has been updated.

Section 11.5.3 Reconciliation/Case Transmission Verification of Single Case Reports
The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

Section 11.9 Study close out
Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Atezolizumab IIS Clinical Operations: anti-pdl-1-mpd3280a-gsur@gene.com

And to Genentech Drug Safety CTV oversight mail box at: ctvistsa@gene.com

Appendix D Schedule of Assessments

- aPPT has been added to the PT/PTT/INR SoA line and associated footnotes b and f.
- Pre-PD-1 archival tumor tissue sample collection has been updated in the SoA and footnotes k, l, an n.

Appendix G Management of Atezolizumab-specific Adverse Events
Appendix updated with the most current data.

Throughout the protocol
Text with "PD-1" treatment and therapy has been updated to "anti-PD-1" treatment and therapy to clarify the protocol.

First use of abbreviations has been updated throughout the document.

"Genentech/Roche" has been updated to "Genentech".

MULTI 29 PROTOCOL SYNOPSIS

Title of Study:	A Phase II study of atezolizumab and tiragolumab in patients with NSCLC or advanced solid tumors who have had prior treatment with a PD-1 inhibitor
Sarah Cannon Development Innovations Study ID:	MULTI 29
Sponsor:	Sarah Cannon Development Innovations, LLC – Nashville - TN
Study Duration:	The total duration of the study is planned to be 2 years. **Phase of Study:** II
Study Centers:	This study will be conducted at 7 sites.
Number of Patients:	Approximately 80 patients are planned to be enrolled in this study: Arm A will enroll approximately 20 patients, and Arm B will enroll approximately 60 patients.
Objectives:	**Primary Objective** The primary objective of this study is to: • Assess the efficacy (Overall Response Rate [ORR]) of atezolizumab combined with SOC chemotherapy in NSCLC, and atezolizumab combined with tiragolumab in patients with advanced solid tumors who have progressed after prior exposure to anti-PD-treatment. **Secondary Objectives** The secondary objectives of this study are to: • Determine the safety of atezolizumab combined with SOC chemotherapy, and atezolizumab combined with tiragolumab, in patients with NSCLC and other advanced solid tumors. • Estimate the 6-month disease control rate (DCR) in patients with NSCLC and other advanced solid tumors. **Exploratory Objectives** The exploratory objectives of this study are: • Estimate the 6-month progression-free survival (PFS) and overall survival (OS) in patients with NSCLC and other advanced solid tumors. • Correlation of programmed death ligand 1 (PD-L1) expression by immunohistochemistry (IHC) with response to therapy. • Characterization of the tumor microenvironment by IHC, ribonucleic acid (RNA) sequencing and/or reverse transcription polymerase chain reaction (RT-PCR) and correlation of immune gene signatures with response to therapy. • In selected patients with paired biopsy samples (pre-anti-PD-1-treated and pre-atezolizumab/tiragolumab-treated; or pre- and post-atezolizumab/tiragolumab-treated tissue): o Assessment of immune escape mechanisms, that may include but is not limited to neoantigen profiling and T cell receptor (TCR) sequencing. o Assessment of tumor mutation burden (TMB) by next-generation sequencing (NGS) and correlation with response to therapy.
Study Design:	This is an open-label, multi-center, Phase II study of atezolizumab and tiragolumab, or atezolizumab combined with SOC chemotherapy in patients with NSCLC or advanced solid tumors that have had prior treatment with a PD-1 inhibitor (e.g. nivolumab or pembrolizumab). Arm A consists of approximately 20 patients with advanced NSCLC who received first-line anti-PD-1 therapy, who have subsequent disease progression. Arm B consists of approximately 15 patients per disease type (renal cell carcinoma [RCC] progressing on prior anti-PD-1 therapy, triple negative breast cancer [TNBC] progressing on prior anti-PD-1 therapy, NSCLC progressing on check-point inhibitors plus

	chemotherapy in the first-line setting; and microsatellite instability-high [MSI-high] solid tumors [as determined by local testing for MSI/mismatch repair (MMR)] progressing on prior anti-PD-1 therapy).
Study Drugs, Doses, and Modes of Administration:	In Arm A, patients with NSCLC will receive chemotherapy plus atezolizumab at a flat dose of 1200 mg intravenously (IV) every 3 weeks. Standard of care chemotherapy is defined as a platinum-doublet therapy (or triplet if bevacizumab is used) of the Investigator's choice. In Part B, patients with advanced solid tumors will be treated with atezolizumab at a flat dose of 1200 mg IV every 3 weeks in combination with tiragolumab at a flat dose of 600 mg IV every 3 weeks until progression or unacceptable toxicity.
Inclusion Criteria:	Patients must meet all of the following criteria in order to be included in the research study: 1. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 - 2 (Appendix A). 2. Adequate hematologic function defined as: − Absolute neutrophil count ≥1500/μL with one exception: Patients with benign ethnic neutropenia (BEN): ANC >1300/ μL − Lymphocyte count ≥0.5 × 10^9/L (500/μL) − Hemoglobin ≥9 g/dL (patients may be transfused to meet this criterion) − Platelets ≥100,000/μL (without transfusion, within 7 days of enrollment) 3. Adequate liver function defined as: − Alanine aminotransferase and aspartate aminotransferase ≤2.5 × the upper limit of normal (ULN) − Total bilirubin ≤1.5 × ULN (patients with known Gilbert syndrome: serum bilirubin level ≤ 3 × ULN) 4. Adequate renal function defined as serum creatinine ≤1.5 mg/dL (133 μmol/L) or calculated creatinine clearance ≥30 mL/min as calculated by the Cockcroft-Gault formula. 5. For patients not receiving therapeutic anticoagulation: INR or aPTT ≤1.5 × ULN. For patients receiving therapeutic anticoagulation: stable anticoagulant regimen. 6. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of <1% per year, during their participation in the study and for 5 months following last dose of study drug(s). Women must refrain from donating eggs during the study and for 5 months following last dose of study drug(s). − 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). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements. − Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not adequate methods of contraception. 7. Male patients with a female partner of childbearing potential or a pregnant female partner must remain abstinent (refrain from heterosexual intercourse) or use a condom during the treatment period and for 5 months after the last dose of study drug. 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 post-ovulation methods) and withdrawal are not adequate methods of contraception. Men must also agree to refrain from donating sperm during their participation in the study and for 5 months after the last dose of study drug. 8. Age ≥18 years. 9. Willingness to provide a mandatory new pre-treatment tumor biopsy. (Archival tissue collected following anti-PD-1 therapy may be used if there have been no subsequent treatment regimens following tissue collection and the tissue meets the criteria in Section 5.4.2). 10. Willingness and ability to comply with study and follow-up procedures. 11. Ability to understand the nature of this study and give written informed consent. 12. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. 13. Asymptomatic patients with treated or untreated CNS lesions are eligible, provided that all of the following criteria are met: - Measurable disease, per RECIST v1.1, must be present outside the CNS. - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage. - The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment. - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. - If the patient is receiving anti-convulsant therapy, the dose is considered stable. **Inclusion Arm A- Non-small cell lung cancer** 14. Advanced squamous or non-squamous NSCLC 15. Disease progression after prior documented clinical benefit, defined as having at least one scan demonstrating at least stable disease (SD), on first-line treatment with anti-PD-1 monotherapy 16. Previously received and tolerated nivolumab or pembrolizumab monotherapy or immunotherapy doublets such as nivolumab/ipilimumab therapy (and was the last therapy prior to enrollment). 17. PD-L1 Tumor Proportion Score ≥1% **Crossover from Arm A to Arm B** 18. Last dose of atezolizumab is ≥21 days **Inclusion Arm B – Advanced Solid Tumors** 19. Patients with: • Advanced RCC progressing on anti-PD-1 therapy • Advanced TNBC progressing on anti-PD-1 therapy • NSCLC progressing on check-point inhibitors plus chemotherapy in the first-line setting • MSI-high solid tumors, as defined by local testing for MSI/MMR, progressing on anti-PD-1 therapy. (Only MSI-high tumors will require MSI/MMR testing results.) 20. Evidence of disease progression after receiving clinical benefit, defined as having at least one scan demonstrating at least SD, during most recent PD-1 inhibitor treatment.
Exclusion Criteria:	Patients who meet any of the following criteria will be excluded from study entry:

	1. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins 2. History of any Grade 3 or 4 toxicities to a prior checkpoint inhibitor (CPI) treatment. 3. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or tiragolumab formulations 4. Most recent immunotherapy ≤21 days and ≥ Grade 2 immunotherapy-related side effects that are unresolved prior to enrollment on study 5. Use of systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) ≤28 days or 5 half-lives (whichever is shorter) prior to the first dose of study drugs. 6. Treatment with chemotherapy in the first line setting. 7. Treatment with investigational therapy within 28 days prior to initiation of study treatment. 8. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions: a. Patients who receive acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study. b. Patients who receive mineralocorticoids (e.g., fludrocortisone), inhaled corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study. 9. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study or within 5 months after the last dose of atezolizumab or tiragolumab. 10. Uncontrolled tumor-related pain – Patients requiring pain medication must be on a stable regimen at study entry. – Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period. – Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment. 11. Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment. – Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or COPD exacerbation) are eligible for the study. 12. Requirement for use of denosumab during the study. Patients who are receiving denosumab for any reason (including hypercalcemia) must be willing and eligible to receive a bisphosphonate instead while in the study.

	13. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy. 14. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement. 15. Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 2 weeks prior to study entry and there is no evidence of CNS disease progression, mild neurologic symptoms, and no requirement for chronic corticosteroid therapy. Anticonvulsant therapy at a stable dose is permitted. 16. Prior allogeneic stem cell or solid organ transplantation 17. Pregnant or lactating females 18. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan a. History of radiation pneumonitis in the radiation field (fibrosis) is permitted. 19. Uncontrolled diabetes mellitus. Patients with Type II diabetes are eligible if they require only oral hypoglycemic agents and fasting blood glucose level is ≤120. Patients with Type I diabetes are eligible if HbAlc is ≤7%. 20. Significant cardiovascular disease, such as New York Heart Association Class II or greater cardiac disease; myocardial infarction or cerebrovascular accident within 3 months prior to initiation of study treatment; unstable arrhythmia; or unstable angina (see Appendix B) 21. History of leptomeningeal disease 22. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently). a. Patients with indwelling catheters (e.g., PleurX®) are allowed. 23. Uncontrolled or symptomatic hypercalcemia (>1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium >ULN) 24. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix E for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions: a. Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study. b. Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study. c. Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met: d. Rash must cover <10% of body surface area e. Disease is well controlled at baseline and requires only low-potency topical corticosteroids

	f. No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months 25. Serious active infection within 4 weeks of treatment (including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia), or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment. 26. Known active Hepatitis B (HBV) or C (HCV) infection; HBV and HCV testing is not required as part of this study. 27. Known history of human immunodeficiency virus (HIV1 or 2); HIV testing is not required as part of this study. 28. Positive Epstein-Barr virus (EBV) viral capsid antigen (VCA) immunoglobulin M (IgM) test at screening. An EBV PCR test should be performed as clinically indicated to screen for acute infection or suspected chronic active infection. Patients with a positive EBV PCR test are excluded. 29. Active tuberculosis 30. In the opinion of the Investigator, any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications 31. Has had malignancies other than NSCLC, RCC, TNBC, or MSI-high solid tumors within 5 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS >90%) treated with an expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal- or squamous-cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent). 32. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol. 33. Prior treatment with anti-T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains (TIGIT) therapeutic antibodies. 34. Major surgical procedure within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study. **Exclusion Arm A Non-small cell lung cancer** 35. NSCLC with an activating *EGFR* mutation or *ALK* fusion oncogene - For patients with non-squamous NSCLC histology: unknown *EGFR* and/or *ALK* status requires testing - For patients with squamous NSCLC histology: unknown *EGFR* and/or *ALK* status does not require test results at screening. However, exclusion is applied if the status of either driver oncogene is known to be positive. - For patients with NSCLC of mixed histology: unknown *EGFR* and/or *ALK* status requires testing at screening Note: *ALK* and/or *EGFR* status may be assessed locally or submitted for central laboratory testing. If *ALK* and/or *EGFR* status is assessed locally, testing must be performed on tissue or cytology using a validated FDA-approved test. If samples are submitted for central laboratory testing, five additional slides are required. 36. Known c-ros oncogene 1 (*ROS1*) rearrangement: *ROS1* testing at screening is not required for study inclusion; however, patients with known *ROS1* rearrangements are excluded.

