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Columbia University Irving Medical Center
Herbert Irving Comprehensive Cancer Center
CUMC IRB – AAAT0174

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TITLE: A phase II trial of atezolizumab + carboplatin + etoposide with liver-directed radiotherapy in extensive stage small cell lung cancer (ES-SCLC) patients with liver metastases

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Study Agent:	Radiation therapy
Other Agent:	Atezolizumab, carboplatin, etoposide

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Site Principal Investigator and Contact Information:	Other Investigators at Site
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Protocol Signature Page

I confirm that 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 ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I will promptly submit the protocol to the applicable IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modification made during the course of the study must first be approved by the IRB, prior to implementation except when such modification is made to remove an immediate hazard to the subject. I certify that I, and the study staff, have received the requisite training to conduct this research protocol. I agree to maintain adequate and accurate records in accordance with Columbia University and Herbert Irving Comprehensive Cancer Center policies, Federal, state and local laws and regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

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Signature of Principal Investigator Date

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Principal Investigator Name (Print)

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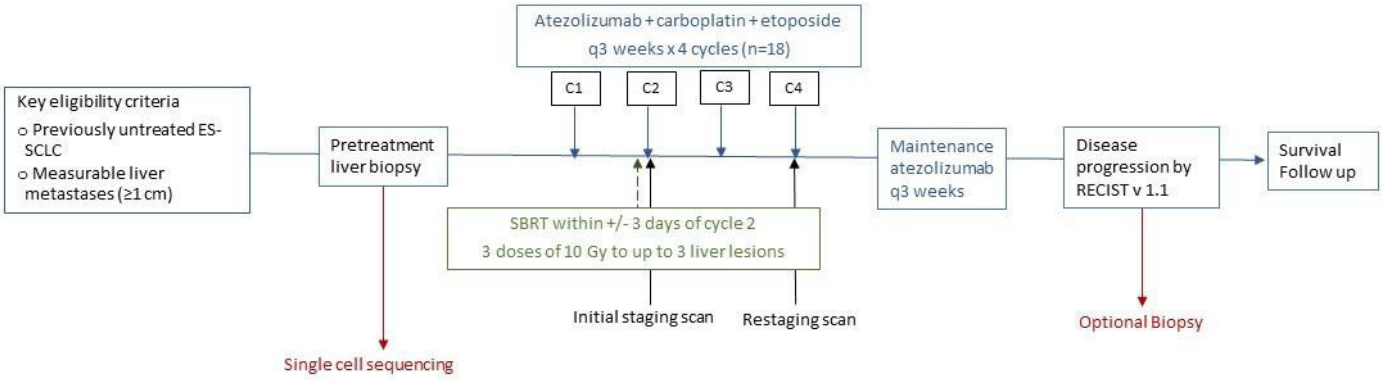
Name of Institution

Protocol Synopsis

Title	A phase II trial of atezolizumab + carboplatin + etoposide with liver-directed radiotherapy in extensive stage small cell lung cancer (ES-SCLC) patients with liver metastases
Short Title	Atezo+chemo+RT in ES-SCLC with liver metastases
Protocol Number	AAAT0174
Phase	Phase II
Methodology	Single arm, open label study
Study Duration	36 months
Study Center(s)	Multicenter, projected 3 centers in total
Objectives	To assess the efficacy of liver-directed SBRT added to standard of care first line chemoimmunotherapy as measured by the 6 month progression free survival rate in ES-SCLC patients with liver metastases
Number of Subjects	18 patients
Diagnosis and Main Inclusion Criteria	Previously untreated ES-SCLC with measurable liver metastases
Study Product, Dose, Route, Regimen	Carboplatin AUC 5 mg/ml/min IV, Day 1, q21 days x4 cycles Etoposide 100 mg/m2 IV, Days 1-3, q21 days x 4 cycles Atezolizumab 1200 mg IV, Day 1, q21 days until disease progression SBRT within +/-3 days of cycle 2, 10 Gy 3 doses on alternating days
Duration of administration	Four 21-day cycles of atezolizumab+chemotherapy followed by atezoliuamb maintenance until progression
Reference therapy	Atezolizumab + carboplatin+ etoposide
Statistical Methodology	A total of 16 evaluable patients are needed to detect an increase in 6 month PFS from 20% (historical control) to 45%. This estimate was based on one-sided exact binomial test, with a type I error of 0.10 and power of 0.80. To account for a 10% dropout rate, 18 patients will be accrued to the study. The remainder of the analysis is exploratory.

Protocol Schema:



Contents

1 INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Columbia University Irving Medical Center institutional research policies and procedures.

The standard of care first-line treatment for extensive stage SCLC is atezolizumab with platinum-etoposide, based on the IMpower133 study. In this study, the overall survival benefit with atezolizumab was 16.8 vs. 11.2 months in patients without liver metastases (63% of patients) but only 9.3 vs.7.8 months in patients with liver metastases (37% of patients)[1]. These data and retrospective studies highlight that liver metastases are a negative prognostic factor in SCLC[2]. Additionally, the IMpower133 results suggest that liver involvement is associated with resistance to immune checkpoint inhibitors (ICI) in SCLC, an observation also seen in metastatic melanoma and non-small cell lung cancer[3]. It is hypothesized that liver-mediated tolerance mechanisms may induce systemic immune suppression that contributes to ICI resistance[4,5]. Using radiation therapy (RT) in this context may be a viable approach to overcoming resistance. Apart from direct cytotoxic effects, RT promotes tumor-specific immunity through several mechanisms. Radiation upregulates MHC-I expression on tumor cells and generates tumor neoantigens that promote immune surveillance. RT also stimulates the release of damage associated molecular patterns (DAMPs) after immunogenic cell death that promote effective T cell priming[6,7]. Preclinical studies suggest that RT can act synergistically with ICI to enhance the anti-tumor response[8]. Early clinical data also suggest that the combination of RT with ICI can promote a strong and durable anti-tumor response within and beyond the boundaries of the radiation target[9-11]. We therefore propose a phase II trial adding stereotactic body radiation therapy (SBRT), directed at liver metastases, to standard of care treatment atezolizumab+chemotherapy in SCLC. We hypothesize that this combination will lead to improved local control and progression free survival in ES-SCLC with liver involvement, and provide key insights into the mechanisms of immune response/evasion.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To assess the efficacy of liver-directed SBRT when added to standard of care atezolizumab+chemotherapy as measured by the progression free survival rate at 6 months

2.2 Secondary Objective

- To assess the efficacy of adding liver-directed SBRT as measured by overall survival, progression-free survival, and the overall response rate
- To evaluate the feasibility and safety of adding liver-directed SBRT to standard of care atezolizumab+chemotherapy
- To describe the rate of in-field local control and out of field disease progression.

3 BACKGROUND

SCLC Background

SCLC accounts for approximately 15% of new cases of lung cancer, and is responsible for an estimated 250,000 annual deaths worldwide. Smoking is the strongest risk factor for SCLC development and the institution of smoking cessation programs has led to decreasing incidence.[12] Nevertheless, treatment options are limited and survival remains poor. SCLC is characterized by rapid tumor growth, earlier development of distant metastases and a high degree of genomic instability. Extensive stage (ES) disease is typically very sensitive to upfront chemotherapy with initial response rates of 60-65% but the disease rapidly recurs leading to median overall survival estimates historically under 10 months[13,14]. For decades the only therapeutic modalities with demonstrated clinical benefit were platinum-based chemotherapy and radiation, although in recent years there have been promising developments incorporating the use of immunotherapy and targeted agents.

