TITLE: A phase II clinical trial of tiragolumab in combination with atezolizumab in patients with non-small cell lung cancer (NSCLC) and untreated brain metastases.

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Table of Contents

Title Page 1

i. PROTOCOL SUMMARY 4

ii. SCHEMA 7

1. BACKGROUND 9
   - 1.1 Lung Cancer 9
   - 1.2 Tiragolumab and Atezolizumab 10
   - 1.3 Rationale 13

2. OBJECTIVES AND ENDPOINTS 14
   - 2.1 Objectives 14
   - 2.2 Endpoints 15

3. PATIENT SELECTION AND ELIGIBILITY CRITERIA 15
   - 3.1 Inclusion Criteria 15
   - 3.2 Exclusion Criteria 17

4. REGISTRATION PROCEDURES 19
   - 4.1 General Guidelines 19
   - 4.2 Registration Process 19

5. TREATMENT PLAN 20
   - 5.1 Agent Administration 20
   - 5.2 General Concomitant Medication and Supportive Care Guidelines 21
   - 5.3 Duration of Therapy 23
   - 5.4 Duration of Follow-up 24

6. DOSING DELAYS/DOSE MODIFICATIONS 24
   - 6.1 Atezolizumab and Tiragolumab Dosing 24
   - 6.2 Carboplatin and Pemetrexed Dosing 25

7. Management Guidelines for Immune-Related Adverse Events 25
   - 7.1 Pulmonary Events 25
   - 7.2 Hepatic Events 26
   - 7.3 Gastrointestinal Events 27
   - 7.4 Endocrine Events 29
   - 7.5 Ocular Events 31
   - 7.6 Immune-mediated Myocarditis 32
   - 7.7 Infusion-related Reactions 33
   - 7.8 Cytokine-release Syndrome 34
   - 7.9 Pancreatic Events 37
   - 7.10 Dermatologic Events 38
   - 7.11 Neurologic Disorders 39
   - 7.12 Immune-mediated Meningoencephalitis 41

7.13 Renal Events 41
7.14 Systemic Immune Activation....**Error! Bookmark not defined.**
7.15 Immune-mediated Myositis 42
7.16 Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome 44

8. PHARMACEUTICAL INFORMATION....45
8.1 Tiragolumab....45
8.2 Atezolizumab 46
8.3 Carboplatin and Pemetrexed....46

9. STATISTICAL CONSIDERATIONS....46
9.1 Study Design/Endpoints....46
9.2 Statistical Analysis Plan....46
9.3 Sample Size/Accrual Rate....48
9.4 Stopping Rule for Excess Toxicity 48
9.5 For Phase 2 Protocols Only: Reporting and Exclusions 49

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS 49
10.1 Adverse Events 49
10.2 Recording/Reporting requirements....53
10.3 Reporting of Serious Adverse Events....**Error! Bookmark not defined.**
10.4 Review of Safety Information: Sponsor-Investigator Responsibilities ....**Error! Bookmark not defined.**
10.5 IND safety reports....**Error! Bookmark not defined.**
10.6 Submission of IND safety reports....**Error! Bookmark not defined.**
10.7 Follow-up....**Error! Bookmark not defined.**
10.8 Disclaimer....**Error! Bookmark not defined.**
10.9 Reporting adverse events to the responsible IRB ..**Error! Bookmark not defined.**

11. STUDY CALENDAR 65

12. MEASUREMENT OF EFFECT....66
12.1 Antitumor Effect – Solid Tumors 66

13. DATA REPORTING / REGULATORY REQUIREMENTS....74
13.1 Data Safety Monitoring Plan 74
13.2 Quality Control and Quality Assurance....75
13.3 Data Handling and Record-Keeping....76
13.4 Institutional Review Board (IRB) Approval....76
13.5 Ethical and Scientific Conduct of the Clinical Study 77
13.6 Informed Consent....77

14. REFERENCES 78

15. APPENDICES 83
15.1 APPENDIX A: PERFORMANCE STATUS CRITERIA....83
16.2 APPENDIX B: Anaphylaxis Precautions 84

15.3 APPENDIX C: Safety Reporting Fax Cover Sheet 85
15.4 APPENDIX D: Administration of Atezolizumab and Tiragolumab infusions 86

i. PROTOCOL SUMMARY

Title	A phase II clinical trial of tiragolumab in combination with atezolizumab in patients with non-squamous non-small cell lung cancer (NSCLC) and untreated brain metastases
Short Title	Tiragolumab and atezolizumab in NSCLC with untreated brain metastases
Protocol Number	HCC 22-045
Phase	Phase II
Study Design	While the current trial was originally designed to investigate the activity of carboplatin, pemetrexed, atezolizumab and tiragolumab in patients with non-squamous NSCLC and untreated brain metastases, in response to the SKYCRAPER-06 interim analysis, the protocol has been amended after the enrollment of the first three patients to an investigation of atezolizumab with or without tiragolumab in patients with newly diagnosed metastatic PD-L1 selected NSCLC and untreated brain metastases. The first three patients accrued on Version 2.0, Version Date: 05/17/2023, will continue to be treated and included in study as cohort one, and the remaining patients will be included as cohort two. The three patients in cohort one will continue to be treated according to the Version 2.0, Version Date: 05/17/2023 schema due to ongoing clinical benefit and tumor response to the four-drug regimen. These three patients have CNS disease that has improved and there have been no unanticipated toxicity or safety signals. The patients have been made aware of the results of SKYSCRAPER-06 and intend to be treated per the cohort one schema. This was discussed with Genentech and agreed upon. Patients with at least one untreated evaluable brain metastasis of 5 mm or more will be enrolled. Lesions previously treated with SRS may not be used as target lesions. Patients will be required to undergo an on-treatment brain MRI at three weeks for safety purposes. Additional restaging will occur at nine-week intervals. PD-L1 tumor proportion score (TPS) will be determined utilizing an FDA-

	approved test by local testing.
Study Duration	36 months
Study Center(s)	Multi-center with 2-3 external sites
Objectives and Endpoints	
Primary	**Objective**: To estimate the rate of initiation of salvage radiation therapy to the CNS in patients with NSCLC and untreated brain metastases treated with the combination of tiragolumab and atezolizumab with or without chemotherapy. **Endpoint**: Proportion of patients that require salvage radiation therapy to the CNS within 18 weeks of study initiation
Secondary	**Objectives**: 1. To characterize the safety and tolerability of the combination of tiragolumab and atezolizumab with and without chemotherapy in patients with NSCLC and untreated brain metastasis, particularly Grade ≥ 2 (symptomatic) CNS related adverse event. 2. To estimate the brain metastasis response rate (BMRR; response assessment in neuro-oncology brain metastases [RANO-BM]). 3. To estimate the overall response rate (ORR), assessed using RECIST v1.1. 4. To estimate progression-free survival (PFS). 5. To estimate overall survival (OS). 6. To estimate progression-free survival 2 (PFS2) after initiation of salvage XRT 7. To estimate PD-L1 tumor proportion score (TPS) as a potential predictive biomarker of response. **Endpoints**: 1. Frequency of Grade ≥ 2 (Symptomatic) CNS related adverse events per CTCAE v5.0 2. Brain Metastasis Response Rate (BMRR) (per RANO-BM) 3. Objective Response Rate (ORR) 4. Progression-free Survival (PFS) 5. Overall Survival (OS) 6. Progression-free Survival after initiation of salvage XRT (PFS2) 7. PD-L1 TPS
Number of Participants	Approximately 35 participants
Main Inclusion and Exclusion Criteria	**Key Inclusion** • Patients must have histologically or cytologically confirmed

	NSCLC. • In patients treated with the combination of tiragolumab and atezolizumab, patients must have PDL1 TPS >50%, as determined by an FDA-approved test. • Patients must have asymptomatic brain metastases with at least one untreated evaluable (per RANO-BM) brain metastasis of 5 mm or more. A growing lesion previously treated with whole brain radiotherapy is acceptable given the lower incidence of radiation necrosis. Lesions previously treated with SRS may not be used as target lesions. • Patients are not required to have measurable disease outside the CNS per RECIST 1.1. • Prior chemotherapy, immunotherapy or radiation given with curative intent in early stage or locoregionally advanced NSCLC is permitted, if completed more than 12 months prior to initiation of study treatment. • Prior radiation with palliative intent in the metastatic setting to non-CNS lesions is permitted (no washout). • Age ≥18 years. • ECOG performance status ≤ 1. • Patients must have normal organ and marrow function. **Key Exclusion** • Symptoms related to brain metastases requiring CNS radiation, steroids greater than prednisone 10 mg/d or equivalent, or anti-epileptic therapy ≤ 2 weeks of treatment initiation are exclusionary. • Prior systemic therapy for metastatic disease is not allowed. • Active or history of autoimmune disease or immune deficiency, requiring systemic therapy ≤ 12 months of study enrollment.
Investigational Product	Cohort 1: Tiragolumab 600 mg intravenously (IV) for induction treatment will be administered on Day 1 of each 21-day cycle for 4 cycles (in combination with atezolizumab plus pemetrexed and carboplatin). Maintenance therapy will continue with tiragolumab in combination with atezolizumab and pemetrexed on Day 1 of each 21-day cycle. Cohort 2: Tiragolumab 600 mg intravenously (IV) for induction treatment will be administered on Day 1 of each 21-day cycle for 4 cycles (in combination with atezolizumab). Maintenance therapy will continue with tiragolumab in combination with atezolizumab on Day 1 of each 21-day cycle.

