Chemotherapy and Atezolizumab for Patients with Extensive Stage Small Cell Lung Cancer (SCLC) with Untreated, Asymptomatic Brain Metastases (HCRN LUN19-427)

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Trial Supported by
Genentech, ML#42196

IND exemption per FDA 8/4/2020

Initial Protocol Version Date: 04AUG2020
Protocol Amendment Version Date:
13MAY2022
10AUG2022

PROTOCOL SIGNATURE PAGE

Chemotherapy and Atezolizumab for Patients with Extensive Stage Small Cell Lung Cancer (SCLC) with Untreated Brain Metastases
(HCRN LUN19-427)

VERSION DATE: 10AUG2022

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable institutional review board(s).

_____ _____
Signature of Site Investigator Date

_____
Site Investigator Name (printed)

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Site Investigator Title

_____
Name of Facility

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Location of Facility (City and State)

PLEASE COMPLETE AND EMAIL A COPY TO HCRN

SYNOPSIS

TITLE	Chemotherapy and Atezolizumab for Patients with Extensive Stage Small Cell Lung Cancer (SCLC) with Untreated, Asymptomatic Brain Metastases (HCRN LUN19-247)
SHORT TITLE	Chemotherapy and Atezolizumab for Untreated SCLC Brain Metastases
PHASE	II
OBJECTIVES	**Primary Objective** 1.) Intracranial progression free survival (iPFS) **Secondary Objectives** 1.) Overall response rate (ORR) 2.) Extracranial Progression free survival (PFS) 3.) Overall survival (OS) 4.) Toxicity of atezolizumab plus carboplatin and etoposide **Exploratory Objectives** 1.) Explore circulating biomarkers in patients with SCLC brain metastases 2.) Explore patient-reported quality of life (QoL) 3.) Investigate the immune and genomic landscape of SCLC primaries that metastasized to the brain
STUDY DESIGN	Single arm, multicenter phase II trial for n=60 patients with untreated extensive stage (ES) small cell lung cancer (SCLC) and asymptomatic brain metastases.
KEY ELIGIBILITY CRITERIA (See Section 3 for full eligibility criteria)	• Histological confirmation of Small Cell Lung Cancer- Stage IV/Extensive Stage (SCLC) per Veterans Administration Lung Study Group (VALG). • Untreated, asymptomatic brain metastases • No prior systemic therapy for metastatic disease [a single cycle of chemotherapy (platinum/etoposide) with or without atezolizumab is allowed within 30 days prior to enrollment]
STATISTICAL CONSIDERATIONS	A Kaplan-Meier curve will graphically describe iPFS, PFS, and OS among patients treated by at least one cycle of Atezolizumab. Median survival, as well as 6-month iPFS and PFS, and 12-month OS will be estimated with their 95% confidence intervals (CI). The impact of patients' demographics and baseline clinical characteristics on survivals will be evaluated in the context of a Cox PH model. The ORR, the proportion of treated subjects with a complete or partial response, will be calculated with its 95% CI. The

	association of ORR with patients' demographics and baseline clinical characteristics will be evaluated in a logistic regression model. The quality of life of treated patients at baseline and during treatment will be summarized and the patients' demographics and baseline clinical characteristics on the change of the quality of life will be evaluated in a linear regression.
TOTAL NUMBER OF SUBJECTS	N = 63 eligible patients (60 evaluable)
ESTIMATED ENROLLMENT PERIOD	Estimated 22 months from lead site opening to accrual
ESTIMATED STUDY DURATION	Estimated 40 months

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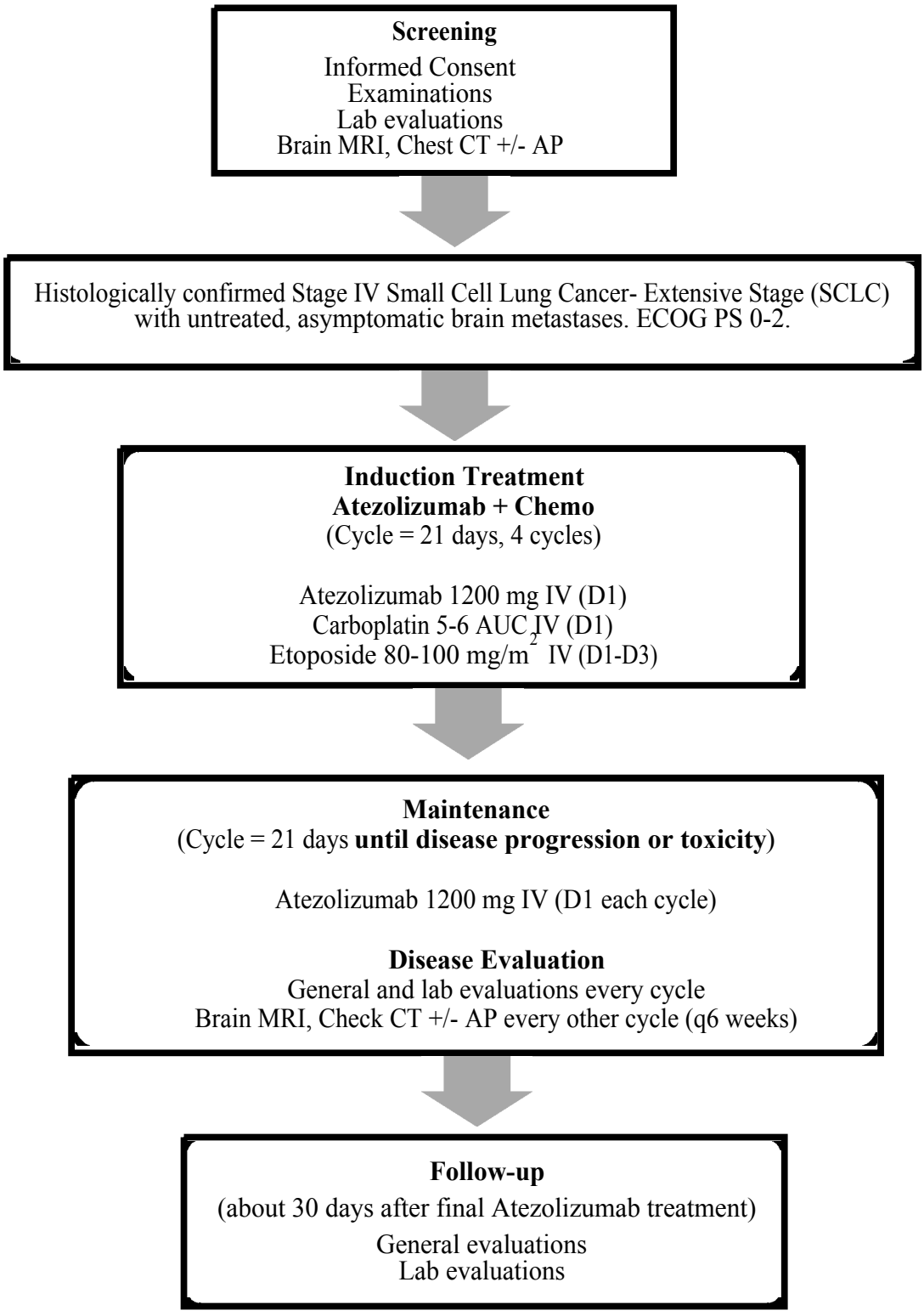
SCHEMA


Screening
Informed Consent
Examinations
Lab evaluations
Brain MRI, Chest CT +/- AP
Histologically confirmed Stage IV Small Cell Lung Cancer- Extensive Stage (SCLC) with untreated, asymptomatic brain metastases. ECOG PS 0-2.
Induction Treatment
Atezolizumab + Chemo
(Cycle = 21 days, 4 cycles)
Atezolizumab 1200 mg IV (D1)
Carboplatin 5-6 AUC IV (D1)
Etoposide 80-100 mg/m2 IV (D1-D3)
Maintenance
(Cycle = 21 days until disease progression or toxicity)
Atezolizumab 1200 mg IV (D1 each cycle)
Disease Evaluation
General and lab evaluations every cycle
Brain MRI, Check CT +/- AP every other cycle (q6 weeks)
Follow-up
(about 30 days after final Atezolizumab treatment)
General evaluations
Lab evaluations

1. BACKGROUND AND RATIONALE

1.1 Extensive Stage Small Cell Lung Cancer (ES SCLC)

Lung cancer is the most deadly cancer globally, accounting for 12% of diagnoses and 18% of cancer-related mortality [1]. An aggressive subtype of lung cancer, small cell lung cancer (SCLC), accounts for approximately 15% of lung cancer cases, and is almost always associated with smoking [2]. Most patients with SCLC have extensive stage (ES) disease at time of diagnosis, where the disease has metastasized (spread) beyond the lung and nearby lymph nodes [3]. SCLC appears to have a higher predilection for spreading to the brain, with upwards of 10-20% of patients with SCLC having brain metastases at initial diagnosis and 40-50% more eventually developing brain metastases during the course of disease [4].