The phase III IMpower133 trial introduced a new standard of care for the first-line treatment of ES-SCLC. Newly diagnosed ES-SCLC patients were randomly assigned to receive carboplatin+etoposide with either atezolizumab or placebo for four 21-day cycles followed by atezolizumab or placebo. Median overall survival (OS) was 12.3 months with atezolizumab vs 10.3 months in the placebo group (p=0.007). PFS was longer, at 5.2 months, with atezolizumab versus 4.3 months with chemotherapy alone.[1] Based on these results the FDA approved atezolizumab in the first line setting in March 2019. Similarly, the addition of durvalumab to platinum based chemotherapy was associated with a 27% improvement in overall survival in the CASPIAN trial, which led to recent FDA approval in March 2020[15].

Thoracic radiation and/or prophylactic cranial radiation can also be included in first-line treatment of ES-SCLC. Consolidative thoracic RT may be considered in patients with complete response to initial systemic therapy or those with low-bulk disease. Jeremic et al demonstrated that accelerated hyperfractionated RT as consolidative treatment was associated with an improved median survival of 17 vs 11 months.[16] The Dutch CREST trial showed an improvement in 2-year but not 1-year survival with consolidative RT.[17] Notably thoracic RT can potentially add significant toxicity depending on the radiation regimen. The role of thoracic RT is under investigation in the chemoimmunotherapy era.

Prophylactic cranial radiation (PCI) is a controversial treatment modality in ES-SCLC, explored due to high rates of brain metastases. In the rare patients who achieve a complete response to chemotherapy, a meta-analysis showed that PCI was associated with a 5.4% survival benefit at 3 years[18]. Additionally, in a randomized trial of PCI vs observation in ES-SCLC patients who had any response to chemotherapy, the PCI arm had reduced incidence of symptomatic brain metastases at one year with improved 1 year OS (27.1% vs 13.3%)[19]. However, this study did not standardize the radiation dose and did not require brain imaging prior to PCI, which may have skewed the results. A subsequent Japanese study found no difference in the OS of patients who received PCI and all patients had a brain MRI prior to radiation.[20] Therefore, PCI or close brain

surveillance imaging are considered acceptable options per the NCCN guidelines, but more definitively beneficial treatments are needed.

Rationale for targeting patients with liver metastases

Several studies have highlighted that liver metastases are a negative prognostic factor in SCLC. In an analysis of 6459 patients with SCLC with metastatic disease from the Surveillance, Epidemiology, and End Results (SEER) database collected between 2010 and 2012, the incidence of liver metastases was 61.9%, and in one third of patients the liver was the only site of metastatic disease. SCLC with liver metastases had a reduced median OS of 4 months compared to 6 months among patients with other metastases ($p=0.017$)[21]. Other retrospective studies also demonstrated poor outcomes for patients with liver metastases, including worse response to chemotherapy[22,23].

A proposed mechanism for worse survival outcomes among patients with liver involvement is that the liver is an immunosuppressive organ with impaired immune surveillance of intrahepatic metastases[2]. This hypothesis may also account for poor response to immunotherapy seen in patients with liver metastases. In the aforementioned IMpower133 study, patients without liver metastases (63% of patients) who received atezolizumab with chemotherapy had an OS of 16.8 months versus 11.2 months in those who received chemotherapy alone. In the 37% of patients who had liver metastases, however, OS was 9.3 months with atezolizumab versus 7.8 months with chemotherapy alone (HR 0.81, 95% CI 0.55-1.20). A similar effect was seen on PFS where patients with liver metastases had no significant benefit from the addition of atezolizumab (4.3 months with atezolizumab vs. 4.2 months with placebo)[1]. These results suggest that not only are liver metastases a poor prognostic factor in SCLC, but they also associate with immunotherapy resistance.

The resistance to immune checkpoint inhibitors seen in SCLC with liver metastases has also been observed in other cancer types including non-small cell lung cancer (NSCLC) and melanoma. Tumeh et al. assessed the response to pembrolizumab in several cohorts of patients treated under the Keynote 001, 002, and 006 trials. Presence of liver metastases was an independent predictive marker of reduced PFS among melanoma patients in a multivariable analysis (odds ratio of PFS 1.85, 95% CI 1.37-2.50, $p<0.0001$). Among 223 patients with melanoma, those with liver metastases had a PFS of 5.1 months compared to 20.1 months for patients without liver metastases ($p=0.001$). Similarly, among 165 patients with NSCLC who were treated with pembrolizumab, including 46 with liver metastases, PFS was significantly reduced in the liver metastases group (1.28 months vs 4.03 months, $p=0.0094$).[3] In this and other retrospective studies in NSCLC, worse clinical outcomes in patients with liver metastases were observed irrespective of PD-L1 status[24].

The degree of tumor CD8+ T cell infiltration at the invasive margin has previously been shown to correlate with response to immunotherapy in melanoma. Tumeh et al. also used pre-treatment tumor samples from melanoma patients who participated in the Keynote trials to show that the subset of patients with liver metastases had depleted marginating CD8+ T cells in their distant and cutaneous metastases[3]. A separate group showed that melanoma patients with liver

metastases had a lower CD8/Foxp3+ T reg ratio and a decreased percentage of activated PD-1+/CTLA-4+ CD8 cells in the immune infiltrates of the distant primary tumor.[4] These findings suggest that the presence of liver metastases has an immunosuppressive effect beyond the liver. However, the systemic impact of liver metastases on antitumor immunity is not well understood.

Preclinical rationale for combining radiation with immunotherapy

Using radiation in combination with immunotherapy may be a promising approach to overcome immunotherapy resistance in patients with liver metastases. Tumor cells evolve to avoid recognition and destruction by the immune system through several escape mechanisms including downregulation of MHC class I expression, upregulation of inhibitory cytokines, and increased infiltration of the tumor by immunosuppressive cells. Beyond its cytotoxic effects through lethal DNA damage, radiation may convert the tumor immune microenvironment into an immune activated state.

Evidence of immunomodulation via radiation therapy (RT) includes upregulation of MHC class I expression on tumor cells in a dose-dependent manner after RT exposure[25]. RT also results in increased peptide production, including formation of novel proteins, and enhanced antigen presentation to primed CD8+ T cells, augmenting the anti-tumor response. Additionally, RT promotes the release of inflammatory cytokines and chemokines by stressed tumor and stromal cells that attract immune effector cells into the tumor microenvironment. This includes the upregulation of interferon by infiltrating myeloid cells, which augments the cross-priming capacity of dendritic cells to expand antigen specific T cells and produce T cell dependent tumor regression[26]. Furthermore, local irradiation promotes increased infiltration and retention of tumor antigen-reactive CD8+ T cells[27]. Notably, in mouse models, CD8+ T cell depletion largely diminishes the therapeutic effect of RT[28]. Together the aforementioned mechanisms may augment the immune system's anti-tumor response and contribute to the abscopal effect, a rare phenomenon, where radiation induces metastatic tumor regression at unradiated sites.

Despite the adaptive immune response that may be triggered by radiation, tumors can also develop resistance mechanisms to escape immune mediated destruction. One mechanism is through the inhibition of T cell function by upregulation of PD-L1 on tumor cells after irradiation through interferon γ mediated signaling[29]. Based on this finding Deng et al. administered anti-PD-L1 blockade with high dose ionizing irradiation (IR) and demonstrated enhanced tumor regression in an animal model. Additionally they found evidence of the abscopal effect in their model. In evaluating the immunomodulating effects of combination treatment, they showed that it enhanced tumor antigen-specific T cell function locally and systemically and decreased inhibitory myeloid-derived suppressor cells (MDSCs) within the tumor microenvironment[8]. Other groups have also provided evidence to support the use of combination PD-L1 or CTLA-4 blockade with radiation in enhancing the anti-tumor response in animal models[29-31].