	37. Intervening treatment with a regimen other than CPI prior to enrollment in this study. **Exclusion Arm B – Advanced Solid Tumors** 38. Prior treatment with anti-TIGIT therapeutic antibodies. 39. Known hypersensitivity to any component of the tiragolumab formulation.
Correlative Testing:	Correlative research in this study provides an opportunity to gain insight into factors contributing to immune escape of the tumor and to investigate biomarkers helping to identify patients deriving benefit from CPI treatment upon progression on anti-PD-1 agents. This research may include, but is not limited to, analysis of neoantigens and the assessment of TMB by whole exome sequencing in tumor samples obtained prior to and post anti-PD-1/PD-L1 agents. Furthermore, research will include the characterization of the tumor microenvironment using IHC to assess PD-L1 and tumor infiltrating immune cells as well as the assessment of gene expression signatures by RNA sequencing. Additional analyses of the tumor tissue or blood samples obtained prior to atezolizumab or tiragolumab therapy and on-treatment may include, but is not limited to sequencing of the TCR repertoire, assessment of immune cell subsets by flow cytometry, genomic profiling of circulating tumor deoxyribonucleic acid (DNA), or RNA by PCR or NGS. All patients are highly encouraged to provide an archival tissue sample obtained prior to anti-PD-1 therapy if available (approximately 50% of patients). All patients are required to submit a new pre-treatment tissue sample from a core biopsy to be taken after progression on anti-PD-1 therapy and prior to anti-PD-L1 therapy (Cycle 1 Day 1). Archival tumor tissue collected following anti-PD-1 treatment may be used if there have been no subsequent treatment regimens following tissue collection and the tissue meets the criteria in Section 5.4.2. An optional tissue biopsy will be requested upon disease progression with anti-PD-L1 therapy (approximately 25% of patients). An optional tissue biopsy will be requested for crossover patients. This sample should be collected prior to the start of treatment on Arm B.
Statistical Methodology:	This is a multi-center, open-label, Phase II study of atezolizumab and tiragolumab in patients with NSCLC or advanced solid tumors that have had prior treatment with a PD-1 inhibitor. Main NSCLC Cohort: In Arm A, precise sample size cannot be determined. Approximately 20 patients will be enrolled to the cohort. Advanced Solid Tumor Cohort: In Arm B, precise sample size cannot be determined. Approximately 60 patients will be enrolled to Arm B. • Overall Response Rate (ORR) is defined as the proportion of patients with confirmed complete response (CR) or partial response (PR (i.e., 2 CRs or PRs at least 4 weeks apart) according to the immune-modified RECIST criteria. • Disease Control Rate (DCR) is defined as the proportion of patients with CR, PR, or SD for at least 6 months according to the immune-modified RECIST criteria. For ORR and DCR, patients without a post-baseline tumor assessment will be classed as not evaluable (NE) and considered as non-responder. For ORR and DCR, the estimates and the associated 95% confidence interval (CI) (based on the Clopper-Pearson method) in each treatment group will be calculated. • Progression Free Survival (PFS), defined as the time from the first day of study drug administration (Day 1) to disease progression as defined by the immune-

	modified RECIST criteria, or death on study. Patients who are alive and free from disease progression will be censored at the date of last tumor assessment. • Overall Survival (OS), defined as the time from the first day of study drug administration (Day 1) to death on study. Patients who are alive will be censored at the date of last known date alive. For PFS and OS, Kaplan-Meier curves will be generated and the median time to event and the associated 95% CI in each treatment group will be provided. All efficacy analyses will be performed using the Full Analysis Set.

MULTI 29 CONTACT INFORMATION

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AR	Adverse reaction
AST (SGOT)	Aspartate aminotransferase
BEN	Benign ethnic neutropenia
CFR	Code of Federal Regulations
CI	Confidence interval
CMP	Comprehensive metabolic profile
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPI	Checkpoint inhibitor
CR	Complete response/remission
CRS	Cytokine release syndrome
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
Development Innovations	Sarah Cannon Development Innovations
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HLH	Hemophagocytic lymphohistiocytosis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
IL-2	Interleukin 2
imAE	Immune-mediated adverse event
IND	Investigational new drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
ISF	Investigator study file
IV	Intravenous
MAS	Macrophage activation syndrome

MMR	Mismatch repair
MSI-high	Microsatellite instability-high
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next-generation sequencing
NK	Natural killer
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PHI	Protected health information
PR	Partial response/remission
PT	Prothrombin time
PTT	Partial thromboplastin time
PVR	Poliovirus receptor
RCC	Renal cell carcinoma
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAR	Suspected adverse reaction
SAS	Safety Analysis Set
SD	Stable disease
SOC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TCR	T-cell receptor
TIGIT	T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains
TMB	Tumor mutation burden
TNBC	Triple-negative breast cancer
TNF	Tumor necrosis factor
TSH	Thyroid-stimulating hormone
UAE	Unexpected adverse event
ULN	Upper limit of normal
USPI	US Package Insert
WES	Whole exome sequencing

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1. INTRODUCTION

1.1 Background

Immune checkpoint inhibitors (CPIs), which target the programmed cell death protein 1 (PD-1) receptor and programmed death ligand 1 (PD-L1) axis, have heralded a paradigm shift in the treatment landscape for many solid tumors. Checkpoint inhibitors improve survival and provide remarkable benefit for 20-40% of patients with advanced malignancies (Brahmer et al. 2012). Benefit is typically associated with increased levels of PD-L1 expression in the tumor and/or infiltrating immune cells. Mutational burden is an independent predictor of response to therapy (Topalian et al. 2012, Rizvi et al. 2015). Currently there are two U.S. Food and Drug Administration (FDA)-approved anti-PD-1 agents: nivolumab (Opdivo® Bristol-Myers Squibb) and pembrolizumab (Keytruda® Merck), and one FDA-approved anti-PD-L1 agent: atezolizumab (Tecentriq® Genentech) with many other compounds in development. In general, CPIs are well-tolerated, and side effects are mild compared to chemotherapy (Brahmer et al. 2012).

1.2 Atezolizumab

Atezolizumab is a CPI which targets PD-L1, blocking its interaction with activated T cell receptors (TCRs), PD-1 and B7-1, enhancing immune-mediated tumor recognition and cytotoxicity. The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005, Keir et al. 2008). B7-1 is a molecule expressed on antigen presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007, Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T cell immunity.

Atezolizumab has been generally well tolerated. Adverse events (AEs) with potentially immune-mediated causes consistent with an immunotherapeutic agent, including pericardial disorders (pericarditis, pericardial effusion, and cardiac tamponade), rash, influenza-like illness endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, myocarditis, myositis, neurological issues (including Guillain-Barré Syndrome), and severe cutaneous adverse reactions have been observed (see atezolizumab Investigator's Brochure [IB] for detailed safety results). To date, the majority of these events have been manageable with treatment.

Atezolizumab has demonstrated efficacy as a single agent and in combinations in a variety of tumor settings and patient populations, and is FDA approved to treat non-small cell lung cancer (NSCLC; Barlesi et al. 2016, Besse et al. 2015, Vansteenkiste et al. 2015, Spira et al. 2015) and advanced bladder cancer (Rosenberg et al. 2016, Infante et al. 2016). Targeting the PD-L1

pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed on standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma (RCC), melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see atezolizumab IB for detailed efficacy results).

1.3 Tiragolumab

Tiragolumab is a fully human IgG1/κ monoclonal antibody that binds TIGIT (T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains), an inhibitory immunoreceptor. TIGIT is highly expressed on the surface of activated T-cell and natural killer (NK)-cell subsets and interacts with high affinity with CD155 (also known as poliovirus receptor [PVR]) (Yu et al. 2009). Genetic ablation in T cells in mice results in exacerbated T cell responses, demonstrating the role of TIGIT in inhibiting T cell responses (Joller et al. 2014, Johnston et al. 2014). Activation of TIGIT on T cells and NK cells was demonstrated to limit proliferation, effector cytokine production, and killing of target tumor cells (Stanietsky et al. 2009, Yu et al. 2009, Johnston et al. 2014).

Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of tumor specific T cell responses, which may result in improved meaningful anti-tumor activity when tiragolumab is combined with other cancer immunotherapy (CIT) and chemotherapy (Tiragolumab IB 2020). The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in patients with cancer. Refer to the tiragolumab IB for details on nonclinical and clinical studies of tiragolumab.

1.4 Rationale for the Study

Despite impressive responses and survival improvements, patients who initially receive benefit with anti-PD-1 agents eventually experience disease progression, and optimal next-line treatments for patients with acquired resistance to PD-1 therapy are unknown. This is particularly true for patients with NSCLC, where both pembrolizumab and nivolumab are approved for patients with advanced disease in the refractory setting. The median progression-free survival (PFS) for patients treated with nivolumab in the Checkmate-017 and Checkmate-057 studies was 2.3 months and 3.5 months respectively, with 1-year PFS for both studies of ~ 20%. Overall survival was improved in each study when compared with docetaxel. Findings from Keynote-010 with pembrolizumab were similar with a PFS and overall survival (OS) of 5.2 months and 14.9 months, respectively, compared with docetaxel with a PFS and OS of 8.1 months and 4.1 months, respectively (Brahmer et al. 2015,Borghaei et al. 2015,Herbst et al. 2016). Clinically, PD-L1 expression may change upon exposure to chemotherapy, targeted therapies, non-therapeutic immune irritants, or immunotherapeutic agents including PD-1 CPIs. Increased PD-L1 expression and PD-1/PD-L1-mediated immune tolerance may be a mechanism of acquired resistance to PD-1 inhibitors. PD-L1 blockade with atezolizumab may restore anti-tumor immunity in patients with acquired resistance to pembrolizumab or nivolumab.

Tiragolumab binds to the inhibitory immunoreceptor TIGIT, which has been shown to limit the effector function of tumor associated lymphocytes. Activation of TIGIT on T cells and NK cells limits proliferation, effector cytokine production, and killing of target T cells. Therefore, in the

context of the tumor microenvironment, TIGIT acts to limit anti-tumor immune responses. Interference with TIGIT - PVR interaction may enhance the magnitude and quality of tumor specific T cell responses through increased expansion of T cells as well as improved T cell priming and/or effector function. Because TIGIT and PD-1 are co-expressed by infiltrating T cells in several human tumors, inhibition of the TIGIT/PVR pathway may complement and potentiate the anti-tumor activity of a PD-L1 pathway inhibitor such as atezolizumab (Tiragolumab IB 2020). Tiragolumab and atezolizumab have been studied in a phase I clinical trial, and have been shown to be safe and tolerable in combination with signals of anti-tumor efficacy (Bendell et al. 2020). Tiragolumab and atezolizumab have also been combined in treatment-naïve NSCLC patient populations with responses and survival outcomes greater than with atezolizumab and placebo combinations, especially in PDL1-high expressing tumors (Rodriguez-Abreu et al. 2020).

This study will investigate the use of atezolizumab and tiragolumab in patients with acquired resistance following prior treatment with anti-PD-1 therapy. The main NSCLC cohort, Arm A, will determine whether adding atezolizumab to standard of care (SOC) chemotherapy will be efficacious. Efficacy of atezolizumab in combination with tiragolumab will be explored in a signal-finding cohort of anti-PD-1-treated tumor types and disease settings (Arm B) including: RCC progressing on prior anti-PD therapy, triple-negative breast cancer (TNBC) tumors progressing on anti-PD-1 therapy, NSCLC progressing on check-point inhibitors plus chemotherapy in the first-line setting and microsatellite-high (MSI-high) solid tumors [as determined by local testing for MSI/mismatch repair (MMR)] progressing on anti-PD-1 therapy.

In Arm A, patients will be receiving an anti-PD-L1 inhibitor in combination with chemotherapy (or chemotherapy alone) after previously receiving an anti-PD-1 inhibitor. While we assume anti-PD-1 and anti-PD-L1 antibodies are synonymous in clinical practice, in truth this has not been (and will never be) tested. There are several reasons these two classes of antibodies may be at least slightly different. Anti-PD-1 antibodies and anti-PD-L1 antibodies target opposing sides the same the PD-1/PD-L1 interaction, and thereby have distinct downstream effectors (PD-1's ligands are most commonly PD-L1 and PD-L2 while PD-L1 most commonly binds to PD-1 and B7-1 (CD80). PD-1 is largely expressed on immune cells, while PD-L1 is expressed on tumor cells. Finally, the impact of tumor heterogeneity on a tumor's predilection to respond to a PD-1 inhibitor vs. PD-L1 is not well understood. It is common in clinical practice for patients to be treated with serial PD-1 inhibitors or PD-1 followed by PD-L1 inhibitors, because these agents are well tolerated and because it is assumed that some portion of cells may remain sensitive to PD-1 blockade even as the therapy has been deemed over all to have lost its usefulness. We see this in the treatment of renal cell carcinoma and melanoma, for example, where options beyond immunotherapy are minimal. Arm A of this study aims to test the effect of continued CPI blockade with the addition of chemotherapy in NSCLC.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to:

- Assess the efficacy (overall response rate [ORR]) of atezolizumab combined with SOC chemotherapy in NSCLC, and atezolizumab combined with tiragolumab in patients with advanced solid tumors who have progressed after prior exposure to anti-PD-treatment.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Determine the safety of atezolizumab combined with SOC chemotherapy, and atezolizumab combined with tiragolumab, in patients with NSCLC and other advanced solid tumors.
- Estimate the 6-month disease control rate (DCR) in patients with NSCLC and other advanced solid tumors.

2.3 Exploratory Objectives

The exploratory objectives of this study are:

- Estimate the 6-month PFS and OS in patients with NSCLC and other advanced solid tumors.
- Correlation of PD-L1 expression by immunohistochemistry (IHC) with response to therapy
- Characterization of the tumor microenvironment by IHC, ribonucleic acid (RNA) sequencing and/or reverse transcription-polymerase chain reaction (RT-PCR) and correlation of immune gene signatures with response to therapy.
- In selected patients with paired biopsy samples (pre-anti-PD1-treated and pre-atezolizumab/tiragolumab-treated; or pre- and post-atezolizumab/tiragolumab-treated tissue):
    - Assessment of immune escape mechanisms, that may include but is not limited to neoantigen profiling and TCR sequencing;
    - Assessment of tumor mutation burden (TMB) by next-generation sequencing (NGS) and correlation with response to therapy.

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 General Inclusion Criteria

Patients must meet all of the following criteria in order to be included in the research study:

1. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 - 2 (Appendix A: ECOG Performance Status Criteria).
2. Adequate hematologic function defined as:
    - Absolute neutrophil count (ANC) ≥1500/μL with one exception:

      Patients with benign ethnic neutropenia (BEN): ANC >1300/μL

BEN (also known as constitutional neutropenia) is an inherited cause of mild or moderate neutropenia that is not associated with any increased risk for infections or other clinical manifestation (Atallah-Yunes et al., 2019). BEN is referred to as ethnic neutropenia because of its increased prevalence in people of African descent and other specific ethnic groups.

- Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
- Hemoglobin (Hgb) ≥9 g/dL (patients may be transfused to meet this criterion)
- Platelets ≥100,000/μL (without transfusion, within 7 days of enrollment)

3. Adequate liver function defined as:
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × the upper limit of normal (ULN)
    - Total bilirubin ≤1.5 × ULN (patients with known Gilbert syndrome: serum bilirubin level ≤3 × ULN)
4. Adequate renal function defined as serum creatinine ≤1.5 mg/dL (133 μmol/L) OR calculated creatinine clearance ≥30 mL/min as calculated by the Cockcroft-Gault formula.
5. For patients not receiving therapeutic anticoagulation: INR or aPTT ≤1.5 × ULN. For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
6. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of <1% per year, during their participation in the study and for 5 months following last dose of study drug(s). Women must refrain from donating eggs during the study and for 5 months following last dose of study drug(s)
    - 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). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.
    - Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods), and withdrawal are not adequate methods of contraception.
7. Male patients with a female partner of childbearing potential or a pregnant female partner must remain abstinent (refrain from heterosexual intercourse) or use a condom during the treatment period and for 5 months after the last dose of study drug. 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 post-ovulation methods) and withdrawal are not adequate

methods of contraception. Men must also agree to refrain from donating sperm during their participation in the study and for 5 months after the last dose of study drug.

8. Age ≥18 years.
9. Willingness to provide a mandatory new pre-treatment tumor biopsy. (Archival tumor tissue collected following anti-PD-1 therapy may be used if there have been no subsequent treatment regimens following tissue collection and the tissue meets the criteria in Section 5.4.2).
10. Willingness and ability to comply with study and follow-up procedures.
11. Ability to understand the nature of this study and give written informed consent.
12. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
13. Asymptomatic patients with treated or untreated CNS lesions are eligible, provided that all of the following criteria are met:
    - Measurable disease, per RECIST v1.1, must be present outside the CNS.
    - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
    - The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment.
    - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.
    - If the patient is receiving anti-convulsant therapy, the dose is considered stable.

3.1.1 Inclusion Arm A – Non-small cell lung cancer

14. Advanced squamous or non-squamous NSCLC
15. Disease progression (PD) after prior documented clinical benefit, defined as having at least one scan demonstrating at least stable disease (SD), on first-line treatment with anti-PD-1 monotherapy.
16. Previously received and tolerated nivolumab or pembrolizumab monotherapy or immunotherapy doublets such as nivolumab/ipilimumab therapy (and was the last therapy prior to enrollment).
17. PD-L1 Tumor Proportion Score ≥1%.

3.1.2 Crossover from Arm A to Arm B

18. Last dose of atezolizumab is ≥21 days

3.1.3 Inclusion Arm B – Advanced Solid Tumors

19. Patients with:
    - Advanced RCC progressing on anti-PD-1 therapy
    - Advanced TNBC progressing on anti-PD-1 therapy

- NSCLC progressing on check-point inhibitors plus chemotherapy in the first-line setting
- MSI-high solid tumors, as defined by local testing for MSI/MMR, progressing on anti-PD-1 therapy. (Only MSI-high tumors will require MSI/MMR testing results).

20. Evidence of PD after receiving clinical benefit defined as having at least one scan demonstrating at least SD during the most recent PD-1 inhibitor treatment.

3.2 Exclusion Criteria

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

1. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
2. History of any Grade 3 or 4 toxicities to a prior CPI treatment
3. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or tiragolumab formulations
4. Most recent immunotherapy ≤21 days and ≥ Grade 2 immunotherapy-related side effects that are unresolved prior to enrollment on study
5. Use of systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) ≤28 days or 5 half-lives (whichever is shorter) prior to the first dose of study drugs.
6. Treatment with chemotherapy in the first line setting.
7. Treatment with investigational therapy within 28 days prior to initiation of study treatment.
8. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [TNF]-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:
   - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.
   - Patients who received mineralocorticoids (e.g., fludrocortisone), inhaled corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
9. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study or within 5 months after the last dose of atezolizumab or tiragolumab

10. Uncontrolled tumor-related pain
    - Patients requiring pain medication must be on a stable regimen at study entry.
    - Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.
    - Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
11. Treatment with therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to initiation of study treatment.
    - Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or COPD exacerbation) are eligible for the study.
12. Requirement for use of denosumab during the study. Patients who are receiving denosumab for any reason (including hypercalcemia) must be willing and eligible to receive a bisphosphonate instead while in the study.
13. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy.
14. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement.
15. Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 2 weeks prior to study entry and there is no evidence of CNS disease progression, mild neurologic symptoms, and no requirement for chronic corticosteroid therapy. Anticonvulsant therapy at a stable dose is permitted.
16. Prior allogeneic stem cell or solid organ transplantation
17. Pregnant or lactating females
18. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan
    - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
19. Uncontrolled diabetes mellitus. Patients with Type II diabetes are eligible if they require only oral hypoglycemic agents and fasting blood glucose level is ≤120. Patients with Type I diabetes are eligible if HbA_{1c} is ≤7%.

20. Significant cardiovascular disease, such as New York Heart Association (NYHA) Class II or greater cardiac disease; myocardial infarction or cerebrovascular accident within 3 months prior to initiation of study treatment; unstable arrhythmia; or unstable angina (see Appendix B:New York Heart Association (NYHA) Classification of Cardiac Disease)
21. History of leptomeningeal disease
22. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
    - Patients with indwelling catheters (e.g., PleurX®) are allowed.
23. Uncontrolled or symptomatic hypercalcemia (>1.5 mmol/L ionized calcium or calcium >12 mg/dL or corrected serum calcium >ULN).
24. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix E: Pre-existing Autoimmune Diseases and Immune Deficiencies for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
    - Patients with a history of autoimmune-mediated hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
    - Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
    - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
        - Rash must cover < 10% of body surface area
        - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
        - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months
25. Serious active infection within 4 weeks of treatment (including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia*)*, or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment.
26. Known active hepatitis B (HBV) or C (HCV) infection; HBV and HCV testing are not required as part of this study.

27. Known history of human immunodeficiency virus (HIV1 or 2); HIV testing is not required as part of this study.
28. Positive Epstein-Barr virus (EBV) viral capsid antigen (VCA) immunoglobulin M (IgM) test at screening

    An EBV PCR test should be performed as clinically indicated to screen for acute infection or suspected chronic active infection. Patients with a positive EBV PCR test are excluded.
29. Active tuberculosis
30. In the opinion of the Investigator any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
31. Has had malignancies other than NSCLC, RCC, TNBC, or MSI-high solid tumors within 5 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS >90%) treated with an expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal- or squamous-cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent).
32. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.
33. Prior treatment with anti-T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains (TIGIT) therapeutic antibodies
34. Major surgical procedure within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study.

3.2.1 Exclusion Arm A –Non-small cell lung cancer

35. NSCLC with an activating *EGFR* mutation or *ALK* fusion oncogene
    - For patients with non-squamous NSCLC histology: unknown *EGFR* and/or *ALK* status requires testing
    - For patients with squamous NSCLC histology: unknown *EGFR* and/or *ALK* status does not require test results at screening. However, exclusion is applied if the status of either driver oncogene is known to be positive.
    - For patients with NSCLC of mixed histology: unknown *EGFR* and/or *ALK* status requires testing at screening

Note: *ALK* and/or *EGFR* status may be assessed locally or submitted for central laboratory testing. If *ALK* and/or *EGFR* status is assessed locally, testing must be performed on tissue or cytology using a validated FDA-approved test. If samples are submitted for central laboratory testing, five additional slides are required.

36. Known c-ros oncogene 1 (*ROS1*) rearrangement: *ROS1* testing at screening is not required for study inclusion; however, patients with known *ROS1* rearrangements are excluded.

37. Intervening treatment with a regimen other than CPI prior to enrollment in this study.

3.2.2 Exclusion Arm B – Advanced Solid Tumors

38. Prior treatment with anti-TIGIT therapeutic antibodies.

39. Known hypersensitivity to any component of the tiragolumab formulation

3.3 Discontinuation from Study Treatment

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the Investigator's discretion and may also include COVID-19)
- Inability of the patient to comply with study requirements
- Patient requests to discontinue treatment
- Patient withdraws consent from the study
- Non-compliance/lost to follow-up
- Study termination

After discontinuation from protocol treatment, patients must be followed for AEs for 30 days, after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Investigator, these values are not likely to improve, because of the underlying disease. In this case, the Investigators must record his or her reasoning for this decision in the patients' medical records and as a comment in the electronic Case Report Form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v 4.0.3) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the Investigator, not likely that these values are to improve. In this case, the Investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment in the eCRF.

4. STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, treatment alternatives, side-effects, risks, and discomforts. Institutional Review Board (IRB) approval of this protocol and informed consent form (ICF) is required. Eligible patients who wish to participate in the study will be enrolled into the study.

Registration must occur prior to the initiation of protocol therapy. Patients eligible to participate in the study may be enrolled by the site following the subject registration instructions provided by Sarah Cannon Development Innovations, LLC (Development Innovations) study contact. Patient registration follow-up and/or confirmation will be provided via email within approximately 24 hours, or by the next business day. Patients enrolling in Arm A will be assigned to atezolizumab and SOC chemotherapy for NSCLC. Patients enrolling in Arm B will be assigned into a cohort based on disease type to receive atezolizumab and tiragolumab for 4 solid tumor types.

5. STUDY DESIGN

This is an open-label, multi-center, Phase II study of atezolizumab and tiragolumab, or atezolizumab in combination with SOC chemotherapy in patients with NSCLC or advanced solid tumors who have had prior treatment with a PD-1 inhibitor (e.g. nivolumab or pembrolizumab).

Arm A

Arm A consists of patients with advanced NSCLC who received first-line anti-PD-1-therapy with prior documented clinical benefit (e.g. ≥ SD) prior to PD. In Arm A, patients with NSCLC will be assigned treatment to chemotherapy plus atezolizumab at a flat dose of 1200 mg IV every 3 weeks. Standard of care chemotherapy is defined as a platinum-doublet therapy (or triplet if bevacizumab is used) of the investigator's choice. Arm A will enroll approximately 20 patients.

Arm B

Arm B consists of approximately 15 patients per disease type. The following solid tumors will be enrolled into Arm B:

- RCC progressing on prior anti-PD-1 therapy
- TNBC progressing on prior anti-PD-1therapy
- NSCLC progressing on check-point inhibitors plus chemotherapy in the first-line setting
- MSI-high solid tumors [as determined by local testing for MSI/MMR] progressing on prior anti-PD-1 therapy.

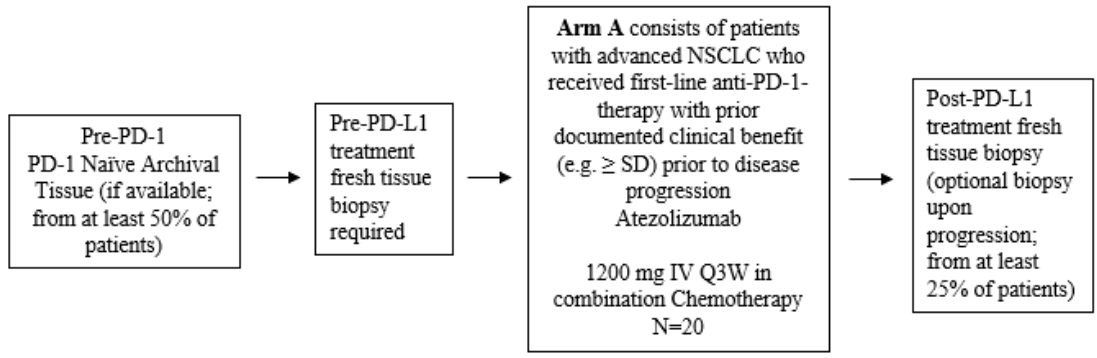
In Arm B, patients with advanced solid tumors will be treated with atezolizumab at a flat dose of 1200 mg IV every 3 weeks and tiragolumab at a flat dose of 600mg IV every 3 weeks. Additional cohorts may be added as emerging clinical data becomes available.

For Arm B the precise sample size cannot be determined. Approximately 60 patients total will be enrolled among the various disease types.

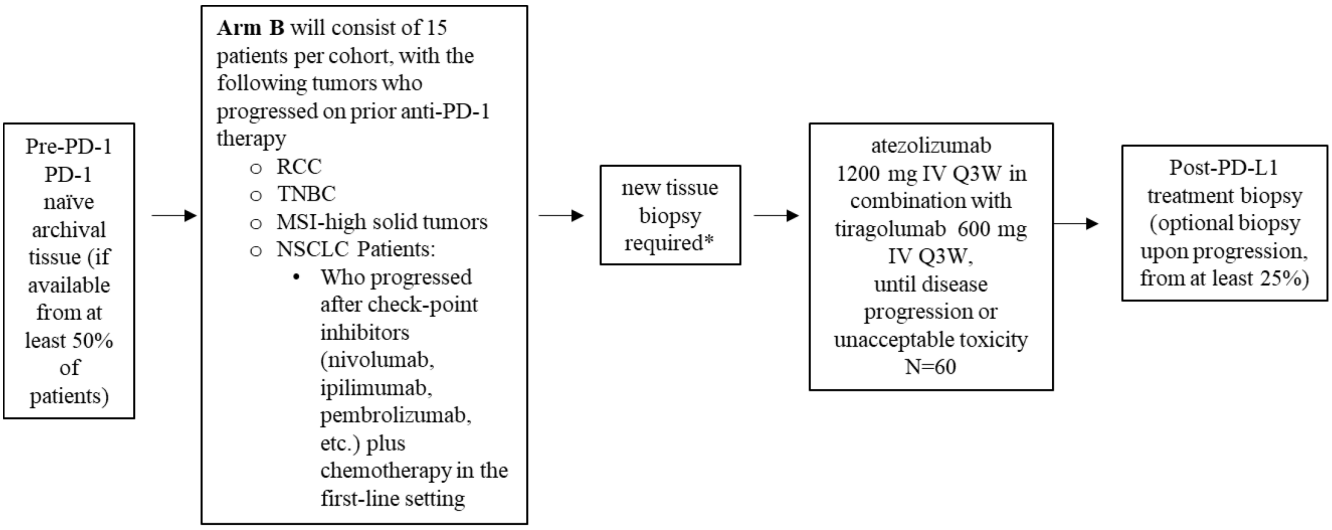
The study schema is presented in Figure 1.