Historically, in the extensive stage setting, platinum-doublet based chemotherapy has been most often utilized as frontline therapy, most commonly using a combination with etoposide. Platinum and etoposide typically results in a very high initial response rate (~60-80%) and modest progression free survival (~4-6 months), with median overall survival of less than twelve months in the majority of patients [5-7]. Despite initial chemosensitivity, a hallmark of SCLC is the development recalcitrant behavior to subsequent lines of chemotherapy resulting in dismal outcomes in the refractory setting. Prophylactic cranial irradiation (PCI) has been studied and utilized extensively over the past several decades to improve outcomes by treating occult micrometastatic disease and reducing the incidence of brain metastases. A meta analysis of PCI in the limited stage setting, in SCLC demonstrated a marked reduction in brain metastases from 59% to 33% and improved 3 year survival from 15.3 to 20.7 months [8]. However, in ES SCLC, data regarding the role of PCI has been conflicting. The initial phase III EORTC study of 286 patients randomized PCI or observation following initial 4-6 cycles of chemotherapy [9]. While the incidence of symptomatic brain metastases and survival improved in the PCI arm, the results were criticized as MRI was not routinely performed prior to PCI and therefore likely included a portion of patients with brain metastases. In a separate study from Japan, 224 patients with response to chemotherapy were randomized to receive either PCI or observation [10]. All patients had a baseline MRI prior to enrollment and every 3 months during follow up. The study was stopped early due to futility and a trend was noted with worse survival in patient receiving PCI compared with observation.

In March 2019, the anti-PD-L1 antibody atezolizumab combined with carboplatin and etoposide, a topoisomerase II inhibitor, was FDA-approved for first-line treatment of ES SCLC [11]. This priority approval was based on the results of the IMpower133 study (NCT02763579), a trial which allowed but was not specifically designed for patients with brain metastases. As a result, of the 403 patients, only 35 (9%) had brain metastases. Additionally, recent results from the CASPIAN study of chemotherapy with or without durvalumab included approximately 10% of patients with brain metastases [12]. Thus, limited data exists currently regarding clinical outcomes of patients with SCLC and brain metastases at time of diagnosis.

1.2 Standard of Care for Small Cell Lung Cancer Brain Metastases

Given the systemic nature of SCLC, the rate of metastatic spread to the brain and concern for micrometastatic disease, whole brain radiotherapy (WBRT) is typically used for the treatment of brain metastases in SCLC. Importantly, WBRT is associated commonly with well-documented short- and long-term neurotoxicity and reduced quality of life [13-15]. For example, in a pooled analysis of over 400 patients receiving PCI for lung cancer resulted in decline in self reported cognitive function at 6 and 12 months, while Hopkins Verbal Learning Test assessment declined as well [15]. Short term effects typically include fatigue, anorexia, headache, nausea, and hair loss [16]. In the EORTC study randomizing patients to receive PCI with ES SCLC, health reported quality of life scores were lower in the patients receiving PCI for global health status, cognitive function, fatigue within three months of follow up [13]. WBRT is also often partnered with systemic therapy, either before or after receipt of radiation, in ES SCLC due to the frequently multifocal metastatic nature of the disease.

Generally, systemic treatment alone with chemotherapy can result in intracranial response in the majority of patients with brain metastases. As a result, a common approach clinically is to start systemic therapy without WBRT in patients with newly diagnosed ES SCLC and asymptomatic brain metastases. However, a limited amount of data exists regarding the outcomes in patients with brain metastases treated with systemic therapy alone. In an analysis of 7 studies including 85 patients with brain metastases treated with chemotherapy, the overall clinical response was 79%. However, in one of the largest studies, 24 patients with synchronous brain metastases and treated with chemotherapy alone were enrolled over 13 years at a single institution [17]. Response rate was much lower with 27% having a response to cyclophosphamide, doxorubicin, and etoposide and was lower than the response rate of the extracranial disease. This study had limitations in that patients only received MRI at baseline, at completion of chemotherapy, and upon development of symptoms. Additionally, platinum with etoposide based chemotherapy was not used in this study population.

Given the recent approval of atezolizumab, the current first-line systemic treatment approach for patients with ES SCLC is a combination of anti-PD-L1 antibody with a chemotherapy regimen of platinum plus etoposide, based on the IMpower133 study (NCT02763579) [18]. The addition of atezolizumab, an anti-PD-L1 antibody, to carboplatin and etoposide for first-line treatment of ES SCLC improved overall (OS) to 12.3 months, from 10.3 months with placebo, and progression-free survival (PFS) to 5.2 months (versus 4.3 months for placebo). While this study allowed ES SCLC patients with brain metastases, only 35 patients (n=17-18 per arm, 9%) had brain metastases; the study was unpowered to access efficacy in this patient population [18].

1.3 Atezolizumab (MPDL3280A)

Immunotherapies that block checkpoint proteins on immune cells inhibit the negative feedback on T cells by these signaling pathways, thereby maintaining activation of the T cells [19]. Two of the most predominant clinical checkpoint targets are PD-1 and its ligand PD-L1. Association of PD-L1 with PD-1 induces inhibitory signals in T cells that reduce proliferation and cytokine production, causing T cell inactivation or exhaustion. Aberrant expression of PD-L1 in tumors leads to immune evasion by the tumor, but also provides a therapeutic opportunity.

Atezolizumab (MPDL3280A; anti−PD-L1 antibody) is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids), and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptors, PD-1 and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells.

1.4 Rationale

The IMpower133 clinical trial evaluated chemotherapy and atezolizumab for first line treatment of patients with untreated ES SCLC. The results from the trial led to an FDA approval and established this regimen as a new standard of care. However, while patients with brain metastases were allowed, prior cranial radiation was required for these patients. Furthermore, only 9% of enrolled patients had brain metastases. There remains an urgent need to define clinical outcomes for patients treated with chemotherapy and atezolizumab with asymptomatic, untreated brain metastases.

Recent studies with systemic immunotherapy in brain metastases patients have demonstrated that outcomes for patients with and without brain metastases are generally similar. The IMpower133 study demonstrated PFS outcomes of 5.2 months for the atezolizumab arm versus 4.3 months for the placebo arm. Thus, we hypothesize that atezolizumab plus chemotherapy (i.e. carboplatin and etoposide) will improve intracranial progression free survival (iPFS) in patients with brain metastases from SCLC relative to historical controls (≥ 5.2 months vs. 4 months).

This study will enroll patients with asymptomatic brain metastases and untreated ES SCLC. Patients will be treated with combination carboplatin, etoposide, and atezolizumab. Restaging radiographic imaging will occur every 6 weeks (approximately every 2 cycles of treatment). At time of progression, patients can pursue standard of care treatment and radiation therapy off study. Our hypothesis is that the addition of atezolizumab will improve intracranial progression free survival in patients with untreated brain metastases. Furthermore, the study will provide valuable insight in the clinical outcomes of the patient population with ES SCLC and brain metastases. In general, chemotherapy response rates are expected to be high, and immune checkpoint therapy is known to have efficacy in other CNS malignancies. We believe treatment with systemic therapy alone will 1) delay time to WBRT 2) preserve quality of life longer 3) allow a subpopulation of patients to avoid WBRT and 4) be able to avoid a detrimental impact on survival given the close radiographic follow up.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- Estimate intracranial progression free survival (iPFS) for atezolizumab when administered with carboplatin and etoposide in subjects with untreated SCLC brain metastases

2.1.2 Secondary Objectives

- Estimate the overall response rate (ORR) for atezolizumab when administered with carboplatin and etoposide in subjects with untreated SCLC brain metastases
- Estimate the extracranial progression free survival (PFS) for atezolizumab when administered with carboplatin and etoposide in subjects with untreated SCLC brain metastases
- Estimate the overall survival (OS) for atezolizumab when administered with carboplatin and etoposide in subjects with untreated SCLC brain metastases
- Evaluate the toxicity of atezolizumab when administered with carboplatin and etoposide in subjects with untreated SCLC brain metastases

2.1.3 Correlative/Exploratory Objectives

- Explore circulating biomarkers in patients with SCLC brain metastases
- Explore patient-reported quality of life (QoL)
- Investigate the immune and genomic landscape of SCLC primaries that metastasized to the brain

2.2 Endpoints

2.2.1 Primary Endpoint

- Intracranial PFS is defined as the time from Day 1 of treatment until the criteria for intracranial disease progression is met as defined by RANO-BM or death as a result of any cause, whichever comes first.

2.2.2 Secondary Endpoints

- ORR will include complete response (CR) + partial response (PR) as determined by RECIST 1.1.
- Extracranial PFS is defined as the time from Day 1 of treatment until the criteria for extracranial disease progression is met as defined by RECIST 1.1 or death as a result of any cause, whichever comes first.
- OS is defined as the time from Day 1 of treatment until death as a result of any cause.
- Toxicity will be graded by Common Toxicity Criteria for Adverse Events (CTCAE V5).