Clinical rationale for combining radiation with immunotherapy

Although the clinical evidence for the combination of radiation therapy and immunotherapy is more limited, numerous case reports, retrospective studies, early stage trials, and ongoing prospective trials highlight the potential for this approach in augmenting the anti-tumor response.

Several phase I trials suggested the safety of combining ipilimumab with radiation in the treatment of solid malignancies. However the efficacy of anti-CTLA-4 blockade with hypofractionated radiation was not robust with clinical benefit defined as partial response or stable disease outside of the radiation field seen in 23-36% of patients[31-33] In a prospective trial of 22 stage IV melanoma patients 50% of patients had a clinical benefit, including 27% who achieved an ongoing complete response[32]. In these trials the combination therapy was generally well tolerated. Clinical benefit was associated with increased markers of T cell reinvigoration and expansion of CD8+ T cells[33]. The increased expression of PD-L1 with this treatment suggests a role for adding anti- PD-1/PD-L1 targeted treatment[31].

Notably, in one study, liver irradiation produced increased proportions of T cells expressing ICOS, GITR, and 4-1BB, that are associated with proimmune activity. However, it also increased the proportion of cells expressing LAG3, TIM3, and PD1, which promote immune inhibition. This finding suggests that hepatic irradiation supports early systemic immune activation with compensatory mechanisms of increasing inhibitory antigen expression[33].

The clinical data regarding anti PD-1/PD-L1 blockade in combination with RT is more limited. In completed and ongoing trials a variety of schedules for immunotherapy and radiation administration have been adopted but the optimal timing and dosage for RT has not been established. In NSCLC, the PACIFIC trial randomized 713 patients with unresectable NSCLC to chemoradiation followed by adjuvant treatment with durvalumab, an anti-PD-L1 agent, or placebo. It demonstrated a significantly prolonged PFS of 16.8 months for the durvalumab patients compared to 5.6 months for those who received placebo[34].

However other studies suggest the superior efficacy of concurrent RT with immunotherapy. Despite inherent limitations of the study design, in a retrospective study of 758 patients who received immunotherapy and radiation, concurrent ICB with RT and hypofractionated RT was associated with improved OS[35]. In a recent phase I trial, 21 patients with stage III NSCLC received pembrolizumab, an anti-PD-1 agent, concurrently with chemoradiation in a 3+3 design. The 12 month PFS was 69.7% in this trial compared to 55.7% seen in the PACIFIC study. Of note, both trials had elevated rates of pneumonitis, including 33% of patients with at least grade 2 pneumonitis in the phase I trial[34,36]. A phase II study of concurrent chemoradiation with pembrolizumab is underway. A signal for synergy between radiation and anti-PD-1 was also seen in the metastatic NSCLC setting in a phase II trial of pembrolizumab with stereotactic body RT (SBRT) on a single tumor site. In this study, the overall response rate was 36% at 12 weeks with combination treatment compared to 18% with pembrolizumab alone. However the trial did not meet its prespecified end point critiera of 50% ORR at 12 weeks for the combination treatment group[10]. In the oligometastatic disease setting, a single-arm phase II study investigating pembrolizumab following local ablative therapy revealed improved PFS compared to historical controls[9].

The trials of combination immunotherapy with RT in ES-SCLC are still in early phases and mostly ongoing. In a phase I trial, patients with ES-SCLC who completed induction chemotherapy received 45 Gy of thoracic RT in 15 daily fractions along with pembrolizumab every 3 weeks for up to 16 cycles in a 3+3 dose escalation design. Thirty-three patients completed treatment per protocol with no dose limiting toxicities and few high-grade adverse events. Notably the trial enrolled patients regardless of their response to induction chemotherapy and PD-L1 status. The reported median PFS was 6.1 months and OS was 8.4 months compared to historical results of 4 months PFS and 8 months OS with thoracic RT alone in chemotherapy responders in a phase III trial[17,37]. Although the clinical benefits are not clear from this trial, a larger study with a homogeneous population is necessary to assess relative efficacy. Several ongoing trials are also evaluating the combination of thoracic RT with anti-CTLA4 and/or anti-PD-1 after induction chemotherapy (NCT03923270, NCT03043599). Additionally there are a few studies under way of immunotherapy with RT in the second line setting (NCT02701400, NCT03262454). Of note, in all of these trials RT has been targeted at thoracic lesions. To our knowledge, no trials with RT targeting metastatic lesions in combination with ICI have been previously done.

Stereotactic radiation therapy for liver metastases

Stereotactic radiation therapy for liver lesions has been well described for both primary hepatocellular carcinoma and metastatic disease[38-40]. In a large multi-institutional retrospective series of 427 patients with 568 liver metastatic lesions (from various histologies) treated with SBRT, local control (LC) of the treated lesions was durable. Median duration of local control was 51 months. Small tumors (< 40 cm^3) were noted to have improved median local control rates of 52 months, compared to 39 months for tumor volumes ≥ 40 cm^3. No grade 3 or higher toxicity was reported. The selected dose/fractionation of 30 Gy in 3 fractions in the study has also been shown to be well tolerated[40]. In a phase I dose-escalation study of SBRT for liver metastases, the 30 Gy in 3 fraction regimen shows no grade 3 or higher toxicity[41]. This regimen is also an accepted treatment dose for the current SABR-COMET-10 phase III trial analyzing the effect of ablative SBRT in patients with oligometastatic disease[42].

The combination of SBRT of liver lesions with immunotherapy has been less well studied. A small series of five patients with unresectable hepatocellular carcinoma who were treated with SBRT followed by anti-PD1 antibodies had 1-year LC and OS rates of 100%. One patient had grade ≥ 3 toxicities (pneumonitis and skin reaction), but no radiation-induced liver toxicity was noted[43].

Given the findings that patients with ES-SCLC and liver involvement have a poor prognosis and a limited response to chemo-immunotherapy, we aim to augment the systemic anti-tumor immune response with RT targeted to liver metastases administered in addition to standard of care treatment. Preclinical data shows that radiation upregulates MHC class I expression, increases tumor antigen release, enhances CD8+ T cell infiltration, modulates the tumor immune microenvironment and upregulates PD-L1 expression, and that immunotherapy can synergize with RT to enhance tumor regression. Prior clinical studies also support a synergistic role for these treatment approaches. We hypothesize that combination RT with chemo-immunotherapy

will lead to improved local control and progression free survival in ES-SCLC patients with liver involvement, and provide key insights into the mechanisms of immune response/evasion. Administration of radiation at the beginning of cycle 2 of chemoimmunotherapy will allow patients to receive the putative immunogenic benefit of radiation without compromising prompt initiaton of standard of care chemotherapy with cycle 1 while awaiting radiation planning.

4 INVESTIGATIONAL AGENTS

4.1 Atezolizumab

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016)[44,45]. Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and clinically relevant associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy. Atezolizumab is approved for the treatment of urothelial carcinoma, NSCLC, SCLC, and triple-negative breast cancer.

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

4.1.1 Preclinical Data

Comprehensive pharmacology, PK, and toxicology evaluations have been undertaken with atezolizumab.

Atezolizumab binds to its target with high affinity and blocks binding to receptors B7-1 and PD-1. It was engineered to reduce its binding to Fcγ receptors and exhibits minimal binding to human Fcγ receptors. Several studies demonstrated enhanced anti-tumor immunity when administered to mice with established tumors of colorectal and melanoma origin, suggesting PD-L1 blockade as a compelling strategy for enhancing the anti-tumor T cell response in solid tumors.