Figure 1 Study Schema

Arm A - NSCLC:



Arm B –Advanced Solid Tumors:



*Archival tissue collected following prior PD-1 therapy may be used if there have been no further treatment regimens following tissue collection

5.1 Treatment Plan

5.1.1 Atezolizumab

Atezolizumab 1200 mg IV every 3 weeks

On days of scheduled infusions, atezolizumab should be administered first, before chemotherapy or tiragolumab. Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix G: Anaphylaxis Precautions. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Atezolizumab Infusions

Study Drug	First Infusion	Subsequent Infusions
Atezolizumab infusion	• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes through an intravenous line with or without a sterile, non-pyrogenic, low-protein binding in-line filter (pore size 0.2-0.22 micron). • If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (±5 minutes for all timepoints) during the infusion and at 30 (±10) minutes after the infusion.	• If the patient experienced an infusion-related reaction with any previous infusion of atezolizumab, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the Investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion through an intravenous line with or without a sterile, non-pyrogenic, low-protein binding in-line filter (pore size 0.2-0.22 micron). • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±5) minutes after the infusion.
Observation period after infusion of atezolizumab	• After the infusion of atezolizumab, the patient begins a 60-minute observation period. • Vital signs should be recorded at 30 (±10) minutes after the infusion of atezolizumab. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient tolerated the previous atezolizumab infusion well without infusion-associated adverse events, the observation period after the next infusions may be reduced to 30 minutes. • If the patient experienced infusion-associated adverse events during the previous infusion, the observation period for the next infusion should be 60 minutes. • If clinically indicated, vital signs should be recorded at 30 (±10) minutes after the infusion of atezolizumab.

5.1.2 Tiragolumab (Arm B only)

Tiragolumab 600 mg IV every 3 weeks

On days of scheduled infusions, atezolizumab should be administered first, before chemotherapy or tiragolumab. Administration of tiragolumab will be performed in a monitored setting where

there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Tiragolumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Tiragolumab Infusions

Infusion of tiragolumab	First Infusion	Subsequent Infusions
	• No premedication is permitted prior to the tiragolumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Tiragolumab should be infused over 60 (±15) minutes. • Vital signs should be recorded every 15 (±5) minutes during the infusion.	• If the patient experienced an IRR during any previous infusion of tiragolumab, premedication with an antihistamine and/or antipyretic may be administered for subsequent doses, at the discretion of the Investigator. • Vital signs should be recorded within 60 minutes prior to the tiragolumab infusion. • Tiragolumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • Vital signs should be recorded during the infusion if clinically indicated.
Observation period after infusion of tiragolumab	• After the infusion of tiragolumab, the patient begins a 60-minute observation period. • Vital signs should be recorded at 30 (±10) minutes after the infusion of tiragolumab. • Patients will be informed about the possibility of delayed post-infusion symptoms and will be instructed to contact their study physician if they develop such symptoms.	• If the patient tolerated the previous infusion of tiragolumab well without infusion-associated adverse events, the observation period may be reduced to 30 minutes. • If the patient experienced an infusion-associated adverse event during the previous infusion, the observation period for the next infusion should be 60 minutes. • If clinically indicated, vital signs should be recorded at 30 (±10) minutes after the infusion of tiragolumab. • Patients will be informed about the possibility of delayed post-infusion symptoms and will be instructed to contact their study physician if they develop such symptoms.

IRR = infusion-related reaction.

5.1.3 Standard of Care Chemotherapy (Arm A only)

Platinum-based SOC doublet chemotherapy (or triplet if bevacizumab is used) will be given by IV every 3 weeks. Platinum chemotherapy may be cisplatin or carboplatin chosen based on

histology and at the discretion of the treating investigator. It should be administered according to the directions in the approved labeling.

5.1.4 Stopping Rules in Dose Expansion

Arm A will enroll 20 patients and each of the four Arm B cohorts will enroll 15 patients. Should the first 7 patients in Arm A, or the first 5 patients consecutively enrolled in any single Arm B cohort develop PD in 2 cycles, that cohort will be stopped and no additional patient enrollment will be allowed.

5.2 Treatment Duration

Patients will be evaluated for toxicity at the start of each cycle. Every 2 cycles, restaging will occur using immune-modified RECIST v1.1 criteria (see Appendix D: Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST)). Because of the possibility of an initial increase in tumor burden caused by immune cell infiltration in the setting of a T cell response (termed "pseudoprogression") with atezolizumab and/or tiragolumab treatment, radiographic progression per RECIST v1.1 may not be indicative of true PD. In the absence of unacceptable toxicity, patients who meet criteria for PD per RECIST v1.1 while receiving atezolizumab and/or tiragolumab will be permitted to continue atezolizumab and/or tiragolumab if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the Investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in ECOG performance status that can be attributed to PD
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions.

Patients who have objective response (OR) or SD will continue treatment with re-evaluations every 2 cycles, until the time of tumor progression or intolerable treatment-related side effects.

The end of the study is expected to occur approximately 1 year after the last patient is enrolled. However, the Investigator or the Sponsor may decide to end the study at any time. The total length of the study from screening the first patient to the end of the study is estimated to be approximately 2 years.

5.3 Concomitant Medications

Patients will be instructed not to take any additional medications during the course of the study without prior consultation with the research team. At each visit, the patient will be asked about any new medications he or she is taking or has taken after the start of the study drug.

5.3.1 Permitted Concomitant Medications

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab and/or tiragolumab infusions only, at the discretion of the Investigator.

Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following:

- Oral contraceptives with a failure rate of <1% per year
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated vaccines (e.g., influenza)
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab and/or tiragolumab infusions only, at the discretion of the Investigator.

In general, Investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Table 12).

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator with the exception of those listed in Section 5.3.3.

5.3.2 Concomitant Medications to be used with Caution

Systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the Investigator except that systemic

corticosteroids may not be given as premedication to patients with an allergy to contrast agents used for tumor scans.

5.3.3 Prohibited Concomitant Medications

The following treatments are prohibited while in this study:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether approved or investigational, is prohibited prior to starting study treatment, and during study treatment, until disease progression is documented and the patient has discontinued study treatment.
- Investigational therapy within 42 days prior to initiation of study treatment and during study treatment
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab and/or tiragolumab, and for 5 months after the last dose of atezolizumab and/or tiragolumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or five half-lives of the drug (whichever is shorter) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab and/or tiragolumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab and/or tiragolumab.

5.4 Correlative Studies

While cancer immunotherapy has been shown to provide a significant survival benefit to cancer patients across tumor types, patients eventually experience progression of their disease. The understanding of the mechanisms underlying innate or acquired resistance to cancer immunotherapy is still evolving. Mutations in JAK1, JAK2 or B2M were shown to be associated with acquired resistance to PD-1 blockade in melanoma (Zaretsky et al. 2016, Tumeh et al. 2014) showed that patients who progressed on PD-1 blockade experienced lower CD8+ cell densities at the invasive margin of the tumor compared to patients who responded to therapy. A better understanding of changes on treatment in the tumor microenvironment and the restoration of anti-tumor immunity upon disease progression are crucial to the development of novel therapies and will help to better sequence cancer immunotherapy agents. Furthermore, it will be imperative to understand which patients will derive benefit from CPI post progression on anti-PD-1 agents.

Correlative research in this study provides an opportunity to gain insight into factors contributing to immune escape of the tumor and to investigate biomarkers helping to identify patients deriving benefit from CPI treatment upon progression on anti-PD-1 agents. This research may include, but is not limited to, analysis of neoantigens and the assessment of TMB by whole

exome sequencing (WES) in tumor samples obtained both prior to and post anti-PD-1/PD-L1 agents. Furthermore, research will include the characterization of the tumor microenvironment using IHC to assess PD-L1 and tumor infiltrating immune cells as well as the assessment of gene expression signatures by RNA sequencing. Additional analyses of the tumor tissue or blood samples obtained prior to atezolizumab and/or tiragolumab therapy and on treatment may include, but are not limited to sequencing of the TCR repertoire, assessment of immune cell subsets by flow cytometry, genomic profiling of circulating tumor deoxyribonucleic acid (DNA), or RNA by PCR or NGS.

Given the complexity and exploratory nature of the analyses, data derived from correlative research will 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.

5.4.1 Blood samples

All patients will have blood samples collected for peripheral blood mononuclear cells (PBMC), plasma, and serum isolation to enable exploratory biomarker research in the future. Blood samples will be collected for PBMCs on Cycle 1 Day 1 and at the end of treatment visit. Blood samples for plasma/serum isolation will be collected on Cycle 1 Day 1, Cycle 3 Day 1 and at the end of treatment visit. Samples will be banked for future correlative studies aiming to determine changes in blood-based biomarkers including but not limited to analysis of circulating immune cell populations, cytokines, or TCR sequencing using NGS, flow cytometry or array-based immunoassays. In addition, whole blood will be collected at baseline as a normal DNA control sample for WES of the tumor. The maximum total amount of blood collected at any time point will be 50 mL.

5.4.2 Tumor Tissue Samples

All patients are highly encouraged to provide an archival tissue sample obtained prior to anti-PD-1 therapy, if available (approximately 50% of patients). At least 15 slides containing unstained, freshly cut, serial sections not older than 180 days should be submitted to the analytical laboratory. Prior PD-L1 expression results by IHC should be captured on the eCRF.

All patients are required to submit a mandatory new pre-treatment tissue sample from a core biopsy prior to initiating anti-PD-L1 therapy (Cycle 1 Day 1) on this study for correlative research (see Section 7.2). Archival tissue collected following anti-PD-1 therapy may be used if there have been no subsequent treatment regimens following tissue collection. Archival tissue must not be older than 180 days and provide at least 15 slides containing unstained, freshly cut, serial sections. One to three core needle biopsies (minimum diameter 18 gauge; however, 16 gauge is desirable) embedded in a single formalin-fixed paraffin-embedded (FFPE) block are required. Alcohol fixation, fine needle aspirates, cell blocks, or cytology specimens are not allowed.

An optional tissue biopsy will be requested for crossover patients. This sample should be collected prior to the start of treatment on Arm B.

An optional tissue biopsy will be requested upon disease progression with anti-PD-L1 therapy (approximately 25% of patients).

5.4.3 Handling, storage and destruction of biological samples

For shipment, handling, etc. of blood and tissue samples see the laboratory reference manual. Samples may be sent to one or more laboratories for analysis.

All blood and tissue samples will be stored for up to 15 years after finalization of the manuscript, with the following exception{s}:

21. Residual material from normal control DNA blood samples will be stored until they are no longer needed for this study or until they are exhausted
22. All storage periods will be in accordance with the IRB-approved ICF and applicable laws (e.g., health authority requirements).

5.4.4 Informed consent for storage of donated biological samples

If a patient withdraws consent to the use of required biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, Development Innovations is not obliged to destroy the results of this research.

As collection of these biological samples is a required part of the study, the patient may not continue in the study after withdrawing this consent.

6. DOSE MODIFICATIONS

If toxicity occurs, the toxicity will be graded utilizing the NCI CTCAE v 4.0.3, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof.

There will be no dose reduction of atezolizumab or tiragolumab; however, treatment delays are allowed.

Resume atezolizumab/tiragolumab if event resolves to Grade 1 or better within 21 days. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 21 days. If atezolizumab is discontinued, the Investigator may continue tiragolumab, provided AEs have returned to Grade 1 or better within 21 days. Permanently discontinue both atezolizumab and tiragolumab if event does not resolve to Grade 1 or better within 12 weeks.

The dose modifications to be used in this study are presented in Table 3.

Table 3 Dose Modifications for Arm A and Arm B

Event	Action to Be Taken
IRRs and anaphylaxis	• Guidelines for management of IRRs are provided in the Atezolizumab IB for atezolizumab and Table 11. For anaphylaxis precautions, see Appendix G: Anaphylaxis Precautions.
Pericardial events	• Guidelines for management of pericardial events are provided in the atezolizumab IB for atezolizumab and Table 5.
Pulmonary events	
Pneumonitis, Grade 1	• Continue atezolizumab/tiragolumab • For recurrent pneumonitis, treat as a Grade 3 or 4 event.

Event	Action to Be Taken
Pneumonitis, Grade 2	• Withhold atezolizumab/tiragolumab. • Resume atezolizumab/tiragolumab if event resolves to Grade 1 or better within 21 days. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 21 days. If atezolizumab is discontinued, the Investigator may continue tiragolumab, provided adverse events have returned to Grade 1 or better within 21 days. • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab. The Investigator may continue tiragolumab provided adverse events have returned to Grade 1 or better within 21 days.
Hepatotoxicity	
Hepatitis, Grade 2	**Events of >5 days' duration:** • Withhold atezolizumab/tiragolumab. • Resume atezolizumab/tiragolumab if event resolves to Grade 1 or better within 21 days. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 21 days. If atezolizumab is discontinued, the Investigator may continue tiragolumab, provided adverse events have returned to Grade 1 or better within 21 days.
Hepatitis, Grade 3 or 4	• Permanently discontinue atezolizumab. If atezolizumab is discontinued, the Investigator may continue tiragolumab provided adverse events have returned to Grade 1 within 21 days.
Gastrointestinal toxicity	
Diarrhea or colitis, Grade 2 or 3	• Withhold atezolizumab/tiragolumab. • Resume atezolizumab/tiragolumab if event resolves to Grade 1 or better within 21 days. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 21 days. If atezolizumab is discontinued, the Investigator may continue tiragolumab, provided adverse events have returned to Grade 1 or better within 21 days.
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab. If atezolizumab is discontinued, the Investigator may continue tiragolumab provided adverse events have returned to Grade 1 or better within 21 days.
Endocrine disorders	
Symptomatic hypothyroidism	• Withhold atezolizumab/tiragolumab. • Resume atezolizumab/tiragolumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH <0.1 mIU/L:** • Follow guidelines for symptomatic hyperthyroidism.