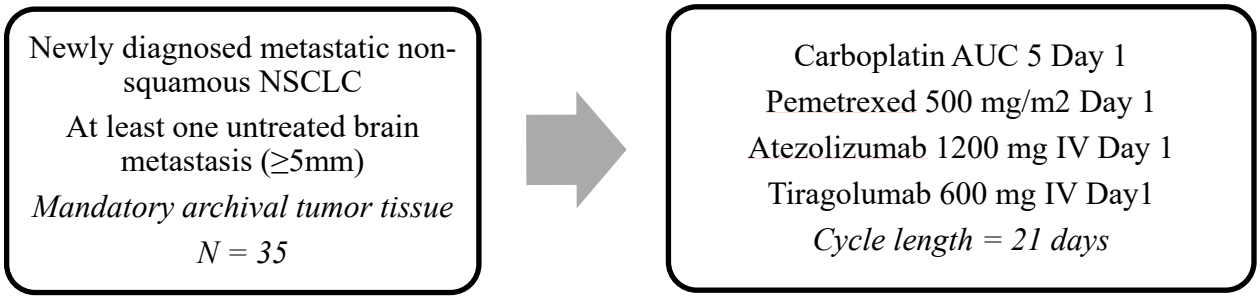
Duration of administration	For up to 2 years on therapy until loss of clinical benefit, unacceptable toxicity, death, or withdrawal of consent.
Reference therapy	Carboplatin AUC 5 Day 1 Pemetrexed 500 mg/m^2 Day 1 Atezolizumab 1200 mg IV Day 1
Statistical Methods	Patients in cohort 1 and cohort 2 will be pooled for all safety and efficacy analyses. For the primary endpoint of whether or not the patient requires salvage radiation therapy to the CNS within 18 weeks, an exact binomial test will be used for the null hypothesis H_o: P (salvage therapy)>0.5 at α=0.05. The sample size of 35 patients will provide 80% power if the true P (salvage therapy) is less than or equal to 0.27. For binary endpoints (including the primary endpoint), the proportion will be calculated with a 95% exact (Clopper-Pearson) confidence interval. Each survival endpoint will be characterized by the product-limit (Kaplan-Meier) method with a 95% Greenwood confidence region. Median survival will be estimated from the survival function with a 95% Brookmeyer and Crowley confidence interval.
Data and Safety Monitoring Plan	Principal Investigator, Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following: • Serious adverse events • Subject safety issues • Recruitment issues • Accrual • Protocol deviations • Unanticipated problems • Breaches of confidentiality Minutes from the DSMB meetings are available to those who are unable to attend the disease center DSMB in person or through conference call.

ii. SCHEMA

This is a phase II clinical trial aimed at the evaluation of the safety and clinical activity of tiragolumab and atezolizumab with or without chemotherapy in the first line treatment of

metastatic NSCLC patients with asymptomatic, untreated brain metastases. Patients must have asymptomatic brain metastases with at least one untreated evaluable brain metastasis of 5 mm or more. Lesions previously treated with SRS may not be used as target lesions. Patients will be required to undergo an on-treatment brain MRI at three weeks for safety purposes while on trial, and additional restaging will occur at nine-week intervals. PD-L1 tumor proportion score (TPS) will be determined utilizing an FDA-approved test by local testing.

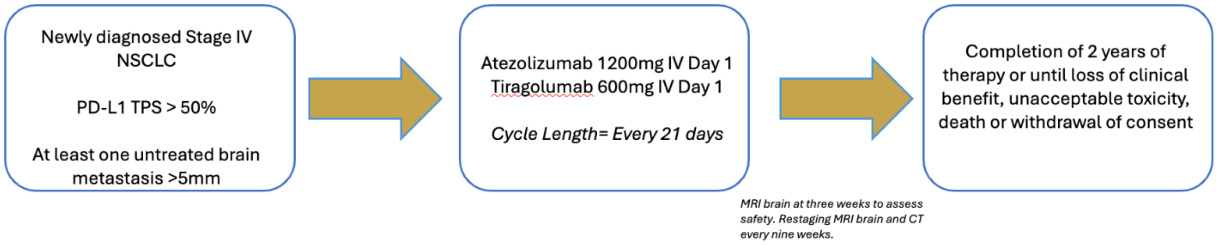
Cohort 1 (accrued to protocol Version 2.0, Version Date: 05/17/2023):



MRI brain at 3 weeks to assess safety
Restaging (CT/MRI brain) every 9 weeks

Induction treatment with tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin will be administered on Day 1 of each 21-day cycle for 4 cycles. Following the induction phase, maintenance therapy will continue with tiragolumab in combination with atezolizumab and pemetrexed on Day 1 of each 21-day cycle.

Cohort 2 (Version 3.0, Version Date 10/16/2024):



Treatment with tiragolumab in combination with atezolizumab will be administered on Day 1 of each 21-day cycle for up to 2 years of therapy until loss of clinical benefit, unacceptable toxicity, death or withdrawal of consent. Patients with progressive brain metastases (based on RANO-BM and/or clinical progression) will be allowed to undergo salvage local therapy, e.g. radiotherapy and be allowed to continue on trial, if they are clinically stable, as deemed by the treating investigator.
Patients will continue up to 2 years on therapy until loss of clinical benefit, unacceptable toxicity, death or withdrawal of consent. Patients with progressive brain metastases (based on RANO-BM and/or clinical progression) will be allowed to undergo salvage local therapy, e.g.

radiotherapy and be allowed to continue on trial, if they are clinically stable, as deemed by the treating investigator.

1. BACKGROUND

1.1 Lung Cancer

Lung cancer remains the leading cause of cancer deaths worldwide; it is the most common cancer in both men and women and accounted for approximately 13% of all new cancers in 2008 (Jemal et al. 2011). In 2012, it was estimated that there were 313,000 new cases of lung cancer and 268,000 lung cancer deaths in Europe (GLOBOCAN 2012). In the United States, there were an estimated 221,200 new cases of lung cancer and 158,040 lung cancer deaths in 2015 (Siegel et al. 2015).

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

Genetic changes that have prognostic and/or predictive significance in NSCLC include mutations in the EGFR gene and rearrangement in the ALK gene. The rates of these mutations differ between squamous cell carcinoma and adenocarcinoma. For example, EGFR mutations have been reported in 10%-40% of patients with adenocarcinoma NSCLC but are infrequently observed in squamous NSCLC (Herbst et al. 2008). Rearrangement in the ALK gene is very rare in the squamous histology but observed in approximately 7% of patients with adenocarcinoma (Herbst et al. 2008; Langer et al. 2010).

In patients without actionable oncogenic drivers, platinum-based chemotherapy regimens without the addition of immunotherapy reached a plateau in overall response rate (approximately 15%-22%) and median overall survival (OS) (7-10 months). The addition of bevacizumab to carboplatin and paclitaxel resulted in an increased response rate of 35% and an increased median OS of 12 months. Further benefit has been demonstrated with pemetrexed maintenance therapy when administered to patients with a response of stable disease or better following four cycles of cisplatin plus pemetrexed (median PFS of 4.1 months with pemetrexed maintenance vs. 2.8 months with placebo maintenance) (Paz Ares et al. 2012).

In previously treated advanced NSCLC patients, unprecedented survival gains have been demonstrated with pembrolizumab, nivolumab and atezolizumab. These survival gains have extended into the 1st line setting in patients with high PD-L1 expressing (tumor proportion score; TPS $\geq$ 50%) tumors with superior OS with pembrolizumab, compared with chemotherapy. Pembrolizumab in combination with carboplatin and pemetrexed was approved in the 1st line treatment of non-squamous NSCLC regardless of TPS, based on superior response rates, progression-free survival and overall survival, compared with chemotherapy alone.

The IMPower150 clinical trial demonstrated the addition of atezolizumab to carboplatin, paclitaxel, and bevacizumab resulted in superior PFS and OS compared with carboplatin-based chemotherapy alone in the 1st line treatment of an all-comer (with regard to TPS) non-squamous NSCLC population. As first line therapy, carboplatin, paclitaxel and bevacizumab has been associated with equivalent survival to carboplatin, pemetrexed, and bevacizumab (Patel et al. 2013). Combinations of a platinum agent with pemetrexed have been used more widely because of a better tolerability and safety profile. Thus, carboplatin, pemetrexed and bevacizumab have been chosen as the platinum backbone in the current clinical trial.

1.2 Tiragolumab and Atezolizumab

1.2.1 Tiragolumab

Tiragolumab is a fully human IgG1/κ mAb that binds T cell immunoreceptor with Ig and ITIM domains (TIGIT), an immune inhibitory receptor that is 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 of TIGIT in T cells in mice results in exacerbated T cell responses, demonstrating the role of TIGIT in inhibiting T cell responses (Joller et al. 2011; 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 CIT and chemotherapy. 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 Investigator's Brochure for details on the nonclinical and clinical studies for tiragolumab.

1.2.2 Atezolizumab

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor specific T cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (see U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no DLTs were

observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight-based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

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

1.2.3 Background on Blockade of the TIGIT Pathway in Cancer as a Potential Anticancer Therapy

TIGIT is a novel immune inhibitory receptor that is a member of the Ig super family (Yu et al. 2009; Manieri et al. 2017). TIGIT expression is elevated in the tumor microenvironment in many human tumors, is coordinately expressed with other checkpoint immune receptors such as PD-1, and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014). Activation of TIGIT on T-cells and NK-cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (TCs) (Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017).

TIGIT is expressed in a wide variety of human tumors, including NSCLC, and is highly correlated with Tcell infiltration and PD1 expression (Johnston et al. 2014). Fluorescence activated cell sorting analysis of fresh tumor samples showed that TIGIT and PD1 are also co-expressed on tumor infiltrating T cells. TIGIT expression ranges from 30% to 80% and from 50% to 80% on tumor infiltrating CD4+ and CD8+ T cells, respectively (Johnston et al. 2014). It has also been reported that tumor infiltrating lymphocytes from early stage primary NSCLCs co-express TIGIT with PD-1, suggesting that TIGIT expression may be important throughout the development of NSCLC (Tassi et al. 2017).

Therefore, TIGIT is a potential target for therapeutic intervention aimed at restoring the immune response against the tumor, especially in NSCLC. Agents that inhibit the activity of TIGIT may relieve an important source of tumor associated immune suppression and may enhance the activity of other immune based therapies, such as atezolizumab, an inhibitor of PD-L1. Early nonclinical results using genetically deficient mice and blocking antibodies reveal a key role for TIGIT in regulating Tcell responses. Together the data support the hypothesis that anti-TIGIT in combination with anti-PD-L1 may reactivate antitumor immunity in NSCLC to provide clinical benefit to patients.