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding toxicity and pharmacokinetics.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the

anticipated pharmacologic activity of down-modulating the PD-L1/PD-1 pathway and supported entry into clinical trials in patients.

For further details please refer to the IB for atezolizumab.

4.1.2 Clinical Pharmacokinetics and Immunogenicity

The clinical pharmacokinetics for atezolizumab have been derived from the following atezolizumab monotherapy studies: PCD4989g, JO28944, IMvigor210, IMvigor211, BIRCH, POPLAR, FIR, and OAK.

Per the IB, the pharmacokinetics of atezolizumab monotherapy have been characterized in patients in Study PCD4989g at doses 0.01 mg/kg to 20 mg/kg q3w, including the fixed dose 1200 mg (equivalent to 15 mg/kg). Exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg. While a subset of antidrug antibody (ADA)-positive patients in Study PCD4989g receiving 0.3 to 3 mg/kg atezolizumab q3w experienced a reduction of atezolizumab Cmin to below the PK assay lower limit of quantification (LOQ), patients receiving 10 to 20 mg/kg atezolizumab, including the fixed 1200 mg dose, maintained geometric mean Cmin that was in excess of both the LOQ and the target serum concentration of 6 μg/mL[46].

Based on an analysis of exposure, safety, and efficacy data, the following factors had no clinically relevant effect: age (21- 89 years), body weight, sex, albumin levels, tumor burden, region or race, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status. Positive ADA status against atezolizumab led to approximately 13% reduction in overall exposure.

Combined atezolizumab PK data obtained in metastatic urothelial carcinoma patients from IMvigor210 and IMvigor211 and in NSCLC patients from BIRCH, POPLAR, FIR, and OAK were consistent with the Phase Ia Study PCD4989g popPK model estimates. These results suggest that atezolizumab PK characteristics are similar across a range of tumor types and studies.

Antidrug antibodies to atezolizumab have been observated at all dosing levels (≤1 mg/kg to 20 mg/kg and 1200 m). Treatment-emergent ADAs were detected at 1 or more post dose timepoints in ADA positive patients across 20 studies of atezolizumab used as monotherapy or in combination. ADA status appeared to have no clinically relevant impact on pharmacokinetics or safety. Although some variability was observed across the studies, overall, ADA status appeared to have no clinically relevant impact on efficacy.

The fixed dose of 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered every 3 weeks was selected on the basis of both nonclinical studies and available clinical data from PCD4989g; this was the dose used in the Impower133 study establishing the survival benefit of atezolizumab in combination with standard of care chemotherapy in ES-SCLC.

Please refer to the IB for additional data regarding clinical pharmacokinetics and immunogenicity.

4.1.3 Clinical Data to Date

As of May 2019, 101 Sponsor studies are ongoing with atezolizumab as a single agent or in combination with other therapies. Of these, efficacy or and/or safety data that are considered sufficiently robust and clinically relevant are available for more than 30 studies. The most efficacy data is available in NSCLC patients (n=1636) with trials including BIRCH, POPLAR, OAK, IMpower150, IMpower131, FIR and the NSCLC cohort of PCD4989g. Additionally 983 patients with metastatic urothelial carcinoma have been administered atezolizumab through PCD4989g, IMvigor210 and IMvigor211.

In NSCLC, use of single agent atezolizumab in the second and third line setting in the PCD4989g, FIR, OAK, POPLAR and BIRCH trials resulted in a meaningful improvement in overall survival compared to standard of care across all PD-L1 expression groups. Additionally, IMpower132 demonstrated benefit of atezolizumab with chemotherapy in NSCLC.

The clinical data for atezolizumab in SCLC comes from the IMpower133. As found in the atezolizumab IB, IMpower133 was a Phase I/III randomized, double-blind placebo-controlled study of carboplatin and etoposide (CE) with or without atezolizumab (1200 mg) in patients with chemotherapy-naïve extensive-stage SCLC.

The study met the co-primary endpoints of OS and investigator-assessed PFS in the ITT population (n=403). As of the CCOD of 24 April 2018, 238 death events had been observed in the ITT population. A statistically significant and clinically meaningful improvement was demonstrated in OS with Atezo + CE (n=201) compared with placebo(PBO) + CE (n=202):stratified HR 0.701 (95% CI 0.541, 0.909; log rank p-value <0.0069; median OS 12.3 months vs. 10.3 months). A statistically significant improvement was also demonstrated in investigator-assessed PFS (stratified HR 0.772; 95% CI: 0.624, 0.955; log-rank p-value 0.017). Consistent with the benefit observed in the overall ITT population, an OS and PFS benefit with atezolizumab + CE arm compared with PBO + CE arm was observed in the majority of the subgroups analyzed. The ORR and median DOR were similar between the treatment arms. More patients in the atezolizumab + CE arm compared with the placebo + CE arm had an ongoing response at the time of the CCOD.

4.1.4 Safety Data to Date

From the IB, pooled safety data for atezolizumab monotherapy are available for 3178 treated patients in 8 studies: IMvigor210, IMvigor211, OAK, BIRCH, POPLAR, FIR, IMmotion150, and PCD4989g.

The majority of patients (over 97%) received atezolizumab at a dose of 1200 mg q3w, and the remaining patients, from Study PCD4989g, received atezolizumab at doses in the range of 1-20 mg/kg q3w. The safety data indicate that atezolizumab was well tolerated and the observed AEs were consistent with the known mechanism of action of atezolizumab or the underlying

disease. The safety profile was generally consistent between the UC population (983 patients) and NSCLC population (1636 patients).

The majority (96.0%) of patients in the overall pooled population experienced at least one AE during the course of study treatment. Treatment-related AEs were reported in 68.2% of patients, with the most common events (≥20%) being fatigue, decreased appetite, nausea, cough, constipation, dyspnea, and pyrexia.

In the pooled population of patients receiving atezolizumab monotherapy, Grade 3-4 AEs were reported by 46.5% of patients. The most common (>3% of patients) events were anemia (5.0%), dyspnea (3.7%), fatigue (3.4%), hyponatremia (3.1%), and pneumonia (3.0%).

The overall incidence of Grade 5 AEs occurring within 30 days of last study drug intake or prior to initiation of non-protocol therapy was 3.8% (122/3178). Grade 5 AEs were reported in a variety of System Organ Classes (SOCs), and the following events were reported for more than 1 patient: death (19), pneumonia (12), sepsis (8), septic shock (5), respiratory failure (5), cardiac failure (3), sudden death (3), disease progression (3), myocardial infarction (2), lung infection (2), pulmonary sepsis (2), respiratory distress (2), pneumonia aspiration (2), pulmonary embolism (2), cerebral hemorrhage (2), cerebrovascular accident (2), ischemic stroke (2), embolism (2), and hepatic failure (2). Eleven Grade 5 events were considered by the investigator as treatment related; one case each of pulmonary hypertension, respiratory failure, death, intestinal perforation, pneumonia, sepsis, general physical condition abnormal, hepatic failure, cardiac failure, pericarditis constrictive, and toxic epidermal necrolysis.

The incidence of serious adverse events (SAEs) in the pooled population of patients receiving atezolizumab montherapy was 41.2%. The most common SAEs were pneumonia (3.1%), dyspnea (2.8%), pyrexia (2.5%), UTI (1.9%) and pleural effusion, pulmonary embolism, and sepsis (1.3%).