Event	Action to Be Taken
Symptomatic hyperthyroidism	• Withhold atezolizumab/tiragolumab. • Resume atezolizumab/tiragolumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab for life-threatening immune-mediated hyperthyroidism. If atezolizumab is discontinued, the Investigator may continue tiragolumab, provided adverse events have returned to Grade 1 or better within 21 days.
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• Withhold atezolizumab/tiragolumab. • Resume atezolizumab/tiragolumab if event resolves to Grade 1 or better within 21 days. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 21 days. If atezolizumab is discontinued, the Investigator may continue tiragolumab, provided adverse events have returned to Grade 1 or better within 21 days.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab/tiragolumab. • Resume atezolizumab/tiragolumab when symptoms resolve and glucose levels are stable.
Ocular toxicity	
Grade 1	• Continue atezolizumab/tiragolumab. • If symptoms persist, treat as a Grade 2 event.
Grade 2	• Withhold atezolizumab/tiragolumab. • Resume atezolizumab/tiragolumab if event resolves to Grade 1 or better within 21 days. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 21 days. If atezolizumab is discontinued, the Investigator may continue tiragolumab, provided adverse events have returned to Grade 1 or better within 21 days.
Grade 3 or 4	• Permanently discontinue atezolizumab. If atezolizumab is discontinued, the Investigator may continue tiragolumab provided adverse events have returned to Grade 1 within 21 days.
Pancreatic toxicity	
Amylase or lipase elevation, Grade 3 or 4	• Withhold atezolizumab/tiragolumab. • Resume atezolizumab/tiragolumab if event resolves to Grade 1 or better within 21 days. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 21 days. If atezolizumab is discontinued, the Investigator may continue tiragolumab, provided adverse events have returned to Grade 1 or better within 21 days. • For recurrent events, permanently discontinue atezolizumab. The Investigator may continue tiragolumab, provided adverse events have returned to Grade 1 or better within 21 days.

Event	Action to Be Taken
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab/tiragolumab. • Resume atezolizumab/tiragolumab if event resolves to Grade 1 or better within 21 days. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 21 days. If atezolizumab is discontinued, the Investigator may continue tiragolumab, provided adverse events have returned to Grade 1 or better within 21 days. • For recurrent events, permanently discontinue atezolizumab. The Investigator may continue tiragolumab, provided adverse events have returned to Grade 1 or better within 21 days.
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab. If atezolizumab is discontinued, the Investigator may continue tiragolumab provided adverse events have returned to Grade 1 or better within 21 days.
Dermatologic toxicity	
Rash, Grade 3	• Withhold atezolizumab/tiragolumab. • Resume atezolizumab/tiragolumab if event resolves to Grade 1 or better within 21 days. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 21 days. If atezolizumab is discontinued, the Investigator may continue tiragolumab, provided adverse events have returned to Grade 1 or better within 21 days.
Rash, Grade 4	• Permanently discontinue atezolizumab. If atezolizumab is discontinued, the Investigator may continue tiragolumab provided adverse events have returned to Grade 1 or better within 21 days.
Neurologic disorders	
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab/tiragolumab. • Resume atezolizumab/tiragolumab if event resolves to Grade 1 or better within 21 days. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 21 days. If atezolizumab is discontinued, the Investigator may continue tiragolumab, provided adverse events have returned to Grade 1 or better within 21 days.
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab. If atezolizumab is discontinued, the Investigator may continue tiragolumab provided adverse events have returned to Grade 1 or better within 21 days.
Myasthenia gravis and Guillain-Barré, all grades	• Permanently discontinue atezolizumab. If atezolizumab is discontinued, the Investigator may continue tiragolumab provided adverse events have returned to Grade 1 or better within 21 days.
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab. If atezolizumab is discontinued, the Investigator may continue tiragolumab provided adverse events have returned to Grade 1 or better within 21 days.

Event	Action to Be Taken
Grade 3 or 4 or intolerable Grade 2 treatment-related toxicities not described above, excluding e.g., alopecia, nausea, and vomiting	• Withhold atezolizumab/tiragolumab. • Resume atezolizumab/tiragolumab if event resolves to baseline or Grade 1 or better within 21 days.

IRR = infusion-related reaction; TSH = thyroid-stimulating hormone.

Clinical trial experience to date suggests that tiragolumab may increase or accentuate the immune-mediated adverse events (imAEs) observed with atezolizumab; please see Table 3 for management of imAEs. If atezolizumab is held for drug-related toxicity, a reasonable guiding principle would be to also hold tiragolumab. If atezolizumab is discontinued, the Investigator may continue tiragolumab, provided adverse events have returned to Grade 1 or better within 21 days.

6.1 Management of Tiragolumab/Atezolizumab-Related Adverse Events

Management of the following tiragolumab/atezolizumab-related AEs is located in Appendix F: Management of Tiragolumab/Atezolizumab-Specific Adverse Events: immune-mediated pericardial disorders, pulmonary (including pneumonitis), hepatic, gastrointestinal, endocrine, immune-mediated myocarditis, ocular, infusion-related reactions (IRRs), pancreatic (including pancreatitis), dermatologic, neurologic, meningoencephalitis, immune-mediated myelitis, and immune-mediated facial paresis.

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study is shown in Appendix C: Schedule of Assessments. The baseline physical examination, medical history, ECOG PS, complete blood counts (CBC), differential and platelets, comprehensive metabolic profile (CMP), urinalysis, and prothrombin time (PT)/ partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT)/ international normalized ratio (INR) should be done ≤7 days prior to initiation of treatment. If these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated. A pregnancy test must be performed within 72 hours of Cycle 1 Day 1. CT scans should be performed ≤28 days prior to initiation of treatment.

7.2 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at screening (±7 days unless otherwise noted):

- Written informed consent prior to any other study-related procedures (≤28 days prior to initiation of treatment)
- Medical history
- Physical examination, measurements of height (first visit), weight, and vital signs (resting heart rate, blood pressure, respiratory rate, and oral temperature)
- ECOG performance status (see Appendix A: ECOG Performance Status Criteria)

- 12-lead electrocardiogram (ECG)
- Concomitant medication review
- CBC including Hgb, hematocrit, white blood cell count with 3-part differential and platelets
- CMP to include: glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein, and albumin.
- Coagulation analysis: PT/PTT or aPTT/INR
- Urine dipstick (if abnormal, additional testing [e.g., microscopic examination, urine protein:creatinine ratio] should be performed, as clinically indicated)
- Serum or urine pregnancy test (must be performed within 72 hours of Cycle 1 Day 1)
- CT scans of the chest, abdomen/pelvis ≤4 weeks prior to initiation of study treatment is preferred.
- Pre-PD-1-treated archival tumor tissue sample provided as at least 15 slides (or whatever is available) containing unstained, freshly cut (not older than 180 days) serial sections.
- PD-L1 expression status by IHC (prior PD-L1 testing results should be captured in the eCRF if available; however, PD-L1 testing is not required as part of this study).
- A mandatory new pre-treatment tumor sample after progression on anti-PD-1 therapy (Archival tumor tissue collected following anti-PD-1 therapy may be used if there have been no subsequent treatment regimens following tissue collection and the tissue meets the criteria in Section 5.4.2).
- Study Treatment Assessments

7.2.1 Day 1 of each cycle (± 3 days)

- Physical examination, including measurement of weight and vital signs (including signs and symptoms of immune-mediated myelitis)
- ECOG performance status
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets
- CMP
- Blood samples collected for plasma/serum on Cycle 1 Day 1 and Cycle 3 Day 1 (prior to treatment)
- Blood sample for PBMC isolation and correlative research (Cycle 1 Day 1)
- Blood sample for whole blood (Cycle 1 Day 1 only)

7.3 Response Assessment Every 2 Cycles (± 7days)

Patients will be evaluated for response to treatment after every 2 cycles of treatment. The following assessments will be performed:

- CT scans of chest, abdomen and pelvis is preferred; however, SOC assessment for disease subtype will be acceptable

Patients with PD or unacceptable toxicity should be discontinued from the study; patients with SD or response to therapy will continue treatment.

7.4 End of Study Treatment

The follow-up evaluations required after treatment ends due to completion of the planned study treatment period, disease progression, or once the patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the study physician are specified in Appendix C: Schedule of Assessments and below.

If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no study treatment is administered, that visit may fulfill the end-of-treatment visit.

After withdrawal from or completion of protocol treatment, patients must be followed for AEs for 30 calendar days after the last dose of study drug. The following assessments will be performed:

- Physical examination, including measurement of weight and vital signs
- ECOG performance status
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets
- CMP
- Serum or urine pregnancy test
- Blood sample for plasma/serum/PBMC isolation and potential correlative research
- CT scans of chest, abdomen and pelvis if not taken within the last 6 weeks
- Tissue biopsy upon disease progression (optional).

7.5 Follow-up

7.5.1 Follow-up for Patients Who Discontinue Prior to Disease Progression

Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months (±1 month) from the date of last dose of study drug until disease progression or for up to 1 year whichever comes first unless otherwise directed due to study termination. Assessments at these visits will be performed as described in Appendix C: Schedule of Assessments.

7.5.2 Survival Follow-Up

After disease progression is documented, patients will be followed every 3 months (±1 month) for survival (e.g., date and cause of death) for up to 1 year or death whichever comes first unless otherwise directed due to study termination. Patients may be contacted during outpatient visits or by telephone.

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

Investigational Product	Dosage Form and Strength	Timing	Manufacturer	Section
atezolizumab	1200 mg	Q3 weeks	Genentech, Inc.	8.1
tiragolumab	600 mg	Q3 weeks	Genentech, Inc.	8.2

8.1 Atezolizumab

8.1.1 Atezolizumab Labeling, Packaging, and Supply

Atezolizumab will be supplied in as a sterile colorless to slightly yellow liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution by Genentech, Inc.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the atezolizumab IB.

The immediate packaging will contain a statement to conform with U.S. FDA Investigational New Drug (IND) requirements as follows: Caution: New Drug - Limited by Federal (or United States) law to investigational use.

All study drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for atezolizumab are included on the investigational product label.

Development Innovations must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.1.2 Preparation and Administration of Atezolizumab

Atezolizumab is administered as an IV infusion.

Preparation, administration, and storage instructions will be provided in the IB.

8.1.3 Risks Associated with Atezolizumab

Immune-mediated myelitis, immune-mediated facial paresis, and immune-mediated pericardial disorders, including pericarditis, pericardial effusion, and cardiac tamponade are an identified risk for atezolizumab. Atezolizumab has also been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome,

myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Precautions and risks are described in detail in the atezolizumab IB. Management of atezolizumab-related AEs is provided in Appendix F: Management of Tiragolumab/Atezolizumab-Specific Adverse Events.

8.2 Tiragolumab

8.2.1 Tiragolumab Labeling, Packaging, and Supply

Tiragolumab will be supplied by Genentech, Inc. as a sterile liquid in a single-use, 15 mL glass vial. The vial contains approximately 10 mL (600 mg) of tiragolumab.

For further information on the formulation and handling of tiragolumab, see the pharmacy manual and the tiragolumab IB.

The packaging will contain a statement to conform with U.S. FDA IND requirements as follows: Caution: New Drug - Limited by Federal (or United States) law to investigational use.

All study drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for tiragolumab are included on the investigational product label.

Development Innovations must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.2.2 Preparation and Administration of Tiragolumab

Tiragolumab is administered as an IV infusion.

Preparation, administration, and storage instructions will be provided in the IB.

8.2.3 Risks Associated with Tiragolumab

Infusion-related reaction is an identified risk of tiragolumab. Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated AEs). In addition, owing to the intact F_c-effector function of tiragolumab, lymphopenia by means of antibody dependent cell cytotoxicity (ADCC) is a theoretical risk.

Precautions and risks are described in detail in the tiragolumab IB. Because tiragolumab may increase or accentuate the immune-mediated AEs (imAEs) observed with atezolizumab, please see Table 3 for management of imAEs.

8.3 Accountability for All Study drugs

The Principal Investigator (or designee) is responsible for accountability of all used and unused study drug supplies at the site.

All study drug inventories must be made available for inspection by the Sponsor or its representatives and regulatory agency inspectors upon request.

Throughout the study and at its completion, Drug Accountability Record Form(s) must be completed by the site and sent to Development Innovations. Study drug supplies must not be destroyed unless prior approval has been granted by Development Innovations or its representative. Please contact Development Innovations regarding disposal of any study drug.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Increasing clinical experience indicates that traditional response criteria (e.g., RECIST v1.1 and World Health Organization criteria) may not adequately assess the activity of immunotherapeutic agents because initial radiographic evidence of PD does not necessarily indicate therapeutic failure. Patients can experience a response in the presence of new lesions or after an increase in tumor burden. Thus, this study will employ immune-modified RECIST for tumor assessments to account for the possible appearance of new lesions and allow radiographic progression to be confirmed at a subsequent assessment (see Appendix D: Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST)).

It is recommended that radiographic progression be confirmed at a subsequent tumor assessment to take into account the potential for pseudoprogression (caused by immune cell infiltration). Given the proposed immunomodulatory mechanism of action of atezolizumab and tiragolumab and the possibility of observing delayed responses, use of immune-modified RECIST will allow for the capture of a greater proportion of potential responses and allow patients to derive maximum clinical benefit.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This is a multi-center, open-label, Phase II study of atezolizumab and tiragolumab in patients with NSCLC or advanced solid tumors that have had prior treatment with a PD-1 inhibitor.

Arm A consists of patients with advanced NSCLC who received first-line anti-PD-1-monotherapy with prior documentation of clinical benefit (e.g. ≥ SD) prior to disease progression. In Arm A, patients with NSCLC will be treated with chemotherapy plus atezolizumab at a flat dose of 1200 mg IV every 3 weeks, until progression or unacceptable toxicity. Standard of care chemotherapy is defined as a platinum-doublet therapy (or triplet if bevacizumab is used) of the Investigator's choice.