1.2.4 Combined Inhibition of the TIGIT and PD-L1/PD-1 Pathways as Potential Anticancer Therapy

The inhibitory immunoreceptor TIGIT 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 TCs. Therefore, in the context of the tumor microenvironment, TIGIT acts to limit antitumor immune responses. Interference with TIGIT/PVR interaction may enhance the magnitude and quality of the tumorspecific Tcell responses through increased expansion of T cells as well as improved Tcell priming and/or effector function. Because TIGIT and PD1 are co-expressed by infiltrating T cells in several human tumors, inhibition of the TIGIT/PVR pathway may complement and potentiate the

antitumor activity of a PDL1 pathway inhibitor such as atezolizumab.

The combined inhibition of the TIGIT and PD-L1/PD-1 pathways by tiragolumab and atezolizumab, respectively, has demonstrated promising clinical activity in the Phase I study GO30103 and the Phase II study GO40290 (hereafter referred to as CITYSCAPE). Study GO30103 is a first-in-human, combined Phase Ia/Phase Ib, open-label, dose escalation, multicenter study. The study evaluated the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of tiragolumab administered as a single agent (Phase Ia) or in combination with atezolizumab (Phase Ib) to patients with locally advanced or metastatic malignancies. As of December 2, 2019, 171 patients with multiple tumor types, including NSCLC, had been enrolled in the Phase Ib portion of the study. Objective responses, including complete responses (CR) in 4 patients, and partial responses (PR) in 23 patients, have been observed.

No maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence or severity of adverse events have been determined for single-agent tiragolumab or tiragolumab in combination with atezolizumab in Study GO30103. Tiragolumab was further evaluated in patients with PD-L1 selected advanced NSCLC (tumor proportion score [TPS] ³ 1%) in the Phase II, global, randomized, double-blind, placebo-controlled CITYSCAPE study. As of the clinical cutoff date of Dec 2, 2019, the confirmed objective response rate (ORR) in the intent-to-treat (ITT) population was higher in the tiragolumab combined with atezolizumab arm (37%) than in the placebo combined with atezolizumab arm (21%). Investigator assessed progression-free survival (PFS) was also improved with a stratified hazard ratio (HR) of 0.58 (95% confidence interval (CI): 0.38 to 0.89), with a median PFS not estimable and 3.9 months in the tiragolumab combined with atezolizumab arm compared to the placebo combined with atezolizumab arm, respectively. Responses to tiragolumab in combination with atezolizumab were observed in patients with both squamous and non-squamous histology (Rodriguez-Abreu et al, 2020).

As of the clinical cutoff date of December 2, 2019 in the CITYSCAPE study, there were 135 safety evaluable patients. The safety profile was comparable between the tiragolumab combined with atezolizumab arm and the placebo combined with atezolizumab arm for all grades of adverse events (99% vs 96%), Grade ≥ 3 adverse events (48% vs 44%), Grade 5 adverse events (4.5% vs 7.4%), serious adverse events (37% vs 35%), and adverse events leading to study treatment withdrawal (10.4% vs 8.8%). Study treatment related adverse events occurred at a higher frequency in the tiragolumab combined with atezolizumab arm (82%) compared to the placebo combined with atezolizumab arm (72%).

Using a comprehensive medical concepts strategy, immune-mediated adverse events were reported with a higher frequency in the tiragolumab combined with atezolizumab arm (69%) compared to the placebo combined with atezolizumab arm (47%). The difference (> 10% difference between arms) was predominantly attributed to events of immune mediated rash (preferred terms of rash, rash maculopapular, dermatitis, erythema, eczema, pruritic rash, folliculitis and skin ulcer) (40% vs 15%) and infusion related reactions (preferred term of infusion related reaction) (30% vs 10%).

Tiragolumab is being investigated in clinical studies as a potential therapy against various tumor

types. Refer to the Tiragolumab Investigator's Brochure for details on the nonclinical and clinical studies for tiragolumab.

1.2.5 Combined Inhibition of TIGIT and PD-L1/PD-1 Pathways in Combination with Chemotherapy

Several Phase III metastatic studies, including MK-3475-189 (KEYNOTE-189), MK-3475-407 (KEYNOTE-407), GO29436 (IMpower150), and GO29537 (IMpower130), have documented that, when co-administered with chemotherapy, the efficacy benefit of PD-L1/PD-1 inhibitors extends across all PD-L1 expression subgroups (Gandhi et al. 2018; Paz-Ares et al. 2018; Socinski et al. 2018; Gadgeel et al. 2019; West et al. 2019).

The data are consistent with the known effects of chemotherapy on the tumor microenvironment that may potentiate the effects of immunotherapies. In addition to direct cytotoxicity, which increases release of tumor antigens and enhances immunogenicity, chemotherapy has been shown to increase expression of PD-L1 (Zhang et al. 2008) and increase levels of CD155 (PVR), the ligand for TIGIT (Yoshida et al. 2019). The expectation that tiragolumab will further enhance atezolizumab efficacy in the context of chemotherapy is supported by nonclinical evidence that the TIGIT pathway is associated with immune dysfunction and chemoresistance (Blake et al. 2016; Burugu et al. 2018). In lung cancer models, TIGIT expression on T cells contributed to carboplatin chemoresistance through the upregulation of CD155 and subsequent T-cell dysfunction (Anestakis et al. 2020).

Furthermore, an exploratory study in gastric cancer has shown that after treatment with platinum chemotherapy, patients with a higher percentage of CD8 + TIGIT + T cells had increased rates of cancer relapse and shorter disease-free survival (DFS) (Tang et al. 2019). Because the TIGIT pathway is associated with immune dysfunction and chemoresistance, these findings suggest that TIGIT blockade to restore T-cell function could potentially improve outcomes for patients undergoing chemotherapy. In support of this hypothesis, in vitro studies have shown that TIGIT blockade countered the suppression of T-cell proliferation and activation following chemotherapy (Tang et al. 2019).

Collectively, the data and preliminary results of the Phase I GO30103 and Phase II CITYSCAPE studies have led to the hypothesis that anti-TIGIT treatment (tiragolumab) in combination with anti-PD-L1 treatment (atezolizumab) plus chemotherapy may result in enhanced and more durable responses. This combination is currently under evaluation in other indications.

1.3 Rationale

Multiple PD1 and PD-L1 directed therapies have been approved as monotherapy (in PD-L1 selected patients) and in combination with chemotherapy (in PD-L1 unselected patients) in the treatment of newly diagnosed metastatic NSCLC. Patients with untreated brain metastases have been excluded from the registrational trials leading to the approval of these agents.

In a single arm phase II clinical trial of carboplatin, pemetrexed, and atezolizumab in patients with metastatic non-squamous NSCLC and untreated brain metastases (ATEZO-BRAIN, Nadal et al., WCLC 2021), this combination was safe and tolerable and associated with a systemic

median PFS of 8.9 months (95% CI 6.7-13.8) and intracranial PFS by RANO-BM of 6.9 months (95% CI 4.7-12.1). The intracranial response by RANO-BM was 40%. This study demonstrated proof of concept that a chemoimmunotherapy regimen is safe and potentially efficacious in newly diagnosed NSCLC patients with untreated brain metastases.

The anti-TIGIT antibody tiragolumab in combination with atezolizumab in the 1st line treatment of metastatic NSCLC with a PD-L1 TPS ≥ 1% was associated with an ORR of 37% and median PFS of 5.6 months compared with an ORR of 21% and median PFS of 3.9 months in patients treated with atezolizumab and placebo (HR for PFS 0.58; 95% CI 0.38-0.89) (CITYSCAPE, Rodriguez-Abreu et al., ASCO 2020).

At initial accrual of this phase II trial, the ongoing SKYSCRAPER-06 clinical trial was evaluating the combination of platinum, pemetrexed, and atezolizumab with or without tiragolumab in patients with newly diagnosed metastatic non-squamous NSCLC patients and excluded patients with untreated brain metastases. This phase II trial aimed at the evaluation of the safety and clinical activity of tiragolumab in combination with carboplatin, pemetrexed and atezolizumab in the first line treatment of metastatic non-squamous NSCLC patients with asymptomatic untreated brain metastases.

At its first interim analysis, the SKYSCRAPER-06 trial did not meet its primary endpoints of progression free survival and overall survival, and the study was halted.

The ongoing SKYSCRAPER–01 clinical trial is investigating tiragolumab in combination with atezolizumab compared with placebo in combination with atezolizumab in patients with previously untreated locally advanced unresectable or metastatic PD-L1-selected non-small cell lung cancer. In this study, patients with brain metastases are excluded.

While this trial was originally designed to investigate the activity of carboplatin, pemetrexed, atezolizumab and tiragolumab in patients with non-squamous NSCLC and untreated brain metastases, in response to the SKYCRAPER-06 interim analysis, the protocol has been amended after the enrollment of the first three patients to an investigation of atezolizumab with or without tiragolumab in patients with newly diagnosed metastatic PD-L1 selected NSCLC and untreated brain metastases. The first three patients will be included in study as cohort one, and the remaining patients will be included as cohort two.

The three patients in cohort one will continue to be treated according to the cohort one schema due to ongoing clinical benefit and tumor response to the four-drug regimen. These three patients have CNS disease that has improved and there have been no unanticipated toxicity or safety signals. The patients have been made aware of the results of SKYSCRAPER-06 and intend to be treated per the cohort one schema. This was discussed with Genentech and agreed upon.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- To estimate the rate of initiation of salvage radiation therapy to the CNS in patients with NSCLC and untreated brain metastases treated with the combination of tiragolumab and atezolizumab with and without chemotherapy.

2.1.2 Secondary Objectives

1. To characterize the safety and tolerability of the combination of tiragolumab and atezolizumab with and without chemotherapy in patients with NSCLC and untreated brain metastasis, particularly Grade ≥ 2 (symptomatic) CNS related adverse event.