Safety data is also available for atezolizumab in combination with chemotherapy, as proposed in this trial. In IMpower133 patients with ES-SCLC received atezolizumab 1200 mg IV on day 1, carboplatin at AUC 5 mg/ml/min on day 1 and etoposide 100 mg/m^2 IV on days 1-3 in 21 days cycles. In the combination atezolizumab+chemotherapy group, 94.9% of patients experienced a treatment related AE. 67.7% of patients experienced a grade 3-4 AE, compared to 63.3% with chemotherapy alone. The most common grade 3-4 AEs included neutropenia (22.7%), anemia (14.1%), and thrombocytopenia (10.1%) with combination therapy. Most immune related AEs (irAEs) were graded as 1-2, including rash (18.2%), hypothyroidism (12.6%), and hepatitis (6.1%) although grade 3-4 irAE also occurred including rash (2%), infusion-related reaction (2%), and hepatitis (1.5%). 3 patients in the atezolizumab+chemotherapy group experienced a death related to trial regimen including 1 from neutropenia, 1 from pneumonia, and one from an unspecified cause. 3 patiens also died in the chemotherapy alone group (1 from pneumonia, 1 from septic shock, and 1 from cardiopulmonary failure).

4.2 Other Agent(s)

A platinum chemotherapy plus etoposide was the previous standard of care treatment for patients with ES-SCLC, and is still an approved regimen per the National Cancer Comprehensive Network guidelines. Carboplatin is preferred over cisplatin given equivalent efficacy with less risk of nephrotoxicity, neuropathy and otoxicity. The carboplatin-etoposide combination has been evaluated in several clinical trials[47-50]. The preferred dosing is etoposide 100 mg/m2 on days 1, 2, and 3 and carboplatin AUC 5 on day 1 every 21 days. Toxicities associated with this regimen include grade 3/4 myelosuppression and infection. A meta-analysis of carboplatin based regimens in ES-SCLC reported a median OS of 9.4 months, PS of 5.3 months and an objective response rate of 66%[13].

4.3 Radiation

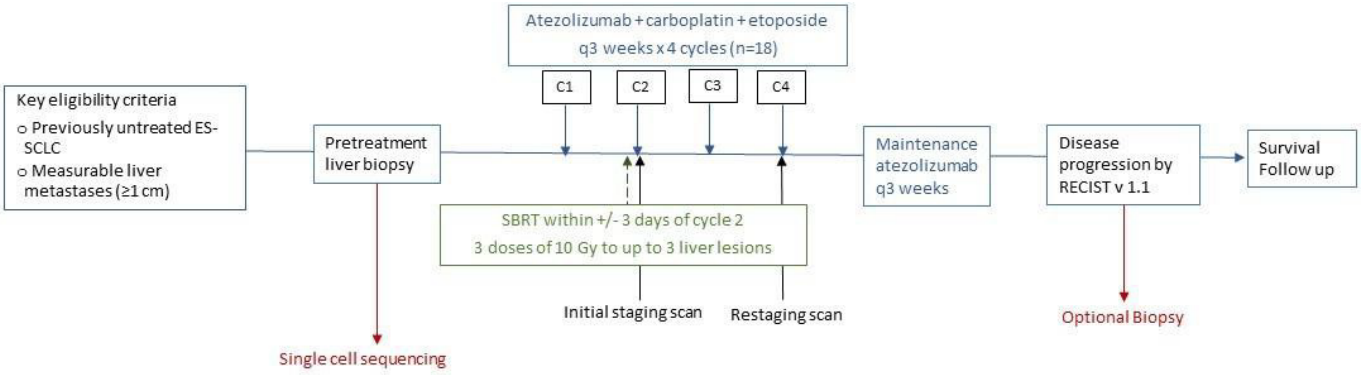
Details regarding radiation administration can be found in Section 8.2.

5 STUDY DESIGN

5.1 General Design

This is a single-arm, open-label phase II study to assess the efficacy of liver-directed SBRT added to first-line atezolizumab, carboplatin, and etoposide in ES-SCLC, as measured by 6-month PFS. We hypothesize that the addition of SBRT, directed at liver metastases, to standard of care treatment atezolizumab+chemotherapy in SCLC patients will increase the 6-month PFS by 25% as compared to 20% historical control rate[1]. A single stage design based on one-side exact binomial test will be used, with a type I error of 0.10 and a power of 80%. This design requires a total of 16 evaluable patients. If at least 6 out of 16 patients have not experienced progression at 6 months, this combination therapy will be considered worthy of further study. **Figure 1** depicts the study design. Schedules of assessments are provided in Study Calendar in **Section 12**.

Figure 1.



5.2 Intervention

All patients must undergo a mandatory biopsy of a liver lesion prior to chemotherapy initiation. Cycle 1 of chemoimmunotherapy will be administered as per standard of care, with radiation planning to be done subsequently in anticipation of liver-directed SBRT (3 doses of 10 Gy administered on alternating days to up to three liver lesions, measuring no greater than 5 cm each) to be given within +/-3 days of cycle 2.

Subjects will continue to receive study treatment (four 21-day cycles of induction chemoimmunotherapy followed by maintenance atezolizumab every 3 weeks) until disease progression or intolerance of treatment. During the maintenance phase, prophylactic cranial irradiation is permitted; consolidative thoracic radiation may be considered if deemed clinically appropriate by the treating investigator in discussion with the principal investigator.

If clinically feasible, it is recommended that the patient undergo a tumor biopsy sample collection at the time of radiographic disease progression. These data will be used to explore whether radiographic findings are consistent with the presence of a tumor. Additionally, these data will be analyzed to evaluate the association between changes in tumor tissue and clinical outcome and to further understand the potential mechanisms of progression and resistance to study treatment. This exploratory biomarker evaluation will not be used for any treatment-related decisions.

Patients will undergo tumor assessments prior to radiation administration and every 6 weeks (± 7 days) for the first 12 months following Cycle 1, Day 1, regardless of treatment dose delays. After 12 months, tumor assessments will be required every 9 weeks (± 7 days). Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by the principal investigator, or death, whichever occurs first.

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will continue to undergo tumor assessments every 6 weeks (± 7 days), or sooner if symptomatic deterioration occurs. For these patients, tumor assessments should continue every 6 weeks (± 7 days), regardless of time in the study, until study treatment is discontinued.

Patients who discontinue treatment for reasons other than radiographic disease progression (e.g., toxicity) will continue scheduled tumor assessments at the same frequency as would have been followed if the patient had remained on study treatment (i.e., every 6 weeks [± 7 days] for the first 12 months following Cycle 1, Day 1 and then every 9 weeks [± 7 days] thereafter, regardless of treatment dose delays) until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by the principal investigator, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.

5.3 Specimen Collection and Processing

Tumor Tissue

Tissue obtained from the pre-treatment liver biopsy will be processed for standard pathology evaluation and remaining tumor tissue will be partitioned and processed in the following ways:

- Snap-frozen in liquid nitrogen at -80 degrees Celcius for future DNA and RNA extraction

- Processed as single-cell suspensions of tumor and infiltrating immune cells and then frozen at -80 degrees Celcius for future T-cell assays
- Processed as formalin-fixed tissue and embedded in paraffin for future IHC assays

Sufficient material must be collected to permit all planned correlative studies including (1) frozen material for DNA/RNA extraction, (2) FFPE material for IHC, and (3) digested cellular material for single-cell suspensions. Adjudication of sufficient material for (1) and (2) will be further certified by review of Diff-Quik or H&E stained slide/touch prep from frozen and FFPE material to ensure tumor is present in collected material Adequacy of material for single-cell suspensions will be determined by collection of at least 20 million live cells total.

Peripheral Blood

- Mononuclear cells will be isolated from patients by centrifugation and cryopreserved for later analysis by ELISpot assay, FLOW cytometry, and/or CyTOF/CyTEK.
- Plasma will be stored for germline sequencing as a companion to somatic tumor DNA sequencing

Please see **Laboratory Manual** for further details.