Arm B consists of approximately 15 patients per disease type: RCC and TNBC progressing on anti-PD-1 therapy; NSCLC progressing on check-point inhibitors plus chemotherapy in the first-line setting; and MSI-high solid tumors [as determined by local testing for MSI/MMR]) progressing on anti-PD-1 therapy. In Arm B, patients with advanced solid tumors will be treated with atezolizumab at a flat dose of 1200 mg IV every 3 weeks and tiragolumab at a flat dose of 600mg IV every 3 weeks, until progression or unacceptable toxicity. Additional cohorts may be added as emerging clinical data becomes available.

10.2 Sample Size Considerations

No formal statistical power calculations to determine sample size were performed for this study.

Hence the numbers of patients have been based on the desire to obtain adequate safety and efficacy data while exposing as few patients as possible to the investigational products and procedures. Approximately 80 patients are planned to be enrolled in this study.

NSCLC Cohort:

In Arm A, precise sample size cannot be determined. A sample size of approximately 20 patients will be enrolled to the cohort.

Advanced Solid Tumor Cohort:

In Arm B, precise sample size cannot be determined. Approximately 60 patients will be enrolled to the cohort.

10.3 Analysis Population

The following analysis populations will be used:

- The Full Analysis Set (FAS) is defined as all patients who received at least one dose of study treatment.
- The Safety Analysis Set (SAS) is defined as all patients who have received at least one dose of study treatment.

10.4 Data Analysis

Descriptive statistics, including mean, median, standard deviations, and ranges for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time to events endpoints will be reported using Kaplan-Meier estimates, with 95% confidence intervals (CI) for median time to event.

10.4.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized. Data to be tabulated will include demographic features such as age, sex and race, as well as disease-specific characteristics.

The number and percentages of patients screened, treated, completed the treatment/study and withdrawn from treatment/study for any reasons will be presented overall and also by treatment group.

10.4.2 Efficacy Analysis

All efficacy analyses will be performed using the FAS.

- Overall Response Rate (ORR) is defined as the proportion of patients with confirmed complete response (CR) or partial response (PR (i.e. 2 CRs or PRs at least 4 weeks apart) according to the immune-modified RECIST criteria.

- Disease Control Rate (DCR) is defined as the proportion of patients with CR, PR, or SD for at least 6 months according to the immune-modified RECIST criteria.

For ORR and DCR, patients without a post-baseline tumor assessment will be classed as not evaluable (NE) and considered as non-responder.

- Progression Free Survival (PFS), defined as the time from the first day of study drug administration (Day 1) to PD as defined by the immune-modified RECIST criteria, or death on study. Patients who are alive and free from disease progression will be censored at the date of last tumor assessment.

- Overall Survival (OS), defined as the time from the first day of study drug administration (Day 1) to death on study. Patients who are alive will be censored at the date of last known date alive.

For ORR and DCR, the estimates and the associated 95% CI (based on the Clopper-Pearson method) in each treatment group will be calculated. The absolute and relative difference in ORR and DCR between the two treatment groups will also be presented.

For PFS and OS, Kaplan-Meier curves will be generated and the median time to event and the associated 95% CI in each treatment group will be provided.

10.4.3 Safety Analysis

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy, and will be graded according to NCI CTCAE 4.03. A copy of CTCAE scoring system may be downloaded from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), and summarized using system organ class and preferred term by treatment group for all patients in the SAS. In addition, summaries of serious adverse events (SAEs), AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented by treatment group.

Other safety endpoints including laboratory results, vital signs, and ECG findings will be summarized for all patients in the SAS.

Concomitant medications will be coded using the World Health Organization-Drug Dictionary and they will be listed and summarized by treatment group.

10.5 Analysis Time Points

10.5.1 Final Analysis

The final analysis of the study will occur following the last visit of the last patient in the treatment arm.

10.5.2 Safety Review

No formal safety review is planned.

10.5.3 Efficacy Review

No formal interim analyses are planned.

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs, adverse events of special interest (AESIs), performing protocol-specified safety laboratory assessments, measurement of protocol-specified hematology, clinical chemistry, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for recognizing and reporting SAEs to the Development Innovations Safety Department (see Section 11.2). It is the Sponsor's responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of that IRB.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1 Definitions

11.1.1 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also known as adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgement about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, dose or including overdose.

11.1.2 Serious Adverse Event

An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:

- **Death (i.e., the AE actually causes or leads to death)**
- **A life-threatening AE (i.e., the AE, in the view of the Investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)**
- **Inpatient hospitalization of at least 24-hours or prolongation of existing hospitalization**
- **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
- **A congenital anomaly/birth defect**

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they

may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" AEs, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. Seriousness serves as the guide for defining regulatory reporting obligations; it is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

11.1.3 Adverse Reaction

An adverse reaction (AR) means any AE caused by a drug. Adverse reactions are a subset of all SARs where there is a reason to conclude that the drug caused the event.

11.1.4 Suspected Adverse Reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about causality than AR, which means any AE caused by a drug.

11.1.5 Recording and Reporting of Adverse Events

Recording of Adverse Events

All AEs of any patient during the course of the research study will be recorded in the eCRF, and the Investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes a SAE or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the Investigator's assessment of causality (i.e., the relationship to the study treatment[s]). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE 4.0.3, and changes will be documented.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living
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
4	Life-threatening consequences or urgent intervention indicated
5	Death related to adverse event

If the AE is serious, it should be reported immediately to Development Innovations Safety Department. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms, abnormal test findings, changes in physical examination, hypersensitivity, and other measurements that occur will be reported as AEs, and collected on the relevant eCRF screen.

Test findings will be reported as an AE if: the test result requires an adjustment in the study drug(s) or discontinuation of treatment, the test findings require additional testing or surgical intervention, a test result or finding is associated with accompanying symptoms, or a test result is considered to be an AE by the Investigator.

Reporting Period for Adverse Events

All AEs and SAEs, regardless of seriousness or relationship to atezolizumab and tiragolumab treatment (called study treatment), spanning from the start of study treatment, until 30 calendar days after discontinuation or completion of study treatment as defined by the clinical study for that patient, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs and SAEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs and SAEs occurring during this period must be reported and followed until resolution unless, in the opinion of the Investigator, the AE or laboratory

abnormality/ies are not likely to improve because of the underlying disease. In this case, the Investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF screen.

Thirty (30) days after completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the Investigator as treatment related are to be reported.

11.1.6 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, Investigators should apply the following general guideline:

> **YES (definitive, probable, possible, unlikely):** There is a plausible temporal relationship between the onset of the AE and administration of the study medication, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies, and/or the AE follows a known pattern of response to the study drug, and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
>
> **NO (unrelated):** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected AEs are those AEs that are listed or characterized in the US Package Insert (USPI) or current IB.

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

11.2 Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating Investigator as serious require expeditious handling and reporting to Development Innovations Safety Department in order to comply with regulatory requirements. Determination of life-threatening or serious is based on the opinion of either the Sponsor or the Investigator.

Serious AEs may occur at any time from the start of study treatment through the 30 days after their last dose of study drug. **The Development Innovations Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.**

To report a SAE, the SAE Report Form should be completed with the necessary information.

The SAE, AEs of Special Interest (AESIs), and Special Situation Reports (including pregnancy reports), and Product Complaints (with or without an AE) originating from the Study for the

Product reports should be sent to Development Innovations Safety Department via fax or e-mail using the following contact information (during both business and non-business hours):

Development Innovations Safety Department

Safety Dept. Fax #: 1-866-807-4325

Safety Dept. Email: CANN.SAE@SCRI-Innovations.com

Transmission of the SAE, AEs of Special Interest (AESIs), and Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to Development Innovations Safety Department as soon as it is available; these reports should be submitted using the Development Innovations SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

11.3 Recording of Adverse Events and Serious Adverse Events

Procedures for Recording Adverse Events

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

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

Infusion-Related Reactions and Cytokine-Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and cytokine-release syndrome (CRS). While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

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

If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF or Cytokine-Release Syndrome eCRF.

NCI CTCAE v4.0 and the American Society for Transplantation and Cellular Therapy (ASTCT) CRS Consensus Grading Scale should be used when reporting severity of CRS on the Adverse Event eCRF. NCI CTCAE v5.0 should be used when reporting severity of organ toxicities associated with CRS on the dedicated Cytokine Release Syndrome eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

Guidelines for medical management of IRRs, imAEs, and CRS are provided in Appendix F: Management of Tiragolumab/Atezolizumab-Specific Adverse Events.

11.3.1 Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. 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 as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF screen). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as an SAE.

11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form (if applicable) and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form (if applicable) and/or AE eCRF screen.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form (if applicable) and/or AE eCRF screen.

11.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant

eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF screen.

Abnormal laboratory values will be reported as an AE if: the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment, the laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms, or a laboratory result is considered to be an AE by the Investigator.

11.3.4 **Deaths**

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "Study Discontinuation" eCRF screen. All other on study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the Development Innovations Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and Adverse Event screen of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF Adverse Event screen. During post-study survival follow-up, deaths attributed to progression of disease will be recorded only on the "After Progressive Disease Follow-Up" eCRF screen.

11.3.5 **Hospitalization, Prolonged Hospitalization, or Surgery**

Any AE that results in hospitalization of >24 hours or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency department or emergency room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, custodial care or respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as an SAE to the Development Innovations Safety Department.

11.3.6 **Pre-Existing Medical Conditions**

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History eCRF screen. A pre-existing medical

condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.7 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria (see Section 11.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.3.8 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form (a paper report form, not available within the eCRF) should be completed and faxed to the Development Innovations Safety Department. Development Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Development Innovations Safety Department.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the Development Innovations Safety Department immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

11.3.9 Lack of Efficacy or Worsening of Cancer

Deterioration that is judged by the Investigator to have unexpectedly worsened in severity or frequency, or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of cancer on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of non-small cell lung cancer" **[spell out name of condition, do not use acronym]**). 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 v.1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

11.3.10 **Atezolizumab and Tiragolumab Overdose**

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Development Innovations Safety Department no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting (see Section 11.1.2) if the overdose is symptomatic.

For information on how to manage an overdose of atezolizumab and tiragolumab, see the IBs.

11.4 **Adverse Events of Special Interest (AESIs)**

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to the other parties (e.g., regulatory authorities) may also be warranted.

The following are events of special interest, and must be reported to Genentech Drug Safety expeditiously, irrespective of regulatory seriousness criteria (see Section 11.2). These AESIs include the following:

- 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 and based on the following observations:
  - Treatment-emergent ALT or AST >3 × baseline value in combination with total bilirubin >2 × ULN (of which ≥35% is direct bilirubin)
  - Treatment-emergent ALT or AST >3 × baseline value in combination with clinical jaundice, as defined by Hy’s Law
- Data related to suspected transmission of an infectious agent via medicinal product (STIAMP), as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT >10 × ULN
- Systemic lupus erythematosus

- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine-release syndrome, influenza-like illness, MAS and HLH
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal, necrolysis)
- Immune-mediated facial paresis
- Immune-mediated myelitis

11.5 Sponsor Serious Adverse Event Reporting Requirements

Development Innovations Safety Department will forward SAE and AESI information, whether related or unrelated to atezolizumab and tiragolumab, pregnancy reports, and Product Complaints (with AE) originating from the Study for the Product to Genentech Drug Safety within 1 business day of Development Innovations Safety Department personnel becoming aware at

Email: **usds_aereporting-d@gene.com**

OR

Fax: (650) 238-6067

Development Innovations will provide case information on a completed MedWatch form with GNE Safety Reporting Fax Cover Sheet (see Appendix I: Safety Reporting Fax Cover Sheet) within 1 business day to the Genentech contact information specified above.

Transmission of these reports (initial and follow-up) will be sent either electronically or by fax and within the timelines specified below:

All Product Complaints without an AE should be called at:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Product Complaints

All Product Complaints (with or without an AE) shall be forwarded to Genentech within one calendar day of the awareness date.

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

Additional reporting requirements to Genentech include the following:

- Any reports of pregnancy following the start of administration with atezolizumab and within the follow-up period (for female patients within five months after the last dose of atezolizumab/tiragolumab or the partner of a male patient within five months of completing therapy) will be transmitted to Genentech within 1 business day of the Awareness Date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.
- Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported to Genentech as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to atezolizumab should be reported to Genentech as an SAE.

In addition to SAEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech even in the absence of an AE within one (1) calendar day:

- Data related to product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, misuse, medication error (including potentially exposed or intercepted medication errors)

In addition, reasonable attempts should made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

Note: Investigators should also report events to their IRB as required.

Development Innovations is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating Investigators, in accordance with International Council for Harmonisation (ICH) guidelines, and FDA regulations.

11.5.1 Sponsor Assessment of Unexpected

The Sponsor is responsible for assessing an adverse event or suspected adverse event as "unexpected."

An AE or SAR is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the IB (or current USPI)
- Event(s) is not listed at the specificity or severity that has been observed

- An event(s) is not consistent with the General Investigative Plan or in the current application
- Includes AEs or SAR that may be anticipated from the pharmacological properties of the study drug, or that occur with members of the drug class, but that have previously been observed under investigation

When applicable, an unexpected adverse event (UAE) may also apply to an event that is not listed in the current USPI or an event that may be mentioned in the USPI, but differs from the event because of greater severity or specificity.

Known as Suspected Unexpected Serious Adverse Reactions (SUSARs), these events suspected (by the Investigator or Sponsor) to be related to the study drug, are unexpected (not listed in the IB or USPI), and are serious (as defined by the protocol) and require expedient submission to relevant health authorities within 7 days (fatal or life-threatening event) or 15 days (all serious events), or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected AEs are those events that are listed or characterized in the USPI or current IB.