2.2.3 Correlative/Exploratory Endpoints

- Circulating biomarkers in patients with SCLC brain metastases will be explored in patient blood, focusing on circulating immune cells, protein analysis, and cell-free DNA
- Patient-reported quality of life (QoL) will be assessed per:
  - FACT-BR
  - FACIT-Fatigue
  - Godin Leisure-Time Exercise Questionnaire
- The immune and genomic landscape of SCLC that metastasized to the brain will be assessed through analysis of archival paraffin tissue of the primary lesion by immunohistochemistry and sequencing

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information prior to registration. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years with ability and willingness to provide informed consent.

3. ECOG Performance Status of 0-2.

4. Histological confirmation of Small Cell Lung Cancer- Extensive Stage (SCLC) per Veterans Administration Lung Study Group (VALG).

5. At least one untreated asymptomatic brain metastasis that is measurable by RECIST 1.1 that has not been previously irradiated.

6. No prior treatment for metastatic disease. **EXCEPTION:** A single cycle of chemotherapy (platinum/etoposide) with or without atezolizumab is allowed within 30 days prior to enrollment.

7. Treatment-free for at least 6 months since last chemo/radiotherapy, among those treated (with curative intent) with prior chemo/radiotherapy for limited-stage SCLC.

8. Any prior cancer treatment must be completed at least 6 months prior to registration and the subject must have recovered from all reversible acute toxic effects of the regimen (other than alopecia) to Grade ≤ 1 or baseline. **NOTE:** a single cycle of chemotherapy (platinum/etoposide) with or without atezolizumab is allowed within 30 days prior to enrollment. **NOTE: Extracranial radiation is allowed.**

9. A concurrent diagnosis of a separate malignancy is allowed if clinically stable and does not require tumor-directed therapy.

10. Demonstrate adequate organ function as defined in the table below

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	≥ 1.5K/mm^3 without GCSF
Hemoglobin (Hgb)	≥ 9 g/dL (without transfusion)
Lymphocyte Count	≥ 500/µL
Platelet Count	≥ 100,000/µL without transfusion
Renal	
Calculated creatinine clearance[1]	≥ 50 cc/min
OR	
Serum Cr	< 1.5 x institutional ULN
Hepatic[2]	
Bilirubin	< 1.5 × upper limit of normal (ULN)
Aspartate aminotransferase (AST)	< 2 × ULN without liver metastasis < 5 × ULN with liver metastasis
Alanine aminotransferase (ALT)	< 2 × ULN without liver metastasis < 5 × ULN with liver metastasis

[1] Cockcroft-Gault formula will be used to calculate creatinine clearance
[2] Patients with known Gilbert disease who have serum bilirubin level < 3x ULN may be enrolled

11. Females of childbearing potential must have a negative serum pregnancy test **within 3 days (72 hours)** prior to enrollment. **NOTE:** Females are considered of childbearing potential unless they are surgically sterile (have undergone a hysterectomy or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.

12. Females of childbearing potential and males must be willing to abstain from heterosexual activity or to use 2 forms of effective methods of contraception, including at least one method with a failure rate of < 1% per year, from the time of informed consent until 150 days (5 months) after treatment discontinuation.

13. Negative hepatitis B surface antigen (HBsAg) test, negative total hepatitis B core antibody (HBcAb) test, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test. The HBV DNA test will be performed only for patients who have a positive total HBcAb test. Testing required at screening only if results are not known.

14. Negative hepatitis C virus (HCV) antibody test, or positive HCV antibody test followed by a negative HCV RNA test. The HCV RNA test will be performed only for patients who have a positive HCV antibody test. A positive HCV RNA test is sufficient to diagnose active HCV infection in the absence of an HCV antibody test.

15. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures.

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Known active CNS metastases which are symptomatic. CNS metastases are considered asymptomatic if the patient does not require high dose or escalating corticosteroids or anticonvulsant therapy. Steroid dose must be equivalent to 2 mg of dexamethasone or less daily.
    - Prior steroid use as part of an anti-emetic regimen with chemotherapy is allowed.
    - Patients must be on a stable dose of corticosteroid. No tapering or decreasing dose within 7 days of enrollment.

2. Leptomeningeal disease. Discrete dural-based metastases will be allowed without evidence of leptomeningeal disease.

3. Radiation therapy within 14 days prior to Day 1 of Cycle 1 Day 1. **NOTE: Extracranial radiation is allowed.**

4. Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN)

5. Known auto-immune conditions requiring systemic immune suppression therapy other than prednisone ≤ 10 mg daily (or equivalent).

6. History of interstitial pneumonitis from any cause.

7. Concurrent severe and/or uncontrolled medical conditions which may compromise participation in the study as assessed by site investigator.

8. Current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment on Cycle 1 Day 1. Patients receiving prophylactic antibiotics (e.g., for prevention of urinary tract infection or chronic obstructive pulmonary disease) are eligible. NOTE: Subjects with active tuberculosis are NOT eligible.

9. Current use of medications specified by the protocol as prohibited for administration in combination with the study drugs. This includes patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to Cycle 1 Day 1. Inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead.

10. History of myocardial infarction, NYHA class II or greater congestive heart failure, or unstable angina, cardiac or other vascular stenting, angioplasty, or surgery within 6 months prior to study enrollment.

11. Known history of HIV seropositivity or known acquired immunodeficiency syndrome (AIDS), Testing not required at screening.

12. Requirement for ongoing anticoagulation with heparin, low molecular weight heparin, or other oral anticoagulant (coumadin, DOAC).

13. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently). **NOTE:** Patients with indwelling catheters (e.g., PleurX®) are allowed.

14. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.

15. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation.

16. History of allergic reactions to carboplatin or etoposide.

17. Intolerance of atezolizumab or other PD-1/PD-L1 axis drug(s), or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways, including prior therapy with anti-tumor vaccines or other immune-stimulatory anti-tumor agents.

18. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, 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 low-potency topical corticosteroids
        - There has been no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors

19. 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.

20. Pregnant or breastfeeding (**NOTE**: breast milk cannot be stored for future use while the mother is being treated on study).

21. Treatment with any investigational drug within 28 days prior to Cycle 1 Day 1.

4. SUBJECT REGISTRATION

All subjects must be registered through HCRN's electronic data capture (EDC) system. A subject is considered registered when an "On Study" date is entered into the EDC system. Subjects must be registered prior to starting protocol therapy.

5. TREATMENT PLAN

This is a single arm, multicenter phase II trial for 60 patients with untreated extensive stage (ES) small cell lung cancer (SCLC) with asymptomatic brain metastases. Subjects will receive 4 cycles of induction treatment with Atezolizumab (1200 mg on Day 1) combined with carboplatin (5-6 AUC on Day 1) and etoposide (80-100 mg/m^2 on Days 1-3). Each cycle equals 21 days. After 4 cycles of induction treatment, subjects will receive atezolizumab maintenance 1200 mg on Day 1 of each 3-week cycle. Subjects will receive treatment until disease progression, unacceptable drug-related toxicity, or withdrawal from study for any reason.

5.1 Study Treatment

5.1.1 ACE (Atezolizumab-Carboplatin-Etoposide) Induction

Drug	Dose[1]	Route	Schedule[2]	Cycle Length	Total # of Cycles
Atezolizumab	1200 mg	Intravenously (IV) over 60 minutes **before carboplatin**	Day 1	3 weeks (21 days)	4
Carboplatin	5-6 mg/mL/min AUC	IV over 30-60 min **after** completion of atezolizumab	Day 1		
Etoposide	80-100 mg/m^2	IV over 60 min **after** completion of carboplatin	Days 1, 2, 3		

[1] Dosing calculations should be based on actual body weight where applicable. Institutional standards for recalculating the dose based on weight changes should be used. All doses should be rounded up or to the nearest milligram per institutional standard.
[2] A window of ±3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).

5.1.2 Atezolizumab Maintenance

Drug	Dose	Route	Schedule[1]	Cycle Length

Atezolizumab	1200 mg	IV over 60 minutes	Day 1	3 weeks (21 days)

[1] A window of ± 7 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).

5.2 Chemotherapy

Institutional standards may be used for the infusion of carboplatin and etoposide. This includes pre-medications, infusion windows and treatment of side effects. Because the effects of corticosteroids on T-cell proliferation have the potential to attenuate atezolizumab-mediated anti-tumor immune activity, premedication with corticosteroids should be minimized to the extent that is clinically feasible. The current package insert should be referenced for additional information regarding these medications. Both medications will be used in the commercially available formulation.

5.2.1 Carboplatin

Carboplatin 5-6 mg/mL/min AUC will be delivered over 30 - 60 minutes intravenously on Day 1 of each 21 day Cycle after completion of atezolizumab. Institutional standards may be used for dose calculation.

5.2.2 Etoposide

Etoposide 80-100 mg/m^2 will be delivered over 60 minutes intravenously on Days 1-3 of each 21 day Cycle after completion of carboplatin (Day 1 only). Institutional standards may be used for dose calculation.

5.3 Atezolizumab

Atezolizumab 1200 mg will be delivered over 60 (± 15) minutes intravenously on Day 1 of each 21 day Cycle. Institutional standards may be used regarding all aspects of the infusion. The investigator's brochure should be utilized for additional details regarding this medication.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Atezolizumab infusions instructions outlined in the Table below.

First Infusion	Subsequent Infusions
● No premedication is allowed. ● Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. ● Infuse atezolizumab (1200 mg in a 250 mL 0.9% NaCl intravenous infusion bag) over 60 (± 15) minutes. ● If clinically indicated, record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion at 15, 30, 45, and 60 minutes	● If the patient experienced an infusion-related reaction during any previous infusion, premedication with antihistamines may be administered for Cycles ≥ 2 at the discretion of the treating physician. ● Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. ● If the patient tolerated the first infusion well, without infusion-associated adverse events,

• (± 5-minute windows are allowed for all time points). • If clinically indicated, record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) at 30 (± 10) minutes after the infusion. • Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	the second infusion may be administered over 30 (± 10) minutes. • If no reaction occurs, subsequent infusions may be administered over 30 (± 10) minutes. o Continue to record vital signs within 60 minutes before starting infusion and during and after the infusion, if clinically indicated. • If the patient had an infusion-related reaction during the previous infusion, the subsequent infusion must be administered over 60 (± 15) minutes. o Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion if clinically indicated or if patient experienced symptoms during the previous infusion. o Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) 30 (± 10) minutes after the infusion if clinically indicated or if patient experienced symptoms during previous infusion.

5.3.1 Infusion -Related Reactions with Atezolizumab

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis. Guidelines for medical management of IRRs during Cycle 1 are provided in the Table below. For subsequent cycles, IRRs should be managed according to institutional guidelines.

5.3.2 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. • Monitor vital signs as clinically indicated
IRR, Grade 2	• Interrupt atezolizumab infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset.

	• For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs. • Monitor vital signs as clinically indicated • Consider permanent discontinuation of atezolizumab treatment if Grade 2 infusion reaction occurs despite adequate premedication
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Monitor vital signs as clinically indicated • Hospitalization indicated for clinical sequelae (examples: renal impairment, pulmonary infiltrates) • Permanently discontinue atezolizumab.[a]

IRR = infusion-related reaction.

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

5.4 Concomitant Medications

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening until the treatment discontinuation visit. Steroid medication use should be reported to the investigator and recorded on the Concomitant Medications eCRF.

5.4.1 Allowed Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

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

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level)
- If palliative radiotherapy is required, it should be discussed with HCRN and the sponsor-investigator.
- Inactive influenza vaccinations
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)
- Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency

In general, investigators should manage a patient's care with supportive therapies as clinically indicated per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist per standard practice (for sites outside the United States,

equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated.

All concomitant steroid medications must be recorded on the appropriate Concomitant Medications eCRF.

5.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations where systemic corticosteroids or TNF- α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered first by the treating physician. If the alternatives are not clinically appropriate, systemic corticosteroids and TNF- α inhibitors may be administered at the discretion of the treating physician except in the case of patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance).

Systemic corticosteroids are recommended, with caution, at the discretion of the treating physician, for the treatment of specific adverse events when associated with atezolizumab therapy.

Refer to the Atezolizumab Investigator's Brochure for additional information on the management of immune-mediated adverse events.

5.4.3 Prohibited Concomitant Medications with Atezolizumab

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

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

- Denosumab; patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead
- Any live, attenuated vaccine (e.g., FluMist®) within 4 weeks prior enrollment, during treatment, and for 5 months following the last dose of atezolizumab
- Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance); in such patients, non-contrast CT scans of the chest and non-contrast CT scans or MRIs of the abdomen and pelvis should be performed

The concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, their use for patients in the study is allowed at the discretion of the investigator, provided that there are no

known interactions with any study treatment. As noted above, herbal therapies intended for the treatment of cancer are prohibited.

5.5 Supportive Care

In general, investigators should manage a patient's care with supportive therapies as clinically indicated per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated.

All concomitant steroid medications must be recorded on the appropriate Concomitant Medications eCRF.

5.6 Reproductive Information

Negative pregnancy test done ≤ 72 hours (or per institutional policy) prior to treatment, for women of childbearing potential only. Female subjects should be using highly effective contraceptive measures, and must have a negative pregnancy test or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

- Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments.
- Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution
- Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation

Men and women of childbearing potential must agree to use highly effective methods of contraception, including at least one method with a failure rate of < 1% per year, during the course of the study and for 5 months after the last dose of study drug, even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of study and for 5 months after the last dose of study drug.

5.6.1 Contraception Options

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in the table below. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action; and triphasic combined oral contraceptive pills). Abstaining from heterosexual intercourse is considered an effective method of contraception.

Highly Effective Methods of Contraception (<1% Failure Rate)

Barrier/Intrauterine methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Etonogestrel implants: e.g. Implanon • Intravaginal device: e.g. ethinylestradiol and etonogestrel • Medroxyprogesterone injection: e.g. Depo-Provera • Normal and low dose combined oral contraceptive pill • Norelgestromin/ethinylestradiol transdermal system

[a] This is also considered a hormonal method

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 will be used to grade adverse events. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose Delays/Dose Modifications

Reasons for dose modifications including dose delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF. The severity of adverse events will be graded according to the NCI CTCAE v5 grading system.

- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment and the dose or administration of that component is delayed or modified, the dose or administration of the other study treatment components do not require modification and may be administered if there is no contraindication.
- When treatment is temporarily interrupted because of toxicity caused by atezolizumab, carboplatin, or etoposide, the treatment cycles should be restarted such that the atezolizumab infusions remain synchronized and aligned with the chemotherapy schedule.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one chemotherapy drug, the dose of the other chemotherapy drug does not require modification.

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

6.2 Atezolizumab Dose Modification

There will be no dose modifications for Atezolizumab. Adverse events will be managed as described in detail in Appendix "Management of Atezolizumab-Specific Adverse Events".

If a dose of atezolizumab is withheld for toxicity, then subjects may resume dosing with atezolizumab if that is appropriate at their next scheduled appointment or when toxicity has improved as described in the Appendix "Management of Atezolizumab-Specific Adverse Events".

Atezolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as below and as listed in appendix.

Subjects who require corticosteroids to manage atezolizumab-related AEs must be at an equivalent dose of ≤ 10 mg per day of prednisone to resume dosing with atezolizumab. Furthermore, an inability to reduce the corticosteroid dose for managing a drug-related adverse event to the equivalent of ≤ 10 mg prednisone per day within 12 weeks of the last atezolizumab dose should prompt discussion between the site investigator and sponsor-investigator regarding the subject's ability to continue on treatment with atezolizumab the study. With site investigator and sponsor-investigator agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the study only if asymptomatic and controlled.

In subjects who continue on atezolizumab having experienced a Grade 3, Grade 4, or persistent (> 4 weeks) Grade 2 atezolizumab-related AE, dosing should be held until the AE resolves to Grade 0-1 or baseline.

However, in subjects who experience Grade 3 or 4 pneumonitis, or recurrent persistent (> 4 weeks) Grade 2 drug-related pneumonitis after re-challenge from a prior episode of persistent (> 4 weeks) Grade 2 drug-related pneumonitis, atezolizumab must be permanently discontinued.

For subjects Hepatotoxicity events of Grade 3-4, patients are to permanently discontinue Atezolizumab, with the exception of patients with liver metastasis who began treatment with Grade 2 AST or ALT; if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then subjects should be discontinued.

Subjects with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Refer to the Atezolizumab Investigator's Brochure for more detailed information regarding dose modification.

6.3 Chemotherapy Dose Modification

Dose modifications for carboplatin and etoposide are permitted for toxicity according to the prescribing information and local standard-of-care. Dose modification guidelines are provided below. Once reduced, the dose cannot be increased back to 100%.

Treatment with carboplatin or etoposide should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or Grade 4 toxicity after two dose reductions or treatment is delayed for more than 63 days due to toxicities.

6.3.1 Criteria for start of Cycle

Prior to the start of each Cycle the following is required:

- ANC ≥1500/uL
- Platelet count ≥ 100,000/uL

6.3.2 Hematologic Toxicity

Treatment may be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) and NCCN guidelines (Smith et al. 2006; NCCN 2015). Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest platelet and neutrophil values from the previous cycle. See the Table below.

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Toxicity [a]	Dose
ANC <500/μL and platelets ≥50,000/μL	75% of previous dose
Platelets <25,000/μL, regardless of ANC	75% of previous dose
Platelets <50,000/μL with Grade ≥2 bleeding, regardless of ANC	50% of previous dose
ANC <1000/μL plus fever of ≥38.5°C	75% of previous dose

[a] Nadir of prior cycle.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

If chemotherapy is withheld because of hematologic toxicity, full blood counts (including differential WBC) should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment can then be resumed.

No dose reductions are recommended for anemia. Patients should be supported per the investigator's institution's guidelines.

6.3.3 Non-Hematologic Toxicity

For a non-hematologic toxicity, treatment may be delayed for up to 63 days until resolution to less than or equal to the patient's baseline value (or Grade ≤ 1 if the patient did not have that toxicity at baseline). Dose reductions at the start of the subsequent cycle should be made on the basis of non-hematologic toxicities from the dose administered in the preceding cycle. Recommended dose modifications for non-hematologic toxicities are in Table below.

Toxicity		Adjusted Dose as % of Previous Dose [a]
Diarrhea	Grade 3 or 4 [b]	75%
Nausea/vomiting	Grade 3 or 4 [c]	75%
Neurotoxicity	Grade 2	75%
	Grade 3 or 4	50% or permanent discontinuation
Transaminase elevation	Grade 3	75%
	Grade 4	Discontinue
Other	Grade 3 or 4	75%

AUC = area under the concentration–time curve.

[a] If deemed appropriate by the investigator, adjust carboplatin dose to the specified percentage of the previous AUC.

[b] Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication or any grade of diarrhea requiring hospitalization.

[c] Despite the use of anti-emetics.

Diarrhea should be controlled with adequate anti-diarrhea medication. Nausea and/or vomiting may be controlled with adequate anti-emetics. For Grade 3 or 4 neurotoxicity chemotherapy should be resumed at 50% of the previous dose upon improvement or discontinued immediately (based on investigator's clinical judgment).

Suggested recommendations for dose modification of etoposide for renal impairment are provided below.

Creatinine clearance (mL/min)	Etoposide Dose
>50	100%
15–50	75% of dose

6.4 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined above, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF)

- Documented disease progression based on RECIST 1.1
- Site investigator determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
  - In a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- Female subject becomes pregnant
- Protocol therapy is interrupted for ≥ 63 days.

6.5 Protocol Discontinuation

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject's protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Study Evaluation Cycle = 21 days	Screening	On Treatment Cycles 1-4			Maintenance Cycles 5+	Safety follow up visit[10]	Long-term Follow up[11]
	-28 days	Day 1 ± 2 days	Day 2	Day 3	Day 1 ± 2 days	30 days post last dose + 7 days	Every 3 months (±14 days)
REQUIRED ASSESSMENTS							
Informed Consent[1]	X						
Medical History[2]	X						
Physical Exam[2]	X	X			X	X	
Vital signs and ECOG Performance Status[2]	X	X			X	X	
Quality of Life Questionnaires[3]		X[3]			X[3]	X[3]	
AEs & concomitant medications	X	X			X	X	
LABORATORY ASSESSMENTS							
Complete Blood Cell Count with diff (CBC)	X	X[9]			X	X	
Comprehensive Metabolic Profile (CMP)	X	X[9]			X	X	
PT/INR and aPTT	X						
Thyroid Function Testing[4]	X	C3D1			X[4]	X	
Hepatitis Testing[4]	X						
Pregnancy test (serum or urine) (WOCBP)[4]	X	X[4]			X[4]		
DISEASE ASSESSMENT[5]							
CT of chest	X[5]	C3D1			X[5]		X[5]
CT or MRI of abdomen and pelvis[5]	X[5]	C3D1			X[5]		X[5]
MRI Brain[5]	X[5]	C3D1			X[5]		X[5]
TREATMENT EXPOSURE[6]							
Atezolizumab[6]		D1			X[6]		
Carboplatin[6]		D1					
Etoposide[6]		D1-D3					
SPECIMEN COLLECTION[7]							
Archival Tumor Tissue[7]	X[7]						
Blood Samples[8]		X[8]				X[8]	
FOLLOW-UP							
Survival Status, Subsequent Therapy							X

1: Medical History; other data to obtained during this assessment includes a smoking history questionnaire and trial awareness question. In addition, prior anti-cancer treatment should be documented including medications (chemotherapy, checkpoint inhibitors, etc) radiation or surgery. In addition, diagnosis and staging to include pathology report and TNM staging documentation. Histological confirmation per VALG of Stage IV Stage Small Cell Lung Cancer (SCLC)- extensive stage. Prior genomic testing (ie NGS) and PD-L1 results are required if available.

2: Physical exam to include a complete neurological exam. Vital signs to include temperature, pulse, respirations, blood pressure weight, and height (screening only) and ECOG performance status.

3: Quality of life evaluations include FACT-Br, FACIT-Fatigue, and Godin Leisure-Time Exercise Questionnaire. Questionnaires to be completed Cycle 1 Day 1 then every other Cycle of treatment (6 weeks; ±1 week) and at the D30 Safety Visit.

4: CBC with platelet and differential (white blood cell count, absolute neutrophil count, hemoglobin and platelet count). Serum chemistries (creatinine, glucose, total bilirubin, aspartate transaminase [AST] and alanine transaminase [ALT] and calcium). Thyroid Function testing should be performed at screening then every 6 weeks (i.e. every other cycle). TSH will be obtained. T4 and T3 including free versus total testing is at the discretion of the site investigator. Hepatitis testing to be performed at screening if results as described in the inclusion criteria are not known. For women of childbearing potential (WOCBP): urine or serum βhCG if clinically appropriate. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Testing is required within 24 hours prior to initiation of study treatment. During treatment, testing should be performed every 3 weeks (on Day 1 of each cycle prior to administering treatment).

5: Tumor response assessment will consist of evaluation by MRI scan of the brain and CT scans of chest +/- abdomen and pelvis. If unable to perform MRI due to medical reasons, CT with contrast is acceptable. Brain MRI used to diagnose brain metastases allowed or a CT with contrast is acceptable. The abdomen/pelvis may be scanned at follow-up timepoints only if positive disease was detected at baseline. Radiology imaging to be performed at screening (within 6 weeks prior to C1D1), then every 6 weeks (prior to Cycle 3 Day 1 and Cycle 6 Day 1) then every 9 weeks (prior to Cycle 9 and so on). Imaging needs to occur every time point regardless of any delay in treatment. Tumor imaging to be done in the follow up period is at discretion of site investigator. If tumor assessments are available for subjects who have not yet experienced progressive disease (PD) at the time treatment is discontinued, the follow-up tumor evaluations will be documented in the eCRF until PD or death is confirmed, or until another treatment is initiated.

6: Induction treatment will consist of 4 cycles of Atezolizumab (1200 mg on Day 1) combined with carboplatin (5-6 AUC on Day 1) and etoposide (80-100 mg/m2 on Days 1-3). After 4 cycles of induction treatment, subjects will receive atezolizumab maintenance 1200 mg on Day 1 of each 3-week cycle. Subjects will receive treatment until disease progression, unacceptable drug-related toxicity, or withdrawal from study for any reason.

7: Archival tissue is required if available. Archival tissue should be identified and requested at screening and shipped by Cycle 2 Day 1, if available. If archival tissue is not available, the subject may still be eligible for the trial. See CLM for collection, labeling, and shipping instructions. Subjects will also be consented for optional storage of any remaining tissue samples after protocol-specified studies are complete. These samples will be stored for future unspecified cancer-related research and are considered “banking samples”.

8: Blood (whole blood for PBMCs, plasma and buffy coat for germline DNA) for correlative analysis will be drawn prior to treatment on Cycle 1 Day1, Cycle 3 Day 1 and at the D30 safety visit/progression. Additional details regarding correlatives can be found in Section 8 and the CLM.

9: If screening (baseline) CBC and Chemistry (CMP) were performed within 7 days of Day 1 of treatment, these do not need to be repeated. All laboratory assessments should be done prior to treatment.

10: Safety Follow Up: The safety follow-up visit should only occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or other reason) and should be performed 30 days (+ 7 days) after the last dose of treatment. Subjects who have an ongoing Grade ≥ 2 or serious AE (SAE) at this visit will continue to be monitored by a member of the study team until the event is resolved, stabilized, determined to be irreversible by the site investigator or a new anti-cancer treatment starts, whichever occurs earlier.

11: Long Term Follow Up: For subjects who discontinue for reasons other than progressive disease, radiographic disease assessment should be performed every 9 weeks until progression, initiating a new cancer treatment, withdrawing consent or becoming lost to follow-up. The scan interval may be reset if scans were done sooner for clinical reasons and the type of scan may be left to discretion of the site investigator. This imaging may be done locally. Once disease progression is documented, subjects will be followed for survival every 3 months for 1 year from documented progression. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate. A window of ± 14 days will be applied to follow up.

8. BIOSPECIMEN STUDIES AND PROCEDURES

The correlative research proposed below represents ideas based upon the state of the field to date. However, the exact correlative research that will be done may be modified based upon the sample availability and best science at the time these assays are ready to be performed. The correlative laboratory manual (CLM) will contain detailed instructions regarding correlatives.

8.1 Archival Tissue

Archival tissue is required if available. If archival tissue is not available, the subject may still be eligible for the trial. Archival tissue should be identified and requested at screening and shipped by Cycle 2 Day 1, if available.

8.3.2 Tumor Immune Infiltrates by Immunohistochemistry (IHC)

Tumor samples may be tested by IHC for expression of proteins that may be associated with sensitivity or resistance to atezolizumab, including but not limited to immune cell populations including CD3, CD4, CD8, Treg, Th17 T-cells and monocyte/macrophage and neutrophil populations, as well as immune and tumor cell expression of PD-1, and PD-L1 and PD-L2, respectively. Multiplex IHC opportunities could be performed by Genentech or other laboratory upon receipt of adequate funding.

8.1.2 Tumor Immune/Inflammatory Analysis by Gene Expression

RNASeq may be conducted in order to assess gene expression of the tumor. Analyses could be conducted by Genentech or other laboratory upon receipt of adequate funding.

8.1.3 Characterization of genomic alterations by whole exome sequencing

Whole exome sequencing or specific targeted DNA panels may be conducted. Analyses could be conducted by Genentech or other laboratory upon receipt of adequate funding.

8.2 Peripheral Blood Samples

Blood (whole blood for PBMCs, plasma and buffy coat) for correlative analysis will be drawn prior to treatment on Cycle 1 Day1, Cycle 3 Day 1 and at the D30 safety visit/progression.

8.2.1 Circulating Immune Cell Analysis

Immune cell correlates using flow-based assays may be performed in collaboration with the Duke Immune Profiling Core (DIPC) laboratory. Changes in the immune cell subtypes that are expected to be altered by treatment will be analyzed. Other technologies approaches may also be considered. The lymphoid panel focuses on T-cell activation, maturation, regulation, and exhaustion. The myeloid panel focuses on myeloid derived suppressor cells (MDSC), M1/M2 polarization, and dendritic cells (DC, pDC).

8.2.2 Circulating Protein Analysis

Analyses may include immune proteins, inflammatory cytokines and tumor growth factors upon receipt of adequate funding. Analyte levels, and changes in analyte levels, will be correlated with clinical outcome (PFS, OS). Plasma may be evaluated for protein markers that may be associated with sensitivity or resistance to atezolizumab. These may include CRP and other markers of inflammation, including but not limited to IFNγ, IL1β, IL4, IL6, IL7, IL10, IL12, IL17A, IL17E, and IL23.

8.2.3 Cell-free DNA for mutational analysis

Tumor-derived cfDNA (ctDNA) has become the focus of intensive investigation in the search for genomic biomarkers that can be used to monitor the presence or absence of disease, disease progression, or the development of resistance mechanisms during the course of treatment. The promise of cfDNA is that it may provide a sensitive and non-invasive means of monitoring the genetic composition of a patient's disease both during treatment and as a means of monitoring response or resistance. ctDNA analysis may be performed upon receipt of adequate funding. The final gene panel will be decided at the time of analysis, allowing for coverage of the most relevant point mutations, amplifications, and gene fusions.

8.2.4 Buffy Coat for Germline DNA

Buffy coat will be collected for germline DNA samples. These samples may be used as a somatic baseline comparison when analyzing ctDNA and/or tumor mutations.

8.2.5 Exosome Analysis

Exosomes are composed of numerous RNA, proteins, lipids and have great biomarker potential, as they transport molecular contents of cells from which they originate. Additional analysis of exosomes may also be performed upon receipt of adequate funding.

8.3 Genetic Testing

Participants will be given information as part of the informed consent process that samples will be used for research purposes that will include genetic testing. The intent is not to give participants (or his/her medical providers) the results of any testing done for research purposes; however, incidental germline (heritable) mutations may be identified of which a participant may or may not already be aware. In the case where an incidental genetic finding is identified, the sponsor investigator of this project will be notified. Possible decisions for handling incidental findings may include notification of the participant (and provider); recommendation for genetic counseling, which may or may not include genetic testing (e.g., if the finding was not done in a CLIA certified laboratory); or, neither. In general, a member of the participant's treating team will be given the information to help with notification. In all cases, the current policy of Duke University Medical Center and local/participating site IRBs, as applicable, will be followed. Any additional approvals that may be required prior to participant notification will be secured in advance.

8.4 Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples collected for study-specific correlative research. Hoosier Cancer Research Network (HCRN) will manage the banked samples. Samples will be coded and banked indefinitely in the Hoosier Cancer Research Network Biorepository and used for future unspecified cancer-related research.

8.5 Confidentiality of Biospecimens

Samples will be identified by the subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

8.6 Quality of Life Assessment

8.6.1 Patient Reported Outcomes

Quality of life evaluations include FACT-Br, FACIT-Fatigue, and Godin Leisure-Time Exercise Questionnaire. These questionnaires are to be completed Cycle 1 Day 1 then every other Cycle of treatment (6 weeks; ±1 week).

Patient-reported Quality of Life (QoL) outcomes will be assessed using the following standardized and validated questionnaires:

- Functional Assessment of Cancer Therapy-Brain (FACT-BR) scale (version 4) [26], which contains subscales for physical (7-items), functional (7-items), emotional (6-items), and social/family (7-items) well-being, as well as a 23-item brain cancer subscale (BCS) that assesses symptoms commonly reported by brain cancer patients
- Functional Assessment of Cancer Therapy-Fatigue (FACIT-Fatigue) subscale (version 4) [27]
- Godin Leisure-Time Exercise Questionnaire Short Scale [28, 29], a simple questionnaire to assess patterns of exercise behavior during a subject's leisure time

9. CRITERIA FOR DISEASE EVALUATION

9.1 Definitions for Response Evaluation – RECIST 1.1

9.1.1 Measurable Disease

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

Malignant Lymph Nodes

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

9.1.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm 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 subject, these are preferred for selection as target lesions.

9.1.3 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.

9.1.4 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.

9.1.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of 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. (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

9.1.6 Evaluation of 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 short axis). **NOTE:** If tumor markers are initially above the upper normal limit, they must normalize for a subject 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 site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.1.7 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

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

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.2 Definitions for Response Evaluation – RANO -BM

MRI scan of head at screening and every other treatment cycle (i.e. 6 weeks) through week 48, then every 9 weeks (i.e. every 3 cycles) until documented disease progression starting after treatment initiation with Cycle 1. Given that imaging following immunotherapy differs greatly from what is typically seen following chemoradiation treatment or treatment with anti-angiogenic compounds, evaluation of response using Macdonald criteria or Response Assessment in Neuro-Oncology (RANO) criteria is not appropriate in this trial. Due to differences in the nature of primary brain tumors and brain metastases, a modified version of RANO called RANO-BM will be used.

9.2.1 Measurable disease

Measurable disease is defined as a contrast-enhancing lesion that can be accurately measured in at least one dimension, with a minimum size of 10 mm, and is visible on two or more axial slices that are preferably 5 mm or less apart with 0 mm skip (and ideally ≤1·5 mm apart with 0 mm skip). Additionally, although the longest diameter in the plane of measurement is to be recorded, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 5 mm for the lesion to be considered measurable. Cystic lesions or surgical cavities should generally be considered non-measurable unless there is a nodular component that measures 10mm or more in longest diameter and 5mm or more in the perpendicular plane. The cystic or surgical cavity should not be measured for the determination of a response.

Non-measurable lesions

Non-measurable disease includes all other lesions, including lesions with longest dimension less than 10 mm, lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, cystic-only lesions, and leptomeningeal disease.

9.2.2 Tumor response assessment

Assignment of CNS response is independent of systemic disease response. All baseline assessments should be done as close as possible to the treatment start and no more than 4 weeks before the beginning of treatment. When more than one measurable lesion in the CNS is present at baseline, all lesions up to a maximum of five CNS lesions should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (longest diameter) and as those that can be measured reproducibly. A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters. All other CNS lesions should be identified as non-target lesions and should also be recorded at baseline.

9.2.3 Evaluation of target lesions

Complete Response (CR)	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 (PR)	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 (PD)	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 (SD)	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.

9.2.4 Evaluation of non-target lesions

Complete Response (CR)	Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.
Non-CR/ Non-PD	Persistence of one or more non-target CNS lesion or lesions.
Progressive Disease (PD)	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 tumor-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease.

9.2.5 Evaluation of best overall CNS response

Target Lesions	**Non-Target Lesions**	**New Lesions****	**Corticosteroids**	**Clinical status**	**Overall Response**
None	None	None	None	Stable or improved	CR
≥30% decrease in sum longest distance relative to baseline	Stable or improved	None	Stable or decreased	Stable or improved	PR
<30% decrease relative to baseline but <20% increase in sum longest distance relative to nadir	Stable or improved	None	Stable or decreased	Stable or improved	SD

≥20% increase in sum longest distance relative to nadir*	Unequivocal progressive disease*	Present*	N/A	Worse*	PD
*Progression occurs when any of these criteria are met. **If ≤ 6 months from initiation of immunotherapy, radiographic progression (including new lesions) with no new or significantly worsened neurologic deficits not due to co-morbid event or concurrent medication should be confirmed on follow-up imaging 3 months after initial radiographic progression (if progression confirmed, the date of actual progression should be back-dated to the date of initial radiographic progression).** **A new lesion is one that is not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion.					