2. To estimate the brain metastasis response rate (BMRR; response assessment in neuro-oncology brain metastases [RANO-BM]).
3. To estimate the overall response rate (ORR), assessed using RECIST v1.1.
4. To estimate progression-free survival (PFS).
5. To estimate overall survival (OS).
6. To estimate PFS2 after initiation of salvage XRT.
7. To estimate PD-L1 tumor proportion score (TPS) as a potential predictive biomarker of response.

2.2 Endpoints

2.2.1 Primary Endpoint

- Rate of initiation of salvage radiation therapy to the CNS (proportion of patients that require salvage radiation therapy to the CNS (within 18 weeks from study initiation)

2.2.2 Secondary Endpoints

1. Adverse Events and Serious Adverse Events per CTCAE v5.0
2. Brain Metastasis Response Rate (BMRR) (per RANO-BM)
3. Objective Response Rate (ORR)
4. Progression-free Survival (PFS)
5. Overall Survival (OS)
6. Progression-free Survival after initiation of salvage XRT (PFS2)
7. PD-L1 TPS

3. PATIENT SELECTION AND ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

- Patients must have histologically or cytologically confirmed NSCLC.
- In patients treated with the combination of tiragolumab and atezolizumab, patients must have PDL1 TPS >50%, as determined by an FDA-approved test.
- Patients must have asymptomatic brain metastases with at least one untreated evaluable (per RANO-BM) brain metastasis of 5 mm or more. A growing lesion previously treated with whole brain radiotherapy is acceptable given the lower incidence of radiation necrosis. Lesions previously treated with SRS may not be used as target lesions.
    - Patients are not required to have measurable disease outside the CNS per RECIST

1.1.

- Prior chemotherapy, immunotherapy or radiation given with curative intent in early stage or locoregionally advanced NSCLC is permitted, if completed more than 12 months prior to initiation of study treatment.
- Prior radiation with palliative intent in the metastatic setting to non-CNS lesions is permitted (no wash-out period).
- Age ≥18 years.
- ECOG performance status ≤ 1.
- Life expectancy ≥12 weeks.
- Patients must have normal organ and marrow function as defined below within 14 days prior to initiation of study treatment:
  - Absolute neutrophil count ≥1,500/mcL without granulocyte colony-stimulating factor support
  - Platelets ≥100,000/mcL without transfusion
  - Hemoglobin ≥ 90 g/L (9 g/dL)

    Patients may be transfused to meet this criterion.
  - Total bilirubin ≤1.5x institutional upper limit of normal (ULN) with the following exception:
    - Patients with known Gilbert disease: total bilirubin ≤ 3 × ULN
  - AST(SGOT)/ALT(SGPT) and ALP ≤2.5 × institutional ULN
  - Creatinine Clearance (CrCl) ≥45 mL/min/1.73 m^2 (calculated using the Cockcroft-Gault formula)
  - Serum albumin ≥ 25 g/L (2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR and aPTT ≤ 1.5 × ULN
  - For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- Negative HIV test at screening
  - Negative hepatitis B surface antigen (HBsAg) test at screening. If positive, an HBV DNA test must also be performed to determine if the patient has an HBV infection, which would render the patient ineligible. Patients receiving treatment with anti-viral therapy for HBV are excluded.
  - Negative hepatitis C antibody. If positive, an HCV RNA test must also be performed to determine if the patient has an HCV infection, which would render the patient ineligible.
  - Availability of a representative tumor specimen for exploratory biomarker research.
  - For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception:
  - Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 90 days after the final dose of tiragolumab, 5 months after the final dose of atezolizumab, and 6 months after the final dose of paclitaxel, pemetrexed, gemcitabine, carboplatin, or cisplatin.
    - 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 (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman

with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
    - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- Women who would like to become pregnant after study treatment discontinuation should seek advice on oocyte cryopreservation prior to initiation of study treatment because of the possibility of irreversible infertility due to treatment with cisplatin and carboplatin.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:
    - With a female partner of childbearing potential, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period, for 90 days after the final dose of tiragolumab, and for 6 months after the final dose of paclitaxel, pemetrexed, gemcitabine, carboplatin or cisplatin. Men must refrain from donating sperm during this same period.
    - With a pregnant female partner, men must remain abstinent or use a condom during the treatment period for 90 days after the final dose of tiragolumab, and for 6 months after the final dose of paclitaxel, pemetrexed, gemcitabine, carboplatin, or cisplatin to avoid exposing the embryo.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- Men who would like to father a child after study treatment initiation should be advised regarding the conservation of sperm prior to treatment because of the possibility of irreversible infertility resulting from chemotherapies used in this study.
- Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

- Symptoms related to brain metastases requiring CNS radiation ≤ 2 weeks of treatment initiation are exclusionary. Steroids greater than prednisone 10 mg/d or equivalent, or anti-epileptic therapy ≤ 2 weeks of treatment initiation are exclusionary.

- Prior systemic therapy for metastatic disease is not allowed.
- Patients whose tumors harbor oncogenic drivers with an approved 1st line therapy (e.g. EGFR, ALK, and ROS1 alterations) are excluded.
- Patients who are receiving any other investigational agents.
- 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, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, 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.
    - 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 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.
- Positive Epstein-Barr virus (EBV) viral capsid antigen immunoglobulin M (IgM) test at screening
    - An EBV polymerase chain reaction (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.
- 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 or fibrosis in a radiation field is permitted.*
- History of leptomeningeal disease.
- Active tuberculosis.
- 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.
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study.
- History of malignancy other than NSCLC within 2 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate ≥ 90%).
- Severe infection within 2 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia.
- Prior allogeneic stem cell or solid organ transplantation.
- 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.

- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab.
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids in excess of prednisone 10 mg/d or equivalent, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, 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), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to atezolizumab, tiragolumab or other agents used in study.
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins.
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or tiragolumab formulation.
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment, within 90 days after the final dose of tiragolumab, 5 months after the final dose of atezolizumab, or 6 months after the final dose of pemetrexed, gemcitabine, paclitaxel, carboplatin, or cisplatin
  - Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally by the Study Team.
Following registration, patients should begin protocol treatment within 7 days.
Issues that would cause treatment delays should be discussed with the Investigator. The Study Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

- Once the signed informed consent has been obtained, all pretreatment evaluations have been performed, and patient's eligibility has been confirmed by the coordination team and the treating physician investigator, central site will be notified and a patient ID number will be assigned. The patient will be registered at this time. To register a patient, the Coordinating Center team must complete the eligibility/registration form

and review the signed Informed Consent and HIPAA authorization form, in addition to reviewing all supporting source documentation.number.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7.

Regimen Description per cohort assignment (To be administered in the order listed below)					
Agent	**Premedications***	**Dose**	**Route***	**Schedule**	**Cycle Length**
Atezolizumab	See below	1200 mg in 250 cc NS	IV over 60 minutes (+/- 15 min.) for the 1st infusion, over 30 minutes (+/- 10 min.) for subsequent infusions, as tolerated	Day 1	21 days
Tiragolumab	See below	600 mg	IV over 60 minutes (+/- 15 min.) for the 1st infusion, over 30 minutes (+/- 10 min.) for subsequent infusions, as tolerated	Day 1	
Pemetrexed	Recommended: Dexamethasone 4 mg po BID day before, day of, and day after Folic acid 1 mg po daily B12 1000 mcg IM q9 weeks +/-1 week	500 mg/m^2 in 100 cc NS	IV over 10 minutes	Day 1	
Carboplatin	Granisetron 1 mg IV X 1 dose	AUC 5 in 250 cc NS	IV over 30 minutes	Day 1	
*May be modified based on institutional standards.					

5.1.1 Atezolizumab

Atezolizumab will be administered 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 B. Atezolizumab infusions will be administered per the instructions in Appendix D.

Refer to the Investigators Brochure for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Section 7.

5.1.2 Tiragolumab

Tiragolumab will be administered 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 B.

Tiragolumab is to be administered by IV infusion either neat, after dilution in 0.9% NaCl, or after dilution in both 0.9% NaCl and manufacturer-provided tiragolumab diluent (Phase I Study GO30103 only). In the co-infusion cohort in the Phase Ib portion of Study GO30103, both tiragolumab and atezolizumab are added to a single 0.9% NaCl bag for administration. Refer to the Pharmacy Manual for additional details. A 0.2 µm in line filter must be used with the infusion set during administration.

Tiragolumab must be prepared for dosing under appropriate aseptic conditions as it does not contain antimicrobial preservatives. The dose solution should be used immediately. If not used immediately, the total storage time of the dose solution prior to administration should not exceed 24 hours to limit the risk of microbial growth in case of accidental contamination. The recommended storage condition for the dose solution is 2°C–8°C, but dose solutions may be stored at room temperature for up to a maximum of 4 hours.

The compatibility of tiragolumab with diluents other than described is unknown. Tiragolumab must not be infused into the same line or cannula concomitantly with other drug infusions, including parenteral nutrition. Infusions of blood products and any electrolyte supplementation must not occur simultaneously with infusion of tiragolumab.

5.1.3 Carboplatin and Pemetrexed

Refer to the full prescribing information and labeling for these individual agents.

5.2 General Concomitant Medication and Supportive Care Guidelines

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

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated influenza vaccinations
- 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 (prednisone >10 mg/d or equivalent ≤ 2 weeks of treatment initiation are exclusionary.)
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain). Treatment with atezolizumab may be continued during palliative radiotherapy.
- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation). Target lesions treated with local therapy are no longer evaluable for radiographic response.

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

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-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.

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

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab and/or tiragolumab therapy (refer to Section 7).

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

Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent, 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 study treatment, for 90 days after the final dose of tiragolumab, and for 5 months after the final dose of atezolizumab.

Patients being treated with chemotherapy (i.e., carboplatin, cisplatin, pemetrexed, paclitaxel, or gemcitabine) should not receive live vaccines.

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

5.3 Duration of Therapy

Treatment may continue for 24 months or until one of the following criteria applies:

- Intolerable toxicity related to study treatment, including development of an immune mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event.
- Grade ≥ 2 intracranial hemorrhage, where grade 2 was defined as symptomatic CNS hemorrhage or for which medical intervention is indicated
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment.
- Investigator determines discontinuation is in the best interest of the patient.
- Pregnancy.
- Radiographic disease progression per RECIST v1.1 or RANO-BM **and** symptomatic deterioration attributed to disease progression.
    - Patients may continue past objective progression of disease if, in the opinion of the treating investigator with consultation of Principal Investigator, the patient continues to benefit clinically from therapy.
    - Patients with progressive brain metastases will be allowed to undergo salvage local therapy, e.g. radiotherapy, and be allowed to continue on trial, if they are clinically stable, as deemed by the treating investigator.
    - Patients with progressive disease outside the CNS will be allowed to undergo salvage local therapy, e.g. radiotherapy, and be allowed to continue on trial, if they are clinically stable, as deemed by the treating investigator.
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease)

The primary reason for study treatment discontinuation should be documented in the patient's medical records. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit ≤ 30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any

reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities.

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

- Withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the Investigator

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented in the patient's medical records. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

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

5.4 Duration of Follow-up

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Investigator terminates the study).

Patients will be followed for a minimum of 30 days after removal from study and, whenever possible, until death. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Atezolizumab and Tiragolumab Dosing

There will be no dose reductions for tiragolumab and/or atezolizumab in this study.

Study treatment may be temporarily suspended as appropriate for management of toxicity. On the basis of the available characterization of mechanism of action, tiragolumab may cause adverse events similar to but independent of atezolizumab, may exacerbate the frequency or severity of atezolizumab related adverse events, or may have non overlapping toxicities with atezolizumab. In addition, given the evolving knowledge about the proposed regimen, investigators must assume that all components of the study treatment may have caused or contributed to the observed AE, without making inference of causality between the observed AE and a particular drug(s) composing the investigational regimen. As such, dose interruptions or treatment discontinuation in response to immune mediated adverse events should be applied to

all components of the study regimen, carboplatin, pemetrexed, tiragolumab and atezolizumab.

Study treatment may be held for a maximum of approximately 12 weeks (or approximately 4 cycles). If study treatment is interrupted for approximately longer than 12 weeks (or approximately 4 cycles), the patient must permanently discontinue all components of the study.

Study treatment may be suspended for reasons other than toxicity (e.g. surgical procedures) with Principal Investigator approval. The investigator and the Principal Investigator will determine the acceptable length of treatment interruption.

6.2 Carboplatin and Pemetrexed Dosing

For adverse events associated with carboplatin and pemetrexed, refer to guidelines in the applicable prescribing information.

7. Management Guidelines For Immune-Related Adverse Events

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

Although most immune-mediated adverse events observed with 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-risk balance for a given patient prior to further administration of atezolizumab and/or tiragolumab.

7.1 Pulmonary Events

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and tiragolumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab and tiragolumab.
Pulmonary event, Grade 2	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL with or without transbronchial biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab 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 the principal investigator. • For recurrent events or events with no improvement after 48-72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. • Bronchoscopy or BAL with or without transbronchial biopsy is recommended. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab 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 based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[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.

7.2 Hepatic Events

Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

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

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

Table 2 Management Guidelines for Hepatic Events

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

LFT = liver function test.

[a] Atezolizumab 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 based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[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.

7.3 Gastrointestinal Events

Management guidelines for diarrhea or colitis are provided in Table 3.

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

check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

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

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab 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. [a] • Initiate symptomatic treatment. • If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab 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 the principal investigator.
Diarrhea or colitis, Grade 3	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab 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 the principal investigator.
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and tiragolumab. • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI: gastrointestinal.

[a] Atezolizumab 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 based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

Event	Management

[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.

7.4 Endocrine Events

Management guidelines for endocrine events are provided in Table 4.

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

Table 4 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue atezolizumab and tiragolumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• Consider withholding atezolizumab and tiragolumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab and tiragolumab when symptoms are controlled, and thyroid function is improving.
Grade 3 and 4 hypothyroidism	• Withhold atezolizumab and tiragolumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer to an endocrinologist. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). • Resume atezolizumab and tiragolumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator for life-threatening immune-mediated hypothyroidism. [c]
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab and tiragolumab.

Event	Management
	• Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for Grade 2 hyperthyroidism. • Consider patient referral to endocrinologist.
Grade 2 hyperthyroidism	• Consider withholding atezolizumab 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.
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab and tiragolumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer to an endocrinologist. • Resume atezolizumab and tiragolumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator for life-threatening immune-mediated hyperthyroidism.
Symptomatic adrenal insufficiency, Grade 2-4	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab and tiragolumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator.
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. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines.

Event	Management
	• Monitor for glucose control. • Resume atezolizumab and tiragolumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab 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 the principal investigator. • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

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

[a] Atezolizumab 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 based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[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.

7.5 Ocular Events

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

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	Continue atezolizumab 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. [a] Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If event resolves to Grade 1 or better, resume atezolizumab 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 the principal investigator.
Ocular event, Grade 3 or 4	Permanently discontinue atezolizumab and tiragolumab. Refer patient to ophthalmologist. Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab 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 based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[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.

7.6 Immune-Mediated Cardiac Events

Management guidelines for cardiac events are provided in Table 6.

Immune-Mediated Myocarditis

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on pericardial disorders below) and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

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

Immune-Mediated Pericardial Disorders

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6. Withhold treatment with atezolizumab and tiragolumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2-4 Immune-mediated pericardial disorders, Grades 2-4	• Permanently discontinue atezolizumab and 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.

7.7 Infusion-related Reactions

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

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with tiragolumab and atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab or tiragolumab administration and are generally mild to moderate in severity. Guidelines for medical management of IRRs during Cycle 1 are provided in Table 7. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 7 Management Guidelines for Infusion-related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs.
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • Permanently discontinue atezolizumab or tiragolumab and contact the principal investigator.

IRR: infusion-related reaction.

7.8 Cytokine-release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab or tiragolumab. However, patients who experience CRS with atezolizumab or tiragolumab may receive premedication with antihistamines, anti pyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions.

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

Severe COVID-19 is 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

Event	Management

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.

Guidelines for medical management of CRS are provided in Table 8.

Table 8 Management Guidelines for 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 CRS.
Grade 2 [a] Fever [b] with at least one of the following: • Hypotension not requiring vasopressors • 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 or tiragolumab and contact the principal investigator. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab or tiragolumab may be administered. For subsequent infusions,

Event	Management
	consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the principal investigator.
Grade 3 [a] Fever [b] with at least one of the following: • Hypotension requiring a vasopressor (with or without vasopressin) Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab or tiragolumab and contact the principal investigator. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator.
Grade 4 [a] Fever [b] with at least one of the following: • Hypotension requiring multiple vasopressors (excluding vasopressin) Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab or tiragolumab and contact the principal investigator. • 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 [e] may be considered at the discretion of the investigator. • 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; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

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

Event	Management

[a] Grading system for management guidelines is based on the ASTCT CRS Consensus Grading Scale. NCI CTCAE v1.1 and the ASTCT CRS Consensus Grading Scale should be used when reporting severity of CRS on the Adverse Event eCRF. NCI CTCAE v1.1 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.

[b] Fever is defined as temperature ³ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

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

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

[e] Refer to Riegler et al. (2019) for information on experimental treatments for CRS.

7.9 Pancreatic Events

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 9.

Table 9 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5-2.0 x 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 x ULN:** • Treat as a Grade 3 event.
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 and tiragolumab atezolizumab and contact the principal investigator. • For recurrent events, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator.
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist.

Event	Management
	• 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 and tiragolumab and contact the principal investigator. • For recurrent events, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator.
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. • 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 based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[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.

7.10 Dermatologic Events

The majority of cases of rash reported with the use of atezolizumab and/or tiragolumab 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 10.

Table 10 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. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset.[a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and contact the principal investigator.
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator.
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 based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[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.

7.11 Neurologic Disorders

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in 11, with specific guidelines for myelitis provided in Table 12.

Table 11 Management Guidelines for Neurologic Disorders

Event	Management
Immune-	• Continue atezolizumab and tiragolumab.

mediated neuropathy, Grade 1	• Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy: – If event resolves to Grade 1 or better, resume atezolizumab 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 the principal investigator. [c] • For facial paresis: – If event resolves fully, resume atezolizumab and tiragolumab [b] • If event does not resolve fully while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. • 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 determined by the investigator.
[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.

Table 12 Management Guidelines for Immune-Mediated Myelitis

Event	Management
Immune-mediated myelitis, Grade 1	• Continue atezolizumab and tiragolumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. • Investigate etiology and refer patient to a neurologist.

	• Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

7.12 Immune-mediated Meningoencephalitis

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

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

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

Table 13 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. • 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.

7.13 Renal Events

Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory

drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in 14.

Table 14 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab and tiragolumab. • Monitor kidney function, including creatinine, closely 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 the principal investigator.
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. • 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 based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[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.

7.14 Immune-mediated Myositis

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in

dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.
Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 15.

Table 15 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 the principal investigator. • 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 the principal investigator.
Immune-mediated myositis, Grade 3	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset [a] and contact the principal investigator. • 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 tiragolumab and contact the principal investigator. • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis,	• Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator.

Grade 4	• 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 based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.
[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.

7.15 Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

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

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.
Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 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 x 10^9/L (100,000/µL)
  - ANC < 1.0 x 10^9/L (1000/µL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

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

having MAS if the following criteria are met:

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

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 16.

Table 16 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact the principal investigator and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 10.1.

8.1 Tiragolumab

Tiragolumab is provided in two configurations:

- The initial formulation and vial configuration (RO709-2284/F01-01), supplied in single-dose 20 mL glass vials containing 20 mL of tiragolumab drug product and buffered in histidine solution containing polysorbate 20, sucrose, and water for injection (WFI). The approximate concentration of tiragolumab antibody in the vials is 20 mg/mL. This formulation and configuration is currently being used in ongoing trials. A matching placebo is provided in single-dose 20 mL glass vials containing 20 mL of histidine solution containing polysorbate 20, sucrose, and WFI.
- A subsequent formulation and vial configuration (RO709-2284/F03-01), supplied in single-dose 15 mL glass vials containing 10 mL of tiragolumab drug product and buffered in histidine solution containing polysorbate 20, sucrose, L-methionine, and WFI.

The approximate concentration of tiragolumab antibody in the vials is 60 mg/mL. This formulation and configuration is currently being used in ongoing trials. A matching placebo is provided in single-dose 15 mL glass vials containing 10 mL of histidine solution containing polysorbate 20, sucrose, L-methionine, and WFI.

8.2 Atezolizumab

The atezolizumab 1200 mg drug product will be supplied in a single-use, 20-mL USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20-mL volume.

8.3 Carboplatin and Pemetrexed

Carboplatin and pemetrexed will be supplied commercially. Refer to the full prescribing information and labeling for these individual agents.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This is a phase II clinical trial aimed at the evaluation of the safety and clinical activity of tiragolumab in combination with atezolizumab with or without chemotherapy in the 1st line treatment of non-squamous NSCLC patients with untreated brain metastases. Patients in cohort 1 and cohort 2 will be pooled for all safety and efficacy analyses.

Primary Endpoint:

- Proportion of patients that require salvage radiation therapy to the CNS (within 18 weeks from treatment initiation)

Secondary Endpoints:

- Adverse Events and Serious Adverse Events per CTCAE v5.0.
- Brain Metastasis Response Rate (BMRR, per RANO-BM)
- Objective response rate (ORR), assessed using RECIST v1.1
- Progression-free survival (PFS)
- Intracranial PFS
- Overall Survival (OS)
- PFS2 after initiation of salvage XRT
- PD-L1 TPS

9.2 Statistical Analysis Plan

Response-evaluable patients (i.e., evaluable for salvage radiation therapy, and ORR) are those who receive at least one dose of all four components of the combination therapy and have at least

one post-treatment scan. For safety endpoints (intracranial hemorrhage and adverse events) and survival endpoints (PFS, PFS2 and OS), participants must have received at least one dose of the combination therapy in order to be regarded as evaluable.

9.2.1 Primary Aim

The primary endpoint is whether or not the patient requires salvage radiation therapy to the CNS within 18 weeks. The proportion of participants requiring salvage therapy will be calculated with a 95% exact (Clopper-Pearson) confidence interval. An exact binomial test will be used for the null hypothesis H_0: P(salvage therapy)>0.5 at α=0.05. Patients who do not reach week 18 of treatment and who have no salvage radiation to the brain before dropping out will not be included in the primary analysis.

9.2.2 Secondary Aims

- To characterize the safety and tolerability of the combination of tiragolumab and atezolizumab with or without chemotherapy in patients with NSCLC and untreated brain metastasis, particularly Grade ≥ 2 (symptomatic) CNS related events. Adverse events will be tabulated by type, grade and relatedness to treatment. The proportion of patients experiencing Grade ≥ 2 (symptomatic) CNS related events will be calculated with a 95% exact (Clopper-Pearson) confidence interval.

- To estimate the brain metastasis response rate (BMRR; response assessment in neuro-oncology brain metastases [RANO-BM]). The proportion of participants experiencing response by RANO-BM will be calculated with a 95% exact (Clopper-Pearson) confidence interval.

- To estimate the objective response rate (ORR), assessed using RECIST v1.1 (detailed in Section 12.1.5.1). The proportion of participants experiencing response by RECIST v1.1 will be calculated with a 95% exact (Clopper-Pearson) confidence interval.

- To estimate progression-free survival (PFS). PFS, defined in Section 12.1.6, will be characterized by the product-limit (Kaplan-Meier) method with a 95% Greenwood confidence region. Median PFS will be estimated from the survival function with a 95% Brookmeyer and Crowley confidence interval.

- To estimate intracranial PFS. Intracranial PFS, defined in Section 12.1.7, will be characterized by the product-limit (Kaplan-Meier) method with a 95% Greenwood confidence region. Median Intracranial PFS will be estimated from the survival function with a 95% Brookmeyer and Crowley confidence interval.

- To estimate overall survival (OS). OS (months from first study treatment to death or last contact) will be characterized by the product-limit (Kaplan-Meier) method with a 95% Greenwood confidence region. Median OS will be estimated from the survival function with a 95% Brookmeyer and Crowley confidence interval.

- To estimate progression-free survival 2 (PFS2, defined in Section 12.1.8) after initiation of salvage XRT. PFS2 will be estimated by the product-limit (Kaplan-Meier) method with a 95% Greenwood confidence region. Median PFS2 will be estimated from the survival function with a 95% Brookmeyer and Crowley confidence interval.

- To explore PD-L1 tumor proportion score (TPS) as potential predictive biomarkers of response. Logistic regression and proportion hazards (Cox) regression will be used to investigate the relationships between PD-L1 TPS and response (RECIST and RANO-BM, as above) and OS, PFS and PFS2. 95% likelihood ratio confidence intervals will be determined for odds and hazard ratios.

9.3 Sample Size/Accrual Rate

Figure 1 displays the power of the hypothesis test of the primary endpoint for true values of P(salvage therapy) ranging from 0.01 to 0.5 for n=35 participants evaluable for efficacy. It is seen that the power is in excess of 80% if the true P(salvage therapy) is less than or equal to 0.27.

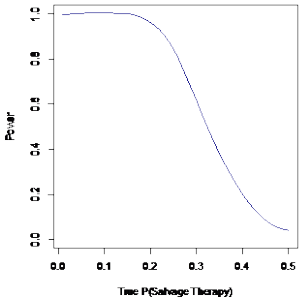


Figure 1 Power of hypothesis test on the primary endpoint

9.4 Stopping Rule for Excess Toxicity

A stopping rule for excess toxicity will be checked after every five participants have received four cycles of treatment.

Stopping rule for excess toxicity	
# Participants	# Toxicities
5	3
10	5
15	7
20	9
25	11
30	13
35	15

The trial will be halted if the number of participants experiencing Grade 2 or worse CNS adverse events equals or exceeds the number in the second column. The table goes to 35 participants because more than 35 participants may be enrolled to accrue 35 participants evaluable for efficacy. The table is generated by a beta-binomal stopping rule: Stop trial if P(P(toxicity)>0.35)>0.75, where the uninformative beta(1,1) prior is employed. Figure 2 shows the expected sample size as a function of the true probability of toxicity.

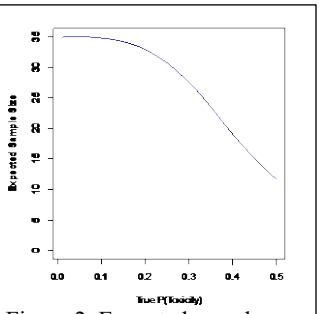


Figure 2 Expected sample size as a function of True P(Toxicity)

In addition, the trial will be halted if any of the following criteria are met:

Any death(s) that is not clearly due to disease progression or extraneous causes.
Two or more Grade 4 AEs that are at least possibly related to any component of the study treatment.

9.5 For Phase 2 Protocols Only: Reporting and Exclusions

9.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with tiragolumab, carboplatin, pemetrexed, and atezolizumab.

9.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial.

10.1 Adverse Events

10.1.1 Tiragolumab

Because tiragolumab is a therapeutic mAb and targets immune cells, IRRs associated with hypersensitivity reactions, and/or target-mediated cytokine release may occur. Infusion reactions may be mild in nature or may be severe. Most of the IRRs associated with tiragolumab have been

Grade 1 and 2, and have most commonly presented with pyrexia and pruritus, but have also included hypertension, chills, nausea, anxiety, joint stiffness, dyspnea, wheezing, rash, and temperature intolerance. In Study GO30103 where tiragolumab was given either as a single-agent (Phase Ia) or in combination with atezolizumab, but given prior to atezolizumab (Phase Ib), IRR events related to tiragolumab occurred roughly 60 to 90 minutes after infusion began. Please refer to the Investigator's Brochure for additional detailed information on adverse events.

10.1.2 Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, and nephritis. In addition, systemic immune activation is a potential risk associated with atezolizumab when given in combination with other immunomodulating agents. Refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

10.1.3 Adverse Event Lists for Carboplatin and Pemetrexed

Please refer to the package inserts for the comprehensive list of adverse events.

10.1.4 Definitions

Adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Life-threatening adverse event or life-threatening suspected adverse reaction is considered "life-threatening" if, in the view of the sponsor-investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction is considered "serious" if, in the view of the sponsor-investigator, it results in any of the following outcomes:

- Results in death
- Is a life-threatening adverse event
- Requires inpatient hospitalization or prolongation of existing hospitalization. The following hospitalizations are NOT considered to be SAEs:
    - A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
    - Elective surgery, planned prior to signing consent

    - Admissions as per protocol for a planned medical / surgical procedure
    - Routine health assessment requiring admission for baseline / trending of health status (eg, routine colonoscopy)
    - Medical / surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
    - Admission encountered for another life circumstance that carries no bearing on health status and requires no medical / surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
    - Admission for administration of anticancer therapy in the absence of any other SAEs
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect
- Is an important medical event 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 the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse event or unexpected suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

> For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 90 days after the final dose of tiragolumab, 5 months after the final dose of atezolizumab, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the Tiragolumab or within 90 days after the final dose of tiragolumab, whichever is later, a report should be completed and expeditiously submitted to Genentech, Inc. 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 as an SAE. Similarly, any

congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

10.1.5 AEs of Special Interest (AESIs)

Adverse events of special interest for this study are as follows:

- 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:
    - Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN
    - Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study drug (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 the study drug is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 x ULN
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS)
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

- Myelitis
- Facial paresis
- Post-Study Adverse Events
    - For studies involving collection of survival data, the investigator after the end of the adverse event reporting period (defined as 90 days after the last dose of study drug) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study that is believed to be related to prior exposure to study drug.
    - Case Transmission Verification will be performed by both parties during this period half-yearly to ensure successful transmission of single case reports.

10.2 Recording/Reporting requirements

10.2.1 Eliciting AE Information

Research subjects will be routinely questioned about AEs at study visits.

10.2.2 Recording Requirements

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a serious adverse event) and; 2) an assessment of the casual relationship between the adverse event and the study drug(s).

Adverse events will be followed until resolution while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study medication will be followed until resolution or stabilization of the adverse event, or until the patient starts a new treatment regimen, or death, whichever comes first. Subjects will be followed for AEs/SAEs for 30 days after their last dose of study drug(s).

AEs or abnormal test findings felt to be associated with the investigational drug or study treatment(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Principal Investigator.

10.2.2.1 Abnormal Test Findings

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy.

Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not

constitute an AE.

- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical study.
- The test finding is considered an AE by the Sponsor-Investigator of the IND application.

10.2.2.2 AE Evaluation

The investigator or designee is responsible for ensuring that all AEs (both serious and non-serious) observed by the clinical team or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's medical records. Source documentation must be available to support all AEs.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, result in a delay or dose modification of study treatment, or judged relevant by the investigator), should be reported as an AE.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all AEs (both serious and non-serious):

- Event term (as per CTCAE version 5)
- Description of the event
- Date of onset and resolution
- Expectedness of the toxicity
- Grade of toxicity
- Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician)
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received concomitant med or other intervention, etc.
- Outcome of event

Descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting.

The following grading scale should be used to assess AE/SAE severity for events not specifically listed in CTCAE version 5.0.

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]

3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

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

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event

d. Grade 4 and 5 events must be reported as serious adverse events

An expected AE is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected AE is an AE not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

Attribution is the relationship between an AE or serious AE and the study drugs. Attributions are required for each drug administered as part of the treatment regimen. Attribution will be assigned as follows:

- Definitely Related – The AE is clearly related to the study drug. There is a reasonable causal relationship between study treatment and the AE. The event responds to withdrawal of study treatment (dechallenge) and recurs with rechallenge when clinically feasible.
- Probably Related – The AE is likely related to the study drug. There is a reasonable causal relationship between study treatment and the AE. The event responds to dechallenge.
- Possibly Related – The AE may be related to the study drug. There is a reasonable possibility that study treatment caused the adverse event. The investigator can provide a rationale or evidence to suggest a causal relationship between study treatment and the AE other than just a temporal relationship.
- Unlikely Related– The AE is doubtfully related to the study drug. There is only a temporal relationship to study treatment, but not a reasonable causal relationship between study treatment and the AE.
- Unrelated – The AE is clearly NOT related to the study drug. There is no temporal relationship to study treatment. There is a reasonable causal relationship to another drug product, concurrent disease, or circumstance.

10.3 Reporting of Serious Adverse Events

10.3.1 Reporting Requirements

All events meeting the definition of a serious adverse event should be reported according to the departmental SAE checklist and SAE form. Serious adverse events are collected from the date of the subject's first dose of treatment until 90 days after the final dose. The initial SAE form should be sent to the following within 24 hours of the Principal Investigator becoming aware of the event:

1. Liza Villaruz @villaruzl@upmc.edu
2. crssafetysubmissions@upmc.edu
3. Local Institutional Review Board when reporting requirements are met (completed by CRS Safety with input from the Principal Investigator).
4. Genentech, as outlined in Section 10.3.2

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the departmental SAE form:

- CTCAE term(s) and grade(s)
- Current status of study drug
- All interventions to address the AE (testing and result, treatment and response)
- Hospitalization and/or discharge dates
- Event relationship to study drug(s)

Follow-up reports:

All SAEs should be followed to resolution or stabilization. Additional information may be added to a previously submitted report by adding to the original departmental SAE form and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original departmental SAE form. All follow-up forms must include the date the form is revised and should be submitted to the contacts listed above within 24 hours of the Principal Investigator becoming aware of the new information.

10.3.2 Reporting to Genentech

Investigators must report all SAEs to Genentech within the timelines described below. The completed form should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 2254682
OR
(650) 2254630
Email: usds_aereporting-d@gene.com

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

Serious AE reports and AEs of Special Interest, whether related or unrelated to atezolizumab, will be transmitted to Genentech within one (1) business day of the Awareness Date.

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 90 days after the last dose of atezolizumab or the partner of a male patient within 90 days of completing therapy) will be transmitted to Genentech within one (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.
- All non-serious atezolizumab AEs originating from the study will be forwarded to Genentech quarterly.

In addition to SAEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech/Roche even in the absence of an Adverse Event within thirty (30) calendar days:

- Data related to product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Data related to a suspected transmission of an infectious agent via a medicinal product (STIAMP)
- Lack of therapeutic efficacy

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

Exchange of Single Case Reports with Genentech

PI will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product. The completed Genentech approved reporting forms should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

[This requirement, based on European Medicines Agency's (EMA) Good Pharmacovigilance

Practices (GVP) Module VI Section B.3, applies to Genentech because it is part of the larger Roche organization that operates in EU territories]

For ALL events that are unexpected based on the drug safety profile in the Investigator's Brochure and/or Informed Consent Form, the Batch ID/lot ID for biologics associated with AE/SSR/PC/AESI must be included when submitting the case reports to Genentech.

All Product Complaints *without* an AE should call via:
PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Investigators must report all the above-mentioned single case reports adequately to Genentech on Genentech approved SAE form within one (1) business day of the awareness date.

PI /UPMC will forward quarterly listings of non-serious AEs originating from the Study to Genentech/Roche

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

Type of Report	**Timelines (for Approved Product/s)**	**Timelines (For Unapproved product/s)**
Serious Adverse Events (related and not related to the Product)	30 calendar days from awareness date	1 calendar days from awareness date
Special Situation Reports (With or without AE and pregnancy)		
Product Complaints (With or without AE)		
AESI		

Case Transmission Verification of Single Case Reports
If Single Case Reports are exchanged via Genentech approved reporting forms, use the following:

- PI/UPMC will verify that all single case reports have been adequately received by Genentech via PI/UPMC emailing Genentech a Quarterly line-listing documenting single case reports sent to Genentech in the preceding time period.

- 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.

- If discrepancies are identified, PI 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 sponsor will receive reconciliation

guidance documents within the 'Activation Package'.

- Following Case Transmission Verification, single case reports that have not been received by Genentech will be forwarded by PI to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

Monthly or quarterly line-listings, Non-serious line listings and cumulative/final CTV should be sent to ctvistsa@gene.com

10.4 Review of Safety Information: Sponsor-Investigator Responsibilities

The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

10.5 IND safety reports

The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under **Sections 10.5.1 to 10.5.4 below**. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

10.5.1 Serious and unexpected suspected adverse reaction

The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known

consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

10.5.2 Findings from other studies

The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under section **10.5.1**), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

10.5.3 Findings from animal or in vitro testing

The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

10.5.4 Increased rate of occurrence of serious suspected adverse reactions

The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

10.6 Submission of IND safety reports

The sponsor must submit each IND safety report in a narrative format or on Form FDA 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a Form FDA 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

10.6.1 Unexpected fatal or life-threatening suspected adverse reaction reports

The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

10.6.2 Reporting format or frequency

FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

10.6.3 Investigations of marketed drugs

A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the post marketing safety reporting requirements.

10.6.4 Reporting study endpoints

Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under Section 10.7 third bullet of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under *Serious and unexpected suspected adverse reaction* as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

10.7 Follow-up

- The sponsor must promptly investigate all safety information it receives.
- Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report."
- If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under **section 10.5 IND safety reports** is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

10.8 Disclaimer

A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

The principal investigator must promptly review all information relevant to the safety of the drug obtained or otherwise received from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States. The study sponsor must notify all participating investigators of potential serious risks, from clinical trials or any other source, as soon as possible.

10.9 Reporting adverse events to the responsible IRB

In accordance with applicable policies of the University of Pittsburgh Human Research Protection Office (HRPO), the Principal Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) *associated with the investigational drug or study treatment(s)*; 2) *serious*; and 3) *unexpected*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the principal investigator's knowledge of the respective information. Adverse events which are 1) *associated with the investigational drug or study treatment(s)*; 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the Principal Investigator's knowledge of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Principal Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Principal Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

AGGREGATE REPORTS

IND ANNUAL REPORTS

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech.

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvistsa@gene.com.

OTHER REPORTS

UPMC /PI will forward a copy of the Publication and/or Final Study Report to Genentech upon completion of the Study.

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:

tiragolumab-gsur-d@gene.com

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

QUERIES

Queries related to the Study will be answered by UPMC /PI . However, responses to all safety queries from regulatory authorities, Ethics Committees and Institutional Review Board 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 Product. UPMC /PI agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests from Regulatory Authorities and/or IRB/IEC 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.

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 UPMC /PI**,** as Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.

If UPMC /PI 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 Roche within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist UPMC /PI with signal and risk management activities related to the Product within the Study.

Genentech will also provide UPMC /PI with any new relevant information that may modify or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

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. STUDY CALENDAR

Baseline evaluations are to be conducted within 28 days prior to start of protocol therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Cycle 1			Cycle 2			Subsequent Cycles			Off Treatment[k]
		Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	
Tiragolumab		X			X			X			
Atezolizumab		X			X			X			
Carboplatin[m]		X			X			X			
Pemetrexed[m]		X			X			X			
Informed consent	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X----------X									X
Physical exam	X	X			X			X			X
Vital signs[a]	X	X			X			X			X
Height	X										
Weight	X	X			X			X			X
Performance status[b]	X	X			X			X			X
CBC w/diff, plts[c]	X	X			X			X			X
Serum chemistry[d]	X	X			X			X			X
Serum β-HCG[f]	X										
Urinalysis[g]	X	X[e]			X[e]			X[e]			X[e]
Thyroid function testing[h]	X	X			X			X			X
Amylase and Lipase	X	X			X			X			X
Viral Serologies[i]	X										
Adverse event evaluation	X	X----------X									X
Radiologic evaluation[j]	X	X----------X									
Additional MRI brain					X						
PD-L1 TPS[l 1]	X										

[a] Heart rate, respiratory rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. For additional guidelines for measurement of vital signs with atezolizumab infusions, please reference Section 6.1.1.
[b] Appendix A.
[c] Hemoglobin, hematocrit, platelet count, WBC count, percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells).
[d] Sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total, total protein, albumin, ALT, AST, and alkaline phosphatase.
[e] As clinically indicated
[f] For women of childbearing potential and who are premenopausal. To be performed at screening and otherwise, if clinically indicated.
[g] Specific gravity, pH, glucose, protein, ketones, and blood.
[h] TSH, free T4
[i] Hepatitis B virus (HBV) serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen), and HCV serology (anti-HCV)
[j] Radiographic evaluation include a CT scans of the chest and all other known sites of metastatic disease, as well as an MRI of the brain. Radiographic evaluations must be performed every 9 weeks ± 1 week. Confirmatory scans will also be obtained ≥4 weeks following initial documentation of an objective response or progressive disease. **In patients with baseline CNS lesions less than 1 cm, MRI imaging with 1.5 mm slice thickness is required.** Please note an additional MRI brain will be performed prior to C2D1 of treatment for safety purposes. **For patients treated past radiographic progression, establishment of new baseline tumor measurements is required for assessment of PFS2.**
[k] Patients who discontinue from treatment will be asked to return to the clinic no more than 30 days after the last treatment for a treatment discontinuation visit. The visit at which a response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who have an ongoing study treatment-related AE upon study completion or at discontinuation from treatment will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.
[l] PD-L1 Tumor Proportion Score required. This can come from an existing pathology report or can be requested to be performed on archival tissue.
[M] Cohort 1 only.

Note: There is a window of ± 1 week available for rescheduling treatment and/or procedures at the discretion of the treating investigator.

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 9 (+/- 1) weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression in the CNS will be evaluated in this study using the new international criteria proposed by the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group revised [*Lancet Oncology* 2015;16: e270–78].

Non-CNS disease will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter

(unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

If progression occurs in both CNS and non-CNS sites of disease, progression events in both compartments should be scored. In cases of discordant response between CNS and non-CNS disease, local therapy to site(s) of progression in either or both compartments is permitted while on study, as is treatment past progression, provided the criteria in Section 6.3 are met.

12.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with tiragolumab and atezolizumab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.1.2 RECIST v1.1 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that 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 which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.1.3 RANO-BM Disease Parameters

Measurable disease is defined as a contrast-enhancing lesion that can be accurately measured in at least one dimension, with a minimum size of 5 mm, and is visible on two or more axial slices. For targets lesions ≥ 10 mm, axial slices are preferably 5 mm or less apart with 0 mm skip (and ideally ≤1.5 mm apart with 0 mm skip). **In patients with baseline CNS lesions less than 1 cm, MRI imaging with 1.5 mm slice thickness is required**.

12.1.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using

calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI for the evaluation of disease outside the CNS is a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.1.5 Response Criteria

12.1.5.1 Disease Evaluation by RECIST v1.1

Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.1.5.2 Disease Evaluation by RANO-BM

Target lesions

Complete response

Disappearance of all CNS target lesions sustained for at least 4 weeks; with no new lesions, no use of corticosteroids, and patient is stable or improved clinically.

Partial response

At least a 30% decrease in the sum longest diameter of CNS target lesions, taking as reference the baseline sum longest diameter sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.

Progressive disease

At least a 20% increase in the sum longest diameter of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, at least one lesion must increase by an absolute value of 5 mm or more to be considered progression.

Stable disease

Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter while on study.

Non-target lesions

Non-target lesions should be assessed qualitatively at each of the timepoints specified in the protocol.

Complete response

Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.

Non-complete response or non-progressive disease

Persistence of one or more non-target CNS lesion or lesions.

Progressive disease

Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumour-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease.

For target lesions 5 mm to 10 mm, complete response and unequivocal progressive disease can probably be interpreted on their merits. However, measurement of small changes, such as the minimum 20% increase in longest diameter to determine progressive disease or the minimum 30% decrease in longest diameter to determine partial response, might not be robust or reproducible. For this reason**, target lesions less than 10 mm in longest diameter should be regarded as unchanged from baseline unless there is a minimum 3 mm change in the measured longest diameter.**

12.1.5.3 Evaluation and recording of bi-compartmental response

CNS (RANO-BM)	Non-CNS (RECIST 1.1)	Response
Complete response, partial response, or stable disease	Complete response, partial response, or stable disease	Log as CNS and non-CNS complete response, partial response, or stable diseases
Complete response, partial response, or stable disease	Progressive disease	Log as CNS complete response, partial response, or stable disease; log as non-CNS progressive disease
Progressive disease	Complete response, partial response, or stable disease	Log as CNS progressive disease; log as non-CNS complete response, partial response, or stable disease
Progressive disease	Progressive disease	Log as both CNS and non-CNS progressive disease

12.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. PFS should be recorded in a bi-compartmental manor:

CNS (RANO-BM)	Non-CNS (RECIST 1·1)	Bi-compartmental PFS	Note
Complete response, partial response, or stable disease	Progressive disease	Log as a progression-free survival event	Log as non-CNS progressive disease
Progressive disease	Complete response, partial response, or stable disease	Log as a progression-free survival event	Log as CNS progressive disease
Progressive disease	Progressive disease	Log as a progression-free survival event	Log as both CNS and non-CNS progressive disease

12.1.7 Intracranial Progression-Free Survival (PFS)

Intracranial PFS is defined as the duration of time from start of treatment to time of progression in the CNS or death.

12.1.8 Progression-Free Survival 2 (PFS2)

PFS2 is defined as months from initiation of salvage radiotherapy to CNS and or non-CNS lesions to time of progression, death or last radiographic assessment without PD, whichever occurs first.

13. DATA REPORTING / REGULATORY REQUIREMENTS

13.1 Data Safety Monitoring Plan

Principal Investigator, Sub-investigators, regulatory, CRS management, clinical research coordinators, research coordinators, clinical research associates, data managers, and clinic staff meet regularly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual

- protocol deviations
- unanticipated problems
- breaches of confidentiality

Minutes from the DSMB meetings are available to those who are unable to participate during the scheduled meeting time.

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 5.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB and FDA. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPMC Hillman Cancer Center DSMC which also meets regularly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly by the disease center DSMB.

Both the UPCM Hillman Cancer Center DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

13.2 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and Guidelines on Good Clinical Practice compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the Education and Compliance Office – Human Subject Research, Research Conduct and Compliance Office, University of Pittsburgh.

The Investigator (i.e., the study site principal investigator) and the University of Pittsburgh and University of Pittsburgh Medical Center will permit direct access of the study monitors and

appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

13.3 Data Handling and Record-Keeping

The Investigator (i.e., the study site principal investigator) will maintain records in accordance with Good Clinical Practice.

The investigator will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational drug; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IND have been discontinued and the FDA so notified.

13.4 Institutional Review Board (IRB) Approval

The investigator (i.e., the study site principal investigator) will obtain, from the University of Pittsburgh Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment, if applicable.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the investigator will promptly notify the University of Pittsburgh IRB of the deviation.

The University of Pittsburgh IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice.

In the event that the University of Pittsburgh IRB requires, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of an sponsor's decision to modify the previously accepted clinical protocol, the sponsor will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of protocol changes requiring the submission of a Protocol Amendment include:

- Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
- Any significant change in the design of the protocol (such as the addition or deletion of a control group).
- The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or AE; or the dropping of a test intended to monitor the safety of the investigational drug.

13.5 Ethical and Scientific Conduct of the Clinical Study

The clinical study will be conducted in accordance with the current IRB-approved clinical protocol; ICH Guidelines on Guidelines on Good Clinical Practice; and relevant policies, requirements, and regulations of the University of Pittsburgh IRB, University of Pittsburgh and University of Pittsburgh Medical Center, Commonwealth of Pennsylvania, and applicable federal agencies.

13.6 Informed Consent

The investigator (i.e., the study site principal investigator) will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The investigator, or a sub-investigator(s) designated by the sponsor, will obtain the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The investigator or sub-investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled subjects for continued participation in the clinical study.

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15. APPENDICES

15.1 APPENDIX A: 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 not 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.

16.2 APPENDIX B: 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.
7. Ask participant to return for washout immunogenicity sample if appropriate

15.3 APPENDIX C: Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

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

APPENDIX NUMBER:

FDA MedWatch 3500 Form

APPENDIX NUMBER#

Current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

Please use the following link to the NCI CTCAE website (CTCAE v5.0 will be utilized for this study):

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

15.4 APPENDIX D: Administration of Atezolizumab and Tiragolumab infusions

Administration of First and Subsequent Infusions of Atezolizumab and Tiragolumab

Study drug	First Infusion	Subsequent Infusions
Atezolizumab infusion	• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse 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. • If clinically indicated, vital signs should be recorded every 15 (± 5) minutes during the infusion.	• If the patient experienced an IRR with any previous infusion of atezolizumab, premedication with an antihistamine and/or antipyretic medication may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded prior to the infusion. • Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an IRR or 60 (± 15) minutes if the patient experienced an IRR with the previous infusion. • If clinically indicated, vital signs should be recorded during 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 experienced infusion-associated adverse events in the previous infusion, the observation period should be 60 minutes. • If clinically indicated, vital signs should be recorded at 30 (± 10) minutes after the infusion of atezolizumab.

IRR = infusion-related reaction.

Table 2 Administration of First and Subsequent Infusions of Atezolizumab and Tiragolumab (cont.)

	First Infusion	Subsequent Infusions
Infusion of tiragolumab	• 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 in the previous infusion, the observation period 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.