Reporting to Regulatory Authorities, Ethics Committees and Investigators
The Sponsor of the study (Development Innovations), will be responsible for the expedited reporting of safety reports originating from the study to the regulatory authority (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

The Sponsor (Development Innovations) will be responsible for the expedited reporting of safety reports originating from the study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

The Sponsor (Development Innovations) will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

11.5.2 Sponsor Reporting for Clinical Studies under an Investigational New Drug Application

All written IND Safety Reports submitted to the FDA by the Development Innovations Safety Department must also be faxed to the pharmaceutical company that is supporting the study with either funding or drug supply:

Atezolizumab and tiragolumab:

Genentech Drug Safety

Fax: (650) 225-4682 or (650) 225-4630.

Email: ctvistsa@gene.com

And Sponsor-Investigator will be responsible for the distribution of safety information to Site IRB.

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

For investigator-initiated IND studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the FDA as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

Development Innovations Safety Department is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the Investigator to be possibly related to the use of atezolizumab and tiragolumab. A UAE is one that is not already described in the atezolizumab IB. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

Development Innovations Safety Department is also required to notify the FDA and all participating Investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of atezolizumab and tiragolumab. A UAE is one that is not already described in the atezolizumab and tiragolumab IBs.

Written IND Safety reports should include an Analysis of Similar Events in accordance with Code of Federal Regulations (CFR) regulation 21 CFR § 312.32. All safety reports previously filed by the Investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports should be commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating Investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

All written IND Safety Reports submitted to the FDA must also be faxed to Genentech Drug Safety and to the site IRB.

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (Section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the AE to each investigational product and suspect medication

Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. date of birth, patient number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an AE was reported. For questions regarding SAE reporting, you may contact Genentech Drug Safety or the medical safety liaison (MSL) assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

Compliance with Pharmacovigilance Agreement/Audit

The Parties shall follow their own procedures for adherence to AE reporting timelines.

Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

11.5.3 Reconciliation/Case Transmission Verification of Single Case Reports

Development Innovations Safety Department agrees to conduct reconciliation for the product. Genentech and Development Innovations Safety Department will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly line listings of cases received by the other party. The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Development Innovations Safety Department to Genentech within five (5) calendar days from request by Genentech.

If discrepancies are identified, Development Innovations Safety Department and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The Development Innovations Safety Department shall receive reconciliation guidance documents within the "Activation Package." At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

Signal Management and Risk Management

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own product. However, it is agreed that Development Innovations, as Sponsor of the study, will be primarily responsible for assessment of the benefit-risk balance of the study.

If Development Innovations issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the study and/or triggers any changes to the study) this will be sent to Genentech within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist Development Innovations with signal and risk management activities related to the product within the study.

Genentech will also provide Development Innovations with any new relevant information that may modify or supplement known data regarding the product (e.g., relevant Dear Investigator Letter).

11.6 Queries

Queries related to the Study will be answered by Development Innovations. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Products (atezolizumab and tiragolumab). Development Innovations agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Products independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Study Monitoring, Auditing, and Inspecting

The Investigator will permit study-related monitoring, quality audits, and inspections by the Sponsor or its representative(s), government regulatory authorities, and the IRB of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The Investigator will ensure the capability for inspections of applicable study-related facilities. The Investigator will ensure that the study monitor or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At the Sponsor's discretion, Source Document Verification (SDV) may be performed on all or partial data as defined in study documents and/or plans.

Participation as an Investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the Sponsor, or its representative(s).

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice (GCP) outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

13.1 Institutional Review Board Approval

The clinical study protocol, ICF, IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going, IRB study review. The Principal Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for atezolizumab and tiragolumab, will be prepared by the Sponsor or its representative as required, for distribution to the Investigator(s) and submission to the relevant IRB.

13.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

13.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each ICF must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the Investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

13.3.1 Confidentiality

13.3.1.1 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date

- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the Investigator and institution permit authorized representatives of the Sponsor, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients in the eCRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

13.3.1.2 Investigator and Staff Information

Personal data of the Investigators and sub-Investigators may be included in the Development Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub Investigator, Development Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

13.4 Financial Information

The finances for this clinical study will be subject to a separate written agreement between Sarah Cannon Development Innovations, LLC, and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

13.5 IND Annual Reports

Copies to Genentech:

All IND annual reports submitted to the FDA by Sarah Cannon Development Innovations should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

Or emailed to the Genentech Drug Safety CTV mailbox: **ctvistsa@gene.com**.

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

13.6 Aggregate Report

The Sponsor will forward a copy of the Publication to Genentech upon completion of the Study.

13.7 Study Close-out

Any study report submitted to the FDA by Development Innovations should be copied to Genentech. This includes all IND annual reports and the final study report. Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be provided to the assigned Clinical Operations contact for the study:

Atezolizumab IIS Clinical Operations: anti-pdl-1-mpd3280a-gsur@gene.com.

And to the Genentech Drug Safety CTV oversight mailbox: ctvistsa@gene.com

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor or its representatives. All amendments require review and approval of all pharmaceutical companies and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the Investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable, and IRB approval obtained, and specifically when an increase to dosing or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment approval from IRB and/or FDA or other regulatory authorities include, but are not limited to, the following:

- Change to study design
- Risk to patient
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

14.2 Documentation Required to Initiate the Study

Before the study may begin certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

Sarah Cannon Development Innovations
Regulatory Department
ATTN: MULTI 29 Study
1100 Dr. Martin L. King Jr. Blvd., Suite 800
Nashville, TN 37203

Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current curricula vitae for the Principal Investigator and any associate Investigator(s) who will be involved in the study
- Indication of appropriate accreditation for laboratories (as required) to be used in the study and the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB-approved ICF containing permission for audit by representatives of Development Innovations, the IRB, and the FDA and other regulatory agencies (as applicable)
- Financial disclosure forms for all Investigators listed on Form FDA 1572 (if applicable)
- Verification of Principal Investigator acceptability from local and/or national debarment list(s)

14.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patient's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The Principal Investigator and each study staff member is responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or Investigator study file [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB approval documents, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, and records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received; and date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation/records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21-CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRFs, medical records), all original signed ICFs, and copies of all eCRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor will notify the Investigator(s)/institutions(s) when the study-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the study, both the Sponsor and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any

records, even if retention requirements have been met. All ISFs will be maintained by the Sponsor (Development Innovations) throughout the study, and will be held by the Sponsor at the conclusion of the study.

14.4 Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable the Sponsor to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study identifier, and patient number along with initials and/or date of birth/year as allowed per institutional policy will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Development Innovations and replaced instead with the patient number and other identifier as allowed per institutional policy. The Investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested in the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Investigator will electronically sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Principal Investigator, once all data for that patient is final.

14.5 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication process.

Inclusion of the Investigator in the authorship of any multicenter publication will be based upon substantial contribution to the study design, analysis, interpretation of data, or the drafting and/or critically revising of any manuscript(s) derived from the study. The Investigator acknowledges that the study is part of a multicenter study and agrees that any publication by the Investigator of the results of the study conducted at any research site shall not be made before the first multicenter publication. In the event there is no multicenter publication within fifteen (15) months after the study has been completed or terminated at all study sites, and all data has been received, the Investigator shall have the right to publish its results from the study, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of

the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the Investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any Development Innovations confidential information from all publications.

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16. APPENDICES

Appendix A: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death no imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

Appendix B: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix C: Schedule of Assessments

ASSESSMENTS	Baseline[a]	**STUDY TREATMENT (*Cycles repeated every 3 weeks*)**			
		Day 1 of every cycle (± 3 days)	**Response every 2 cycles(± 7 days)**	**End of Treatment[p](± 3 days)**	**Follow-Up[q,r] (±3 days)**
Tests and Observations					
Informed consent[a]	X				
Medical history	X[b]				
Physical exam[c]	X[b]	X		X	
Vital Signs[d]	X[b]	X		X	
ECOG PS	X[b]	X		X	
12-lead ECG	X[b]				
Adverse event evaluation		X		X	
Concomitant medication review	X	X		X	
Laboratory Observations					
CBC, 3-part differential, and platelets	X[b]	X		X	
CMP[e]	X[b]	X		X	
Thyroid Function Tests[s]	X[s]	X[s]			
PT/PTT or aPTT/INR[f]	X[b]				
Urine Dipstick	X				
Serum or Urine Pregnancy Test[g]	X[b]			X[g]	
Plasma/serum blood sample[h]		X		X	
PBMC blood sample[i]		X		X	
Whole blood sample[j]		X			
Pre-PD-1 archival tumor tissue[k]	X				
PD-L1 Testing Results (if available)[l]	X				
Fresh tumor sample[n]	X				
Optional tumor sample	X[t]				
Optional tumor sample at PD[o]				X	
Staging					
CT scan	X[b]		X[m]	X	X[q]
Survival					X[r]

Appendix C: Schedule of Assessments (continued)

a Informed consent must be obtained ≤28 days prior to the initiation of treatment.

b The baseline physical examination, medical history, ECOG PS, complete blood counts (CBC) with 3-part differential and platelets, comprehensive metabolic profile (CMP), urinalysis, and PT/PTT or aPTT/INR should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated. A pregnancy test must be performed within 72 hours of Cycle 1 Day 1. CT scans should be performed ≤28 days prior to initiation of treatment. ECG and research samples should be performed ≤28 days prior to initiation of study treatment.

c Physical examination will include measurements of height (pretreatment visit only), weight, and vital signs. Include monitoring for signs and symptoms of immune-mediated myelitis.

d Vital signs will include resting heart rate, blood pressure, respiratory rate, and oral temperature.

e CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, ALP, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

f If PT/PTT or aPTT/INR are normal at baseline they do not need to be repeated. Patients requiring the initiation of an anti-coagulation therapy during study treatment should have coagulation tests performed according to standard practice guidelines.

g Serum or urine pregnancy tests are to be conducted in women of childbearing potential.

h Blood samples collected for plasma/serum on Cycle 1 Day 1, Cycle 3 Day 1 (prior to treatment), and EOT.

i Blood sample for PBMC isolation and correlative research will be collected on Cycle 1 Day 1 and EOT.

j Blood sample for whole blood will be collected on Cycle 1 Day 1 only.

k Pre-PD-1 archival tumor tissue sample (highly recommended if available) provided as at least 15 FFPE slides (or whatever is available) containing unstained, freshly cut (not older than 180 days) serial sections.

l If prior PD-L1 testing results by IHC are available it should be captured in the eCRF and does not need to be repeated.

m Patients should have CT scans done

n A mandatory fresh tumor sample will be collected from each patient prior to treatment. Archival tissue collected following PD-1 therapy may be used if there have been no subsequent treatment regimens following tissue collection.

o Tissue biopsy upon disease progression (optional)

p EOT evaluations must be completed within 30 days after the last dose of study treatment. Patients must be followed for AEs for 30 calendar days after the last dose of study drug and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment.

q Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months (±1 month) from the date of last dose of study drug until disease progression or for up to 1 year whichever comes first unless otherwise directed due to study termination.

r After disease progression is documented, patients will be followed every 3 months (±1 month) for survival (e.g., date and cause of death) for up to 1 year or death whichever comes first unless otherwise directed due to study termination. Patients may be contacted during outpatient visits or by telephone.

s Thyroid function tests will include TSH, FT4, and T3. TFTs will be collected at C1D1 and every 4th cycle thereafter.

t Optional tissue biopsy for crossover patients only; sample should be collected prior to start of treatment on Arm B.

Appendix D: Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab and tiragolumab, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immune-modified response criteria have been developed to incorporate new lesions into the assessment of total tumor burden and allow radiographic progression to be confirmed at a subsequent assessment. Immune-modified RECIST, as described within this appendix, were adapted from RECIST, Version 1.1 (v1.1) (Eisenhauer et al. 2009), in the same manner that immune-mediated response criteria were adapted from WHO criteria (Wolchok et al. 2009) and RECIST v1.0 (Nishino et al. 2014). When not otherwise specified, RECIST v1.1 conventions will apply. Differences between immune-modified RECIST and RECIST v1.1 are summarized below.

	RECIST v1.1	Immune-Modified RECIST
Measurable new lesions	Always represent progression	Incorporated into the total tumor burden [a] and followed
Non-measurable new lesions	Always represent progression	Do not represent progression, but preclude CR
Non-target lesions	Contribute to defining CR, PR, SD, and PD	Contribute to defining CR only
CR	Disappearance of all lesions	Disappearance of all lesions
PR	≥30% decrease in sum of diameters of target lesions, in the absence of CR, new lesions, and unequivocal progression in non-target lesions	≥30% decrease in tumor burden, [a] in the absence of CR
PD	≥20% increase in sum of diameters of target lesions, unequivocal progression in non-target lesions, and/or appearance of new lesions	≥20% increase in tumor burden [a]
SD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Tumor burden is the sum of diameters of target lesions and measurable new lesions.

Tumor Measurability

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

Definition of 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:

40. 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval ≤5 mm)
41. 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
42. 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 ≤5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions," "New Lesions," and "Calculation of Sum of Diameters").

Definition of Non-Measurable Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with short axis ≥10 mm 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:

43. Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and 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.
44. 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.

45. Blastic bone lesions are non-measurable.

Cystic Lesions:

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

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Methods for Assessing Lesions

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the 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 and MRI Scans

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scans have slice thickness

of >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

Endoscopy, Laparoscopy, Ultrasound, Tumor Markers, Cytology, Histology

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

Assessment of Tumor Burden

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

Identification of Target and Non-Target Lesions

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

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

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the

plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), 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").

New Lesions

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST (e.g., non-lymph node lesions must be ≥10 mm on the longest diameter; new lymph nodes must be ≥15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden that is performed as part of the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the calculation of tumor burden and thus will not affect overall tumor response evaluation. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint can be included in the tumor response evaluation from that point on, if the maximum number of measurable new lesions has not been reached.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is ≥15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is ≥10 mm and <15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is <10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is ≥15 mm.