10 DRUG INFORMATION

All drugs used in this clinical trial will be standard of care. Please refer to the latest version of the prescribing information that can be found at *http://www.accessdata.fda.gov/scripts/cder/drugsatfda/*, and/or each manufacturer's website.

10.1 Atezolizumab

PD-L1 may be expressed on tumor cells and/or tumor infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response in the tumor microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production. Atezolizumab (TECENTRIQ®) is a monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody dependent cellular cytotoxicity. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

Please refer to the current version of the Investigator's Brochure (IB) for additional information regarding this drug.

10.1.1 Supplier/How Supplied

GNE will supply atezolizumab at no charge to subjects participating in this clinical trial. Atezolizumab Injection, 1200 mg/20 mL (60 mg/mL). Atezolizumab is provided in a single-use, glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The atezolizumab Drug Product is formulated as 60 mg/mL atezolizumab in a solution containing histidine acetate, sucrose, and polysorbate 20 at pH 5.8.

The site investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.2 Preparation

Visually inspect drug product for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the vial if the solution is cloudy, discolored, or visible particles are observed. Do not shake the vial. Prepare the solution for infusion as follows:

- Select the appropriate vial(s) based on the prescribed dose.
- Withdraw the required volume of atezolizumab from the vial(s).
- Dilute into a 250 mL polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% Sodium Chloride Injection, USP.
- Dilute with only 0.9% Sodium Chloride Injection, USP.
- Mix diluted solution by gentle inversion. Do not shake.

10.1.3 Storage and Stability

Storage of Infusion Solution: This product does not contain a preservative. Administer immediately once prepared. If diluted Atezolizumab infusion solution is not used immediately, store solution either:

- At room temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration of the infusion, or
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from time of preparation.
- Do not freeze or shake

10.1.4 Dispensing

Atezolizumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Atezolizumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.5 Adverse Events

Please refer to the latest version of the prescribing information that can be found at *http://www.accessdata.fda.gov/scripts/cder/drugsatfda/*, and/or on the manufacturer's website.

10.2 Carboplatin and Etoposide

Carboplatin and etoposide will be used as standard of care in the study and sourced commercially.

For information regarding these medications, please refer to the latest version of the prescribing information that can be found at *http://www.accessdata.fda.gov/scripts/cder/drugsatfda/*, and/or on the manufacturer's website.

11 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom (including an abnormal laboratory finding)
- A disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution
- An intercurrent illness or injury that impairs the well-being of the subject
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with extensive stage Small Cell Lung Cancer (SCLC) with untreated asymptomatic brain metastases that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

A SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Results in a congenital anomaly or birth defect in a neonatal/infant born to a mother exposed to IMP.

- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3 Adverse Events of Special Interest (AESI)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the site investigator to Hoosier Cancer Research Network who will then report to GNE is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

The following AEs are considered of special interest:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
  - Treatment-emergent ALT or AST > 3 × ULN (or > 3 × baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin > 2 × ULN (of which ? 35% is direct bilirubin)
  - Treatment-emergent ALT or AST > 3 × ULN (or > 3 × baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study treatment, as defined below
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, macrophage activating syndrome and hemophagocytic lymphohistiocytosis
- Nephritis
- Ocular toxicities (e.g. uveitis, retinitis, optic neuritis)
- 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)

11.2 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the atezolizumab, carboplatin and etoposide (see following guidance), and actions taken.
To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

11.2.1 Relatedness

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy. AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

Yes (Definite/Probable/Possible/Unlikely)
There is a plausible temporal relationship between the onset of the AE and administration of atezolizumab, carboplatin or etoposide and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to atezolizumab, carboplatin or etoposide or with similar treatments; and/or the AE abates or resolves upon discontinuation of the atezolizumab, carboplatin or etoposide or dose reduction and, if applicable, reappears upon re- challenge.

No (Unrelated)
Evidence exists that the AE has an etiology other than the atezolizumab, carboplatin or etoposide (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to atezolizumab, carboplatin or etoposide administration (e.g., cancer diagnosed 2 days after first dose of study drug).

11.2.2 Assessment of Adverse Events (Expectedness)

Expected Adverse Events
For atezolizumab, expected adverse events are those adverse events that are listed or characterized in the current Investigator Brochure (I.B). For carboplatin and etoposide, expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I).

Unexpected Adverse Event
For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current I3 , prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the I3 as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.2.3 Procedures for Eliciting, Recording and Reporting Adverse Events

Eliciting Adverse Events
A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events
Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

Diagnosis vs. Signs and Symptoms
If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Deaths
All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death"

Preexisting Medical Conditions
A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Hospitalizations for Medical or Surgical Procedures
Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.
Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

11.2.4 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0 Update current versions) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
NOTE: Based on the most recent version of NCI CTCAE (v 5.0), 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

11.2 Reporting

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs and AESIs to HCRN

- SAEs will be reported from time of signed informed consent until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs will be reported on the SAE Submission Form **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event**.** The form will be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines listed above), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

11.2.2.2 HCRN Requirements for Reporting SAEs and AESIs to Genentech

HCRN will report all SAEs and AESIs to Genentech **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to Genentech as it is received from site. Genentech Drug Safety: Fax: 650-238-6067 or Email: usds_aereporting-d@gene.com

11.3 Other Reportable Events

11.3.1 Pregnancy reports

If a female subject or a female partner of a male subject becomes pregnant while receiving the study drug or within 5 months after the last dose of study drug, an SAE submission form will be completed. The site should report the event **within 1 business day** of discovery of the event to HCRN and HCRN will report the event to Genentech **within 1 business day** of receipt of the SAE submission form. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and 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.

If after the 30 day safety visit, the investigator should become aware of a congenital anomaly in a subsequently conceived offspring of a female subject, including pregnancy occurring in the partner of a male study subject, who participated in the study, this should be reported as an SAE from the site to HCRN who will report to Genentech drug Safety.

11.3.2 Post-Study Adverse Events

SAEs occurring after discontinuation of study drugs will be reported as outlined in section 11.2.2 if attributed to prior atezolizumab, carboplatin or etoposide exposure.

11.3.3 Special Situation Reports

In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to HCRN from the site and HCRN to GNE **within thirty (30) calendar days**.

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be 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

11.3.4 Product Complaints

All Product Complaints (with or without an AE) shall be forwarded to HCRN from the site and HCRN to GNE **within fifteen (15) calendar days of the awareness date.** A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

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

11.4 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.5 HCRN Responsibilities to FDA

For protocols exempt from the requirements of an IND, the above stated requirements are not applicable. HCRN will continue to facilitate compliance of applicable requirements for the sponsor-investigator in relation to this study. This includes but is not limited to 21 CFR 50.20 informed consent, 21 CFR Part 56 IRB, and pertinent sections of the Public Health Service Act and FDAAA.

11.6 IND Safety Reports Unrelated to this Trial

Genentech will provide to HCRN IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12 STATISTICAL METHODS

12.1 Study Design

This is a multicenter, single arm, open label phase II trial to evaluate the safety and efficacy of atezolizumab in combination with carboplatin and etoposide in patients with untreated extended stage small cell lung cancer (ES-SCLC) brain metastases.

12.2 Endpoints

The primary endpoint of the trial is intracranial progression free survival (iPFS).

The secondary endpoints include overall response rate (ORR), intracranial or extracranial progression free survival (PFS), overall survival (OS), and the grade and type of toxicity of atezolizumab in combination with carboplatin and etoposide.

12.2.1 Definition of Primary Endpoint

The primary endpoint of the study is intracranial progression free survival (iPFS), which is defined as the time from Day 1 of protocol treatment until the criteria for iPFS is met as defined by RANO-BM or death from any cause, whichever comes first.

12.2.2 Definition of Secondary Endpoints

ORR is the proportion of patients whose best response to protocol treatment are either complete response (CR) or partial response (PR) by the investigator using RECIST 1.1. Patients not meeting these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders.

PFS is defined as the time from Day 1 of protocol treatment until the criteria for disease progression (intracranial or extracranial) is met as defined by RECIST 1.1 and RANO-BM, or death from any cause, whichever comes first. Subjects who have not progressed will be right-censored at the date of the last disease evaluation. If progression occurs in either intracranial or extrancranial or both compartments, the criteria for progression-free survival will have been met per RANO-BM.

OS is defined as the time from Day 1 of protocol treatment until death from any cause.

CTCAE V5 will be utilized to define the grade and type of toxicities and adverse events.

12.3 Sample Size and Accrual

The study will enroll 63 eligible patients who receive at least one dose of the study agent.

The sample size of the study is determined by the analysis of iPFS. To detect an improvement of median iPFS = 5.2 months from 4.0 months in historical control (IMpower 133) (HR = 0.77) using a logrank test, 60 treated patients will be required to achieve approximately 81% power at a one-sided significance level of 0.15. Patients are accrued for a period of 22 months. Follow-up continues for 12 months after the last patient is enrolled. The probability that a patient experiences an event during the study is 0.9707. The expected number of events during the study is 58. It is assumed that the survival time is exponentially distributed. The sample size calculation above is conducted in PASS v16.0.2. Assuming a 5% rate of dropout prior to protocol treatment, a total of 63 eligible patients will be treated by at least one doses of the study agent.

The sample size calculation is determined to have adequate power to reject the null hypothesis when the alternative hypothesis is true for the primary endpoint iPFS. Whether it has sufficient power for addressing secondary endpoints or exploratory analysis is not of concern.

12.4 Assessment of Safety

All subjects that have received one dose of study treatment will be evaluable for safety. Adverse events will be continuously monitored. Safety assessments using the NCI-CTCAE version 5 will be performed as outlined in Section 7 of the Study Calendar.

12.5 Assessment of Efficacy

All subjects with measurable disease who have received at least one cycle of treatment and have their disease re-evaluated will be evaluable for assessment of iPFS, PFS, ORR, OS, and HRQol.

12.6 Data Analysis Plans

12.6.1 Analysis Plans for Primary Objective

Median iPFS and 6-month iPFS rate along with their 95% conference intervals (CIs) will be estimated using Kaplan-Meier (KM) approach. KM curve will be used to characterize iPFS. Cox proportional hazard models will evaluate the relationship between iPFS with the patients' baseline characteristics, including age at enrollment, gender, race, and ECOG Performance Status and the estimated HRs and their 95% Cis will be provided.

12.6.2 Analysis Plans for Secondary Objectives

ORR and its 95% CI will be estimated.

Median PFS and OS and their 95% CIs will be estimated using Kaplan-Meier approach. KM curves will be used to characterize PFS and OS. Six-month PFS and 12-month OS rates and their 95% CIs will also be estimated. Cox proportional hazard models will evaluate the relationship between PFS or OS with the patients' baseline characteristics, including age at enrollment, gender, race, and ECOG Performance Status and the estimated HRs and their 95% Cis will be provided.

The types and frequencies of toxicities will be summarized by the severities.

12.6.3 Analysis Plans for Exploratory Objectives

The summary statistics (mean, standard deviation, median, Q1, Q3, and range) of subscale and overall scores derived from FACT-BR questionnaires will be calculated.

12.6.4 Other Planned Analyses

Patients' baseline characteristics will be summarized. Mean, SD, median and range for continuous variables (age at enrollment), and frequencies and percentages for categorical variables (sex, race, ethnicity, performance status) will be calculated.

12.7 Interim Analysis/Criteria for Stopping Study

One interim analysis for futility will be conducted at half of the required events for the final analysis (approximately 29 events) based on the Wieand rule [30]. If the one-sided p-value of the logrank test exceeds 0.50, the trial will be terminated for futility, declaring the probability of rejecting the null hypothesis is very low. The Wieand rule to futility monitoring negligibly reduces the power of the trial, usually less than 2% and offers a 50% chance of early stopping accrual to an ineffective therapy.

13 TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted with guidance from the Duke University Cancer Center's DSMP.

HCRN oversight activities include:

- Review and process all adverse events requiring expedited reporting as defined in the protocol.
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator.
- Submit data summary reports to the lead institution Data Safety Monitoring Committee.

13.2 Data Safety Monitoring Board

This study will have a Data and Safety Monitoring Board (DSMB). The DSMB is chaired by an independent medical oncologist external to this trial. The DSMB will provide a recommendation to the sponsor-investigator after all information is reviewed. This information will also be provided to HCRN who will distribute to the site investigator/participating sites for submission to their respective IRB according to the local IRB's policies and procedures.
The DSMB review will include but is not limited to:

- Adverse event summary report
- Audit results if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

The DSMB will review study data at least semi-annually while subjects are on study treatment.. Issues of immediate concern by the DSMB will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with HCRN to address the DSMB's concerns.

13.3 Data Quality Oversight Activities by HCRN

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. For cause audits may be performed as necessary. During onsite monitoring visits, source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

The trial site may also be subject to quality assurance audit by Genentech or its designee as well as inspection by appropriate regulatory agencies.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform (EDC system), a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. Select data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, Genentech, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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APPENDIX I: MANAGEMENT OF ATEZOLIZUMAB-SPECIFIC ADVERSE EVENTS

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

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.

Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • Consider withholding atezolizumab
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. • For recurrent events, or events with no improvement after 48-72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact HCRN. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 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 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Sponor-Investigator is available to advise as needed.

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

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

Sponsor-Investigator is available to advise as needed

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment.

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

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

Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Event	Management
In patients with HCC	
AST/ALT is within normal limits at baseline and increases to > 3×ULN to ≤ 10×ULN or AST/ALT is > ULN to ≤ 3×ULN at baseline and increases to > 5×ULN to ≤ 10× ULN or AST/ALT is > 3×ULN to ≤ 5×ULN at baseline and increases to > 8×ULN to ≤ 10×ULN	• Monitor LFTs more frequently until return to baseline values. • Withhold atezolizumab for up to 12 weeks after event onset. [a] **Events of > 5 days' duration:** • Consider initiating treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. • If event resolves to baseline or to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to baseline or to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor-Investigator. [c]
AST or ALT increases to >10×ULN or total bilirubin increases to > 3×ULN	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [c] • Consider patient referral to GI 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 baseline, taper corticosteroids over ≥ 1 month.

LFT = liver function tests.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Sponsor-Investigator is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Sponsor-Investigator is available to advise as needed

GASTROINTESTINAL EVENTS

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

Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Sponsor-

investigator is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Sponsor-Investigator is available to advise as needed

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab.

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.

Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism. • Consider patient referral to endocrinologist.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab. c
Symptomatic adrenal insufficiency, Grade 2−4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging.

	• Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. ◦ Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Sponsor-investigator is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Sponsor-Investigator is available to advise as needed

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events).

Management Guidelines for Ocular Events

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Sponsor-investigator is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Sponsor-Investigator is available to advise as needed

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of GI 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 below.

Management Guidelines for Immune-Related Myocarditis

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

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Sponsor-investigator is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Sponsor-Investigator is available to advise as needed

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

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

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

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

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

Management Guidelines for Infusion-Related Reactions

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

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

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

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

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

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

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

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Sponsor-investigator is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit−risk ratio.

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

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests.

Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, permanently discontinue atezolizumab. [c]
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, permanently discontinue atezolizumab. [c]
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to GI specialist. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Sponsor-investigator is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Sponsor-Investigator is available to advise as needed

DERMATOLOGIC EVENTS

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

Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1−2 mg/kg/day if event does not improve within 48−72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor- Investigator. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [c]
Stevens Johnson syndrome or toxic epidermal necrolysis (any grade)	• Additional guidance for Stevens Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Sponsor-investigator is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Sponsor-Investigator is available to advise as needed

NEUROLOGIC DISORDERS

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

Management Guidelines for Neurologic Disorders

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Sponsor-investigator is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Sponsor-Investigator is available to advise as needed

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness.

Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted. Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines below.

Management Guidelines for Immune-Mediated Meningoencephalitis

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

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Sponsor-Investigator is available to advise as needed.

RENAL EVENTS

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as nonsteroidal 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. If no alternative cause of acute kidney injury is identified, patients with signs and symptoms of acute kidney injury, in the absence of an identified alternate etiology, should be treated according to the management guidelines for immune-related renal events in the table below.

Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function closely, including creatinine and urine protein, until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Sponsor-investigator is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Sponsor-Investigator is available to advise as needed

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are amongst the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatinine-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.

Management Guidelines for Immune-Related Myositis

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

	• Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases • Initiate treatment with corticosteroid equivalent to 1-2 mg/kg/day IV methylprednisolone or higher dose bolus if subject is severely compromised (eg, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Sponsor-investigator is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Sponsor-Investigator is available to advise as needed

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab. Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged. Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

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

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

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

Patients with suspected HLH or MAS should be treated according to the guidelines below

Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Sponosr-Investigator. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids and/or an immunosuppressive agent. • If event does not respond to treatment within 24 hours, contact Sponsor-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.

IMMUNE-MEDIATED PERICARDIAL DISORDERS

The following recommendations will be included in the updated atezolizumab Investigator's Brochure (IB) and study protocols for immune-mediated pericardial disorders:

- The diagnosis of immune-mediated pericarditis should be considered in all patients presenting with chest pain.
- The diagnosis of immune-mediated pericardial effusion and cardiac tamponade should be considered in all patients presenting with chest pain associated with dyspnea or hemodynamic instability.
- Cardiac tamponade should be treated as a medical emergency and consultation with a cardiologist should be sought for further management.
- 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.
- Atezolizumab should be withheld for patients with suspected immune-mediated pericardial disorders.
- Atezolizumab should be permanently withdrawn for any grade confirmed immune-mediated pericardial disorders.
- Caution should be used when considering the use of atezolizumab in a patient experienced a pericardial disorder on prior treatment with other immune-stimulatory anticancer agents.

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