6 SUBJECT SELECTION AND WITHDRAWAL

Patients may be eligible if they are chemotherapy- and immunotherapy-naïve and have ES-SCLC with liver metastases if the following criteria are met.

6.1 Inclusion Criteria

1. Age≥ 18 years
2. Histologically or cytologically confirmed ES-SCLC (per the Veterans Administration Lung Study Group [VALG] staging system)
3. No prior treatment for ES-SCLC
4. ECOG performance status 0 or 1
5. Patients with a history of treated, asymptomatic CNS metastases are eligible providing they meet the following criteria
    - Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)
    - No ongoing requirement for corticosteroids as therapy for CNS disease
    - No stereotactic brain radiation within 7 days
    - No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
    - Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to randomization, if all other criteria are met.

6. At least one liver metastasis measuring 1 cm.
7. Measurable disease, as defined by RECIST v1.1, in addition to the liver lesion(s) to which SBRT is planned.
8. Patients must submit a pre-treatment tumor tissue sample from a liver metastasis. Tumor tissue must be obtained prior to the start of treatment.
9. Adequate hematologic and end organ function, defined by the following laboratory results:
    - ANC ≥1500 cells/μL without granulocyte colony-stimulating factor support
    - Lymphocyte count ≥500/μL
    - Platelet count ≥100,000/μL without transfusion
    - Hemoglobin ≥9.0 g/dL Patients may be transfused to meet this criterion.
    - INR or aPTT ≤1.5×upper limit of normal (ULN)

      This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.
    - AST, ALT, and alkaline phosphatase ≤5×ULN
    - *Serum albumin ≥ 25 g/L (2.5 g/dL)*
    - Serum bilirubin ≤1.25×ULN
        - Patients with known Gilbert disease who have serum bilirubin level ≤3×ULN may be enrolled.
    - Serum creatinine ≤1.5×ULN
10. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods as defined below:

    - Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 6 months after the final dose of atezolizumab, carboplatin and etoposide
    - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.
    - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception
11. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

With female partners of childbearing potential or pregnant female partners, men must remain

abstinent or use a condom during treatment with atezolizumab and chemotherapy (i.e.,carboplatin and etoposide) and for at least 6 months after the last dose of atezolizumab and chemotherapy to avoid exposing the embryo.

- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence and withdrawal are not acceptable methods of contraception.

12. Negative HIV test at screening, with the following exception: patients with a positive HIV test at screening are eligible, provided they are stable on anti-retroviral therapy, have a CD4 count[3] 200/μL, and have an undetectable viral load
13. Ability to understand and the willingness to sign a written informed consent document.
14. Ability to comply with the study protocol, in the investigator's judgment

6.2 Exclusion Criteria

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

1. Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments
2. Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥1 week prior to randomization
3. Leptomeningeal disease
4. Prior radiation treatment of SCLC outside of the CNS
5. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently). Patients with indwelling catheters (e.g., PleurX®) are allowed.
6. Uncontrolled or symptomatic hypercalcemia (>1.5 mmol/L ionized calcium or calcium >12 mg/dL or corrected serum calcium >ULN)
7. Patients who are receiving denosumab prior to randomization must be willing and eligible to discontinue its use and replace it with a bisphosphonate while in the study.
8. Malignancies other than SCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS >90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous-cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
    a. Prior radiation for non-SCLC malignancies >5 years prior to randomization will be permitted, with the exception of those who have undergone liver-directed treatments
9. Child-Pugh class B cirrhosis or worse
10. History of liver-directed ablative therapy for any indication, including radiation, chemoembolization, radiofrequency ablation, or other similar modalities
11. Women who are pregnant, lactating, or intending to become pregnant during the study. Pregnant women are excluded from this study because carboplatin and etoposide are category D agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in

nursing infants secondary to treatment of the mother with atezolizumab, breastfeeding should be discontinued if the mother is treated with atezolizumab.

12. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
13. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
14. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 21.1 for a more comprehensive list of autoimmune diseases)
    a. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
    b. Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen are eligible for this study.
15. Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted, provided that they meet the following conditions:
    - Rash must cover less than 10% of body surface area
    - Disease is well controlled at baseline and only requires low potency topical steroids
    - No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency, or oral steroids)
16. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
    - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
17. Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C
    - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. HBV DNA must be obtained in these patients prior to randomization.
    - Patients positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV RNA.
18. Active tuberculosis

19. Severe infections within 4 weeks prior to study initiation and at the time of enrollment, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
20. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina
    - Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
21. Major surgical procedure other than for diagnosis within 28 days prior to randomization or anticipation of need for a major surgical procedure during the course of the study
22. Prior allogeneic bone marrow transplantation or solid organ transplant
23. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk for treatment complications
24. Previous anti-cancer therapy for ES-SCLC
25. Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to enrollment
26. Administration of a live, attenuated vaccine (e.g., FluMist®) within 4 weeks before randomization or anticipation that such a live attenuated vaccine will be required during the study
    - Influenza vaccination should be given during influenza season only (approximately October through May in the Northern Hemisphere and approximately April through September in the Southern Hemisphere).
    - Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to randomization, during treatment or within 90 days following the last dose of atezolizumab/placebo.
27. Prior treatment with immune checkpoint blockade therapies, anti−PD-1, and anti−PD-L1 therapeutic antibodies
28. Treatment with systemic immunosuppressive medications (including, but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to randomization
    - Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Principal Investiator
    - The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical

insufficiency are allowed.

29. History of allergic reactions to carboplatin or etoposide
30. Uncontrolled tumor-related pain:
    a. Patients requiring pain medication must be on a stable regimen at study entry.
    b. Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.
    c. Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
31. Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment: Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
32. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
33. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment.

6.3 Inclusion of Women and Minorities
Both men and women of all races and ethnic groups are eligible for this trial.

6.4 Subject Recruitment
Patients will be recruited from the referral population within the investigator and co-investigators' clinical practices.

6.5 Early Withdrawal of Subjects
6.5.1 When and How to Withdraw Subjects
Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator determines it is in the best interest of the patient
- Use of another non-protocol anticancer therapy
- Pregnancy
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see **Section**

6.5.2 for details)

- If one component of study treatment is discontinued permanently because of tolerability concerns, the patient may continue with other components of study treatment until disease progression if agreed upon by the investigator and patient
- If the patient fails to comply with the defined treatment plan and follow-up evaluations
- If the patient withdraws consent for continued participation

6.5.2 Treatment Beyond Radiographic Progression

To better accommodate standard clinical practice which is guided by the fact that these patients have, in general, limited treatment options and such options also have limited efficacy and significant toxicity, patients may be considered for treatment beyond radiographic progression per RECIST v1.1 at the discretion of the investigator and after appropriate discussion with the patient and obtaining informed consent, only if all of the following criteria are met:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-permitted medical interventions

- Patients must provide written consent to acknowledge deferring alternative treatment options in favor of continuing study treatment at the time of initial progression.

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 should be closely monitored clinically and a follow-up scan should be performed in 6 weeks, or sooner if symptomatic deterioration occurs. Treatment should be discontinued if clinical deterioration due to disease progression occurs at any time or if persistent disease growth is confirmed in a follow-up scan. In addition, patients should be discontinued for unacceptable toxicity or for any other signs or symptoms of deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status.

6.5.3 Data Collection and Follow-up for Withdrawn Subjects

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented in the patient's medical records. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study before on-treatment study effects can be assessed will be replaced. If >3 patients (~20% of projected enrollment) require replacement, enrollment will be paused for the study team to review safety data until that point to assure safe continuation of the study. If it is determined that DLTs of special interest from liver-directed SBRT are occurring at a higher rate than would be expected in previous studies of chemoimmunotherapy and liver-directed SBRT, respectively, we will implement a dose reduction of SBRT as described in Section 9.6 for an additional 3 patients and reassess the rate of toxicity before completing enrollment.

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

7 REGISTRATION PROCEDURES

<u>CUIMC Research Participant Registration</u>

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirmation subject eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

CPDM Central Registration Procedures:

Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@columbia.edu or fax to 212.305.5292, with the subject line "AAAT0174 Pending Subject Registration Request (PHI)". Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable.
- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by an Physician level Investigator)
- Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:
    - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
    - Copy of pathology and surgical reports

Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)

- Protocol deviation/waiver approvals (if applicable)

- **Please note**: subject line of email or fax should include the following: "AAAT0174 Complete Subject Registration Request (PHI)".

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. All applicable finalized registration/eligibility information will then be entered into HICCC's institutional CTMS database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

8 TREATMENT PLAN

8.1 Agent Administration

See **Section 11** for further information

8.2 Radiation Therapy

Radiation will be administered in 3 fractions of 10 Gy, given every other day. As many as 3 lesions, each no greater than 5 cm in diameter on study tumor assessment scan, will be targeted. If more than 3 lesions meeting study criteria are present, those to be targeted will be selected based on the Radiation Oncologist and treating investigator's shared judgment of those least likely to cause toxicity. The SBRT treatment planning, normal tissue constraints, and delivery methods used in this study have been previously described[51].

8.3 General Concomitant Medication and Supportive Care Guidelines

Permitted Therapy

Premedication with antihistamines may be administered for any atezolizumab infusions after Cycle 1.

The following therapies should 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)

- Palliative radiotherapy (e.g., treatment of known bony metastases) only if deemed appropriate by principal investigator
    - At minimum, palliative radiotherapy should not interfere with the assessment of tumor target lesions (e.g., the lesion being irradiated is not the only site of disease, as that would render the patient not evaluable for response by tumor assessments according to RECIST v1.1)
- 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 (e.g., supplemental oxygen and β2-adrenergic agonists; see **Appendix 21.2, 21.3**). All medications must be recorded on the appropriate Concomitant Medications eCRF.

Cautionary Therapy
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.

Prohibited Therapy
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 patient has discontinued study treatment. This includes, but is not

limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (unless otherwise noted).

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

- Traditional herbal medicines, because their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity
- Denosumab; patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while in the study
- Any live, attenuated vaccine (e.g., FluMist®) within 28 days prior to randomization, during treatment, or within 90 days following the last dose of atezolizumab/placebo
- 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

8.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 2 years (34 cycles) or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

8.5 Duration of Follow Up

Patients will be followed for 2 years after completion or removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

8.6 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in **Section 6.5** applies. The reason for study removal and the date the patient was removed will be documented in the Case Report Form.

9 DOSING DELAYS/DOSE MODIFICATIONS

9.1 General Notes Regarding Dose Modification

Reasons for dose modifications or 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 v5.0 grading system.

- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes.
- When several toxicities with different grades of severity occur at the same time, dose modifications should be made 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 (i.e., atezolizumab, carboplatin, etoposide, or radiation) and the dose of that component is delayed or modified in accordance with the guidelines below, other components may be administered if there is no contraindication.
- When treatment is temporarily interrupted because of toxicity caused by atezolizumab, carboplatin, etoposide, or radiation, 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.

9.2 Atezolizumab Dose Modification

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment for up to 105 days beyond the last dose if they experience an adverse event that requires a dose to be held. If atezolizumab is withheld because of adverse events for more than 105 days beyond the last dose, then the patient will be discontinued from atezolizumab treatment. If a patient must be tapered off steroids used to treat adverse events, atezolizumab may be withheld for additional time beyond 105 days from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤10 mg/day. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor. Dose interruptions for reason(s) other than adverse events, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should

be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect and, in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids or other immunosuppressive agents. The investigator should consider the benefit-risk balance a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening immune-mediated adverse events.

The primary approach to Grade 1−2 immune-related adverse events (irAEs) is supportive and symptomatic care with continued treatment with atezolizumab; for higher grade irAEs, atezolizumab should be held and oral/parenteral steroids administered. Recurrent Grade 2 irAEs may also mandate holding atezolizumab or the use of steroids. Consideration for benefit/risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening immune-related adverse events.

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

9.3 Carboplatin Dose Modification

Dose modifications for carboplatin are permitted according to the carboplatin prescribing information and local standard-of-care. The following are suggested recommendations for dose modification of carboplatin for hematologic and non-hematologic toxicities.

9.3.1 Hematologic toxicity

At the start of each cycle, the ANC should be ≥1500/mm3 and the platelet count should be ≥100,000/mm3. Treatment should be delayed for up to 42 days to allow sufficient time for recovery. If the counts have not recovered in 3 weeks, the patient's carboplatin may be dose-reduced, held until adequate neutrophil recovery, or discontinued, according to physician judgment and local standard practice. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) and the 2015 NCCN guidelines[52]. Upon recovery, dose adjustments at the start of a subsequent cycle may be made on the basis of the lowest platelet and neutrophil values from the previous cycle (see Table 1).

Table. 1 Carboplatin Dose Modification for Hematologic Toxicities

Toxicity[a]	**Carboplatin**
ANC <500/mm^3 and platelets ≥50,000/mm^3	75% of previous dose
Platelets <25,000/mm^3, regardless of ANC	75% of previous dose
Platelets <50,000/mm^3, with grade ≥2 bleeding regardless of ANC	75% of previous dose
ANC <1000/mm^3 plus fever of ≥38.5°C	75% of previous dose
[a]Nadir prior to cycle	

Dose reductions for the first episode of neutropenic fever or thrombocytopenia (platelet count <25,000 or <50,000 with bleeding or that requires transfusion) should be considered permanent.

If a second episode of neutropenic fever or thrombocytopenia requiring dose reduction occurs, the dose of carboplatin should be reduced according to physician judgment and local standard practice. Colony-stimulating factors, such as granulocyte colony-stimulating factor, may be used instead of dose reduction for neutropenic fever or Grade 4 neutropenia according to the local standard practice and ASCO guideline. Patients who require a third dose reduction should be considered for permanent discontinuation of carboplatin.

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

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 carboplatin 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 schedule should then proceed in the usual sequence.

No dose reductions are needed for anemia. Patients may be supported per the treating physician's institution's guidelines.

9.3.2 Non-hematologic toxicity

For Grade 3 or 4 non-hematologic toxicities, treatment should be delayed until resolution to less than or equal to the patient's baseline value. 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. **Table 2** provides recommended dose adjustments for non-hematologic toxicities.

Table 2 Carboplatin Dose Modification on the Basis of Non-Hematologic Toxicities in the Preceding Cycle

Toxicity		**Adjusted Carboplatin Dose as % of Previous Dose[a]**
Diarrhea	Grade 3 or 4[b]	100%
Oral mucositis	Grade 3 or 4	75%
Nausea/vomiting	Grade 3 or 4	75%
Neurotoxicity (motor or sensory)	Grade 2 Grade 3 or 4	100% 75%
Transaminase elevation	Grade 3 Grade 4	75% Discontinue
Other	Grade 3 or 4	75%
AUC= area under the concentration-time curve [a]If deemed appropriate by the treating physician, adjust carboplatin dose to the specified percentage of the previous AUC		

[b]Or any grade of diarrhea requiring hospitalization

Nausea and/or vomiting may be controlled with adequate anti-emetics. If Grade 3 or 4 nausea/vomiting occurs despite the use of anti-emetics, the dose may be reduced by 25% for the next course. If tolerated, the dose may be increased back to 100% as soon as possible. If, on Day 1 of any treatment cycle, the patient has oral mucositis, carboplatin may be withheld until the oral mucositis is cleared. If the oral mucositis has not cleared in 3 weeks, carboplatin may be discontinued. If acute Grade 3 oral mucositis occurs at any time, the dose may be given at a 75% dose when the oral mucositis is completely cleared. This may be considered a permanent dose reduction.

9.3.3 Other toxicity

For any Grade 3 or 4 toxicity not mentioned above, carboplatin may be withheld until the patient recovers completely or to Grade 1 toxicity. The treatment may then be resumed at 50% dose. This may be considered a permanent dose reduction. If recovery to Grade 1 toxicity does not occur within 3 weeks, the patient's carboplatin may be discontinued. For Grade 1 and 2 toxicities, no dose reduction should be made.

9.4 Etoposide Dose Modification

Dose modifications for etoposide are permitted according to the etoposide prescribing information and local standard-of-care. Once reduced, the current dose cannot be increased back to 100%. Suggested recommendations for dose modification of etoposide are provided in **Table 3**.

Table 3. Etoposide Dose Modification for Renal Impairment

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

9.5 Radiation Dose Modification

We will assess the rate of liver SBRT-specific toxicities in excess of those expected from atezolizumab + chemotherapy. If >3 patients (~20% of projected enrollment) require replacement, enrollment will be paused for the study team to review safety data until that point to assure safe continuation of the study.

Specifically, toxicities of special interest will include those anatomically relevant to the radiation field, including but not limited to: dysfunction, pain, inflammation, obstruction, stenosis, ulceration, perforation, hemorrhage, necrosis, or vasculopathy of the alimentary or hepatopancreaticobiliary tracts. Excess irAEs will also be investigated as possibly related to study combination therapy.

If it is determined that excess toxicity is resulting from the study combination, enrollment may resume at an SBRT dose reduction from 10 to 6 Gy to per dose. After dose-reduction, if an additional patient requires replacement due to toxicity, we will again pause enrollment for safety review. An additional dose-reduction to 4 Gy per dose may then be considered. If further toxicity of special interest is observed we will close the study.

9.6 Potential Overlapping Toxicities

The risk of overlapping toxicities between atezolizumab, carboplatin, and etoposide is thought to be minimal. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hepatotoxicity, skin and gastrointestinal toxicity) may be ambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory AEs associated with carboplatin and etoposide (e.g., dermatitis, infusion-associated symptoms) could be exacerbated by the immunostimulatory activity of atezolizumab.

Toxicities should initially be managed according to the recommendations in **Sections 9.1-9.3** with dose holds and modifications (if applicable) applied to the component of the study drug judged to be the primary cause. For severe (Grade 3) or persistent Grade 1−2 diarrhea, an endoscopic evaluation should be considered. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology for adverse events listed above. If, in the opinion of the investigator, atezolizumab is a potential inciting factor, the dose of atezolizumab may be held for a maximum of 105 days beyond when the next dose should have been given (see **Section 9.1**). Prompt symptomatic management is appropriate for mild immune-mediated adverse events. In severe cases, immune-mediated toxicities may be acutely managed with systemic corticosteroids or TNF-α inhibitors. These cases should be discussed with the Medical Monitor.

10 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

10.1 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study. Assessment will occur per protocol. Certain types of events require immediate reporting to the Principal Investigator, as outlined in **Section 10.4**.

A comprehensive list of all reported adverse events and any potential risks associated with atezolizumab, carboplatin, and etoposide can be found in the manufacturer's package insert for each agent.

10.2 Definitions

Adverse Event:
An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including abnormal sign, symptom or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

AE could also be a Pre Existing medical condition (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.

Serious Adverse Event:
Adverse events are classified as serious or non-serious. A serious adverse event (SAE) is any AE that is:

- Death(i.e., the AE actually causes or leads to death).
- life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- requires inpatient hospitalization/prolongation of existing hospitalization, unless:

  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above/below and not resulting in hospital administrations
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- results in persistent or significant disability or incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious events should be regarded as non-serious adverse events.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 10.4 for reporting instructions).

Unanticipated Problem:
An unanticipated problem is any incident, experience or outcome involving risks to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approved protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (e.g., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Adverse Event 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 to the Principal Investigator 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 Principal Investigator to other parties (e.g., Regulatory Authorities) may also be warranted.

The following AEs are considered of special interest and must be reported to the Principal Investigator expeditiously, irrespective of regulatory seriousness criteria:

The following confirmed treatment-emergent autoimmune conditions:

- Systemic lupus erythematosus
-
- 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)
- Events suggestive of hypersensitivity, cytokine release syndrome, infusion-related reactions, macrophage activating syndrome, hemophagocytic lymphohistiocytosis

- Cases of potential drug--induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law
  - Treatment-emergent ALT or AST ≥3x ULN in combination with total bilirubin ≥2x ULN
  - Treatment-emergent ALT or AST ≥3x ULN in combination with clinical jaundice

- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

Adverse Event Reporting Period

The study period during which AEs and SAEs where the patient has been exposed to Genentech product must be reported during the reporting period which begins after informed consent is obtained. Subjects will be followed for serious adverse events and adverse events of special interest for 90 days after their last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. For all other adverse events, Subjects will be followed for 30 days after their last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. Investigators are instructed to report all SAEs and AESIs considered related to study treatment regardless of time after study.

Post-study Adverse Event

Subjects who have an ongoing study treatment−related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject or the treating physician believes might reasonably be related to participation in this study.

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.

Baseline/Preexisting Condition

A baseline/preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or if the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity

- The abnormality is of a degree that requires active management (e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.).

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the treating investigator.

10.3 Recording of Adverse Events

At each contact with the subject, the treating investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

10.3.1 Assessment of Adverse Event

Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, severity, casuality (see following guidance), and actions taken.

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

Yes **(definitive, probable, possible, unlikely)**

There is a plausible temporal relationship between the onset of the AE and administration of study drugs or radiation 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, etoposide, or liver-directed radiation; and/or the AE abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.

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

Expected adverse events are those adverse events that are listed or characterized in the **Package Insert (PI)** or current **Investigator Brochure** (**IB**).

Unexpected adverse events are those not listed in the **PI** or current **IB** or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the **PI** or **IB.** For example, under this definition, hepatic necrosis would be unexpected if the **PI** or **IB** referred only to elevated hepatic enzymes or hepatitis.

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

10.3.2 Assessment of Severity of Adverse Events
The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. **Table 4** should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

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

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

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

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

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

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

Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 5 months after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. 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 expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

10.4 Reporting of Serious Adverse Events

10.4.1 Collection of Adverse Event Reports

The Sponsor will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product.

10.4.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see **Section 10.2**), 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”

10.4.3 IRB Notification by Investigator

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator’s learning of the unanticipated problem in accordance with IRB policy. Additionally, the investigator will submit a summary of all Unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

Sponsor of the study will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

10.4.4 FDA Notification by Sponsor-Investigator
The Columbia University Irving Medical Center Sponsor Investigator must report to the FDA and any affiliate site investigators as follows:

- Any unexpected fatal or life-threatening event must be reported as soon as possible, but no later than 7 calendar days after the sponsor investigator initial receipt of the information
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the investigator determines that the information qualifies for reporting
- Any findings from animal or in vitro testing whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any clinically important increase in the rate of a serious suspected adverse