Calculation of Sum of Diameters

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline as a measure of tumor burden. At each subsequent tumor assessment, a sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions plus measurable new lesions (up to five new lesions, with a maximum of two new lesions per organ) that have emerged after baseline. Hence, each net percentage change in tumor burden per assessment accounts for the size and growth kinetics of both old lesions and new lesions as they appear.

Measuring Lymph Nodes

If at first appearance the short axis of a new lymph node lesion is ≥15 mm, it will be considered a measurable new lesion and may be included in the sum of the diameters. If the new lymph node lesion is included in the sum of diameters, it will continue to be measured and included in the sum of diameters at subsequent timepoints, even if the short axis decreases to <15 mm (or even <10 mm). However, if it subsequently decreases to <10 mm and all other lesions are no longer detectable or have also decreased to a short axis of <10 mm (if lymph nodes), a response assessment of complete response may be assigned.

Lymph nodes should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to <10 mm during the study. Thus, when lymph nodes are included in the sum of diameters, the sum may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions and up to five measurable new lesions (lymph node and non–lymph node) should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" 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 "too small to measure" should also be ticked).

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

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. 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 maximum longest diameter for the coalesced lesion.

Evaluation of Non-Target Lesions and Non-Measurable New Lesions

Measurements are not required for non-target lesions or non-measurable new lesions. Non-target lesions should be noted at baseline, and non-measurable new lesions should be noted at the time of identification. At subsequent evaluations, non-target lesions and non-measurable new lesions will be categorized as "present" or "absent."

After baseline, changes in non-target lesions or non-measurable new lesions (or measurable new lesions in excess of five total or two per organ) 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 non-measurable new lesions) and will not be used to assess progressive disease.

Response Criteria

Definitions of the criteria used to determine objective tumor response are provided below:

- Complete response (CR): Disappearance of all lesions
- Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the smallest sum of diameters on study (including baseline)
  - In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥5 mm.
  - New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is factored into the sum of the diameters, which is used to determine the overall immune-modified RECIST tumor response.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

Criteria for Overall Response at a Single Timepoint

The table below provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions and Measurable New Lesions[a]	Non-Target Lesions and Non-Measurable New Lesions[b]	Overall Response
CR	Absent	CR
CR	Present or not all evaluated	PR
PR	Any	PR
SD	Any	SD
Not all evaluated	Any	NE
PD	Any	PD

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

[a] Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden, in addition to the target lesions identified at baseline.

[b] Also includes measurable new lesions in excess of five total or two per organ.

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 measurements are made on only a subset of target or measurable new lesions at a timepoint, 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 lesions 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.

Special Notes on Response Assessment

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

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Appendix E: Pre-existing Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone or patients with controlled Type 1 diabetes mellitus who are on an insulin regimen may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease - chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cirrhosis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren's syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix F: Management of Tiragolumab/Atezolizumab-Specific Adverse Events

Toxicities associated or possibly associated with atezolizumab or tiragolumab treatment should be managed according to standard medical practice for the management of immune-mediated adverse events. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

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

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

Pericardial Events

Immune-mediated pericardial disorders, including pericarditis, pericardial effusion, and cardiac tamponade are an identified risk with atezolizumab.

Pericardial disorders encompass a range of diseases of the pericardium. Underlying causes include infection (particularly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders. Pericardial disorders are also known to be associated with drugs including immune-checkpoint inhibitors.

Pericarditis may be associated with pericardial effusion, which if significant in volume, may result in hemodynamic instability and progress to cardiac tamponade. Cardiac tamponade is a life-threatening condition and should be treated as a medical emergency.

The diagnosis of immune-mediated pericarditis should be considered in all patients presenting with chest pain.

The diagnosis of immune-mediated pericardial effusion and cardiac tamponade should be considered in all patients presenting with chest pain associated with dyspnea or hemodynamic instability.

Cardiac tamponade should be treated as a medical emergency and consultation with a cardiologist should be sought for further management.

Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a pericardial disorder on prior treatment with other immune-stimulatory anticancer agents.

Management guidelines for pericardial events are presented in Table 5.

Table 5 Management Guidelines for Pericardial Events, Including Pericarditis, Pericardial Effusion, and Cardiac Tamponade

Event	Management
Immune-mediated pericardial disorders, including pericarditis, pericardial effusion, and cardiac tamponade, any grade	• Withhold atezolizumab for any patient with suspected immune-mediated pericardial disorders and contact the principal investigator. • Permanently discontinue atezolizumab for any grade confirmed immune-mediated pericardial disorders. • Refer patient to cardiologist. • 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.

Pulmonary Events

Immune-mediated pulmonary events are a potential risk with tiragolumab.

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

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 6.

Table 6 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and tiragolumab, and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset.[b] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • Resume atezolizumab and tiragolumab if event resolves to Grade 1 or better within 12 weeks. [a, b] • Permanently discontinue atezolizumab and tiragolumab if event does not resolve to Grade 1 or better within 12 weeks of withholding tiragolumab/atezolizumab.[a, b, c] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and tiragolumab, and contact Medical Monitor.[c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = bronchoscopic alveolar lavage; IVIG = intravenous immunoglobulin

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

b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent.

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

Hepatic Events

Immune-mediated hepatic events are a potential risk with tiragolumab.

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 7.

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(s).

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

Table 7 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab and tiragolumab. • 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 and tiragolumab for up to 12 weeks after event onset. [b] • Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • Resume atezolizumab and tiragolumab if event resolves to Grade 1 or better within 12 weeks.[a, b] • Permanently discontinue atezolizumab and tiragolumab and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks of withholding tiragolumab/atezolizumab.[a, b, c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and tiragolumab, and contact Medical Monitor.[c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

LFT = liver function tests.

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

b Atezolizumab and tiragolumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

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

Gastrointestinal Events

Immune-mediated gastrointestinal events are a potential risk with tiragolumab.

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 8.

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 CRP, 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 8 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

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

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and tiragolumab, and contact Medical Monitor.[c] • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1−2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI=Gastrointestinal

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

b Atezolizumab and tiragolumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the Investigator and Medical Monitor.

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

Endocrine Events

Immune-mediated endocrine events are a potential risk with tiragolumab.

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 9.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. Patients should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine (T3) and thyroxine (T4) 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) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Table 9 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab and tiragolumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab and tiragolumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab and tiragolumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	• **TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab and tiragolumab. • Monitor TSH every 4 weeks. • **TSH <0.1 mU/L:** • • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab and tiragolumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab and tiragolumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and tiragolumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism.[c]
Symptomatic adrenal insufficiency, Grades 2−4	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. [a,b] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1−2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • Resume atezolizumab and tiragolumab if event resolves to Grade 1 or better and patient is stable on replacement therapy (if required) within 12 weeks.[a, b] • Permanently discontinue atezolizumab and tiragolumab and contact Medical Monitor if event does not resolve to Grade 1 or better or patient is not stable on replacement therapy within 12 weeks of withholding tiragolumab/atezolizumab.[a, b, c]

Hyperglycemia, Grade 1 or 2	• Continue atezolizumab and tiragolumab. • 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 and tiragolumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab and tiragolumab when symptoms resolve and glucose levels are stable.
Hypophysitis (panhypopituitarism), Grade 2 or 3	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. [b] • 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 and tiragolumab. [a] • Permanently discontinue atezolizumab and tiragolumab and contact Medical Monitor if event does not resolve to Grade 1 or better or patient is not stable on replacement therapy within 12 weeks of withholding tiragolumab/atezolizumab. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (panhypopituitarism), Grade 4	• Permanently discontinue atezolizumab and tiragolumab 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 If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab and tiragolumab can be resumed.

b Atezolizumab and tiragolumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

c Resumption of atezolizumab and tiragolumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be rechallenged with atezolizumab and tiragolumab only after approval has been documented by the Investigator (or an appropriate delegate).

Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 10.

Table 10 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab and tiragolumab. • 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 and tiragolumab for up to 12 weeks after event onset. [b] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • Resume atezolizumab and tiragolumab if event resolves to Grade 1 or better within 12 weeks.[a, b] • Permanently discontinue atezolizumab and tiragolumab and contact if event does not resolve to Grade 1 or better within 12 weeks of withholding tiragolumab/atezolizumab.[a, b, c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and tiragolumab and contact Medical Monitor.[c] • Refer patient to ophthalmologist. • Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

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

b Atezolizumab and tiragolumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent.

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

Immune-Mediated Myocarditis

Immune-mediated myocarditis is a potential risk with tiragolumab and has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

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

Table 11 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2-4 Immune-mediated pericardial disorders Grade 2-4	• Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

Infusion-Related Reaction and Cytokine-Release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab or tiragolumab. 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-L1 or PD-1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for the medical management of IRRs and CRS are provided in Table 12. 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 12 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. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab and tiragolumab 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.
Grade 3 [a] fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or**	• Permanently discontinue atezolizumab and tiragolumab 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.

hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• 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 tiragolumab 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.

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

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

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.03 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature≥38°C not attributable to any other cause. In patients who develop CRS and who 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 and tiragolumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab and tiragolumab 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

Immune-mediated pancreatic events are a potential risk with tiragolumab.

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 13.

Table 13 Management Guidelines for Pancreatic Events

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 · ULN:** • Continue atezolizumab and tiragolumab. • 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 Grade 3.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab and tiragolumab 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 and tiragolumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and tiragolumab, and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab and tiragolumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab/tiragolumab and contact Medical Monitor. [c]

Event	Management
	• For recurrent events, permanently discontinue atezolizumab and tiragolumab, and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and tiragolumab, 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 and tiragolumab 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 and tiragolumab can be resumed.

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

Dermatologic Events

Immune-mediated dermatologic events are a potential risk with tiragolumab.

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 14.

Table 14 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab and tiragolumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab and tiragolumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. [a]

	• Refer patient to dermatologist. • 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 and tiragolumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab, and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and tiragolumab, 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 and tiragolumab 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 and tiragolumab.

[a] Atezolizumab and tiragolumab 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 and tiragolumab can be resumed.

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

Neurologic Disorders

Immune-mediated neurologic events are a potential risk with tiragolumab.

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 15.

Table 15 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab and tiragolumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab and tiragolumab 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 and tiragolumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact Medical Monitor. c
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and tiragolumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and tiragolumab 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 and tiragolumab 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 and tiragolumab can be resumed.

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

Immune-Mediated Meningoencephalitis

Immune-mediated meningoencephalitis is a potential risk with tiragolumab.

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 16.

Table 16 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and tiragolumab, 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 and tiragolumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab and tiragolumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

Renal Events

Immune-mediated nephritis is a potential risk with tiragolumab and 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 17.

Table 17 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab and tiragolumab. • Monitor kidney function closely, including creatinine, until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab and tiragolumab 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 and tiragolumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and tiragolumab 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 and tiragolumab 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 and tiragolumab can be resumed.

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

Immune-Mediated Myositis

Immune-mediated myositis is a potential risk with tiragolumab and 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 18.

Table 18 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab and tiragolumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab and tiragolumab 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 and tiragolumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab, and contact Medical Monitor. [c]
Immune-mediated myositis, Grade 3	• Withhold atezolizumab and tiragolumab 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 and tiragolumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.

[a] Atezolizumab and tiragolumab 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 and tiragolumab can be resumed.

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

Table 18 Management Guidelines for Immune-Mediated Myositis (cont.)

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

[a] Atezolizumab and tiragolumab 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 and tiragolumab can be resumed.

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

Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

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

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 et al. 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/⌈L)
  - ANC < 1.0×10^9/L (1000/⌈L)
- 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 NK 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/⌈L)
  - 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 19.

Table 19 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and tiragolumab 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 according to published guidelines (La Rosée et al. 2015; Schram et al. 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. [a]

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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

Immune-Mediated Myelitis

Immune-mediated myelitis is an identified risk with atezolizumab.

- Patients should be monitored for clinical signs and symptoms that are suggestive of myelitis. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies.
- Refer patients to neurologist.
- For Grade 1 myelitis, continue immunotherapy unless symptoms worsen or do not improve.
- Initiate treatment as per institutional guidelines.
- Atezolizumab should be permanently withdrawn for ≥Grade 2 immune-mediated myelitis.

Immune-Mediated Facial Paresis

Immune-mediated facial paresis is an identified risk with 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.
- Refer patient to neurologist.
- Initiate treatment as per institutional guidelines.
- Atezolizumab should be withheld for patients with Grade 1 or 2 immune-mediated facial paresis and permanently withdrawn for ≥Grade 3 immune-mediated facial paresis.

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Appendix G: Anaphylaxis Precautions

Equipment Needed

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

Procedures

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

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
4. Administer antihistamines, epinephrine, or other medications as required by participant status and as directed by the physician in charge.
5. Continue to observe the participant and document observations.
6. Draw serum/plasma samples for immunogenicity testing.

Ask participant to return for washout immunogenicity sample if appropriate.

Appendix H: Biological Sample Laboratory Testing Information

Patients with paired pre-PD1 and pre-Atezolizumab tissue sample or paired pre-Atezolizumab and post-Atezolizumab tissue sample *:

1. PD-L1/CD8 IHC (central testing, Genentech-defined laboratory).

2. Gene expression analysis using RNA sequencing or whole transcriptome sequencing (WTS) (via Genentech at a third party lab)

3. Whole exome sequencing (via Genentech at a third party lab)

B. Patients with only a pre-Atezolizumab tissue sample*:

1. PD-L1/CD8 IHC (central testing, Genentech-defined laboratory)

2. Gene expression analysis using RT-PCR, RNA sequencing or WTS (via Genentech at a third party laboratory).

*Note: Whenever possible a post-atezolizumab tissue sample will be obtained.

C. Plasma, serum, and PBMC samples:

Banking for future analysis, which may include but are not limited to cfDNA (plasma) analysis using NGS or RT-PCR, proteomic/cytokine analysis (serum), immune profiling (PBMC).

Appendix I: Safety Reporting Fax Cover Sheet

Genentech
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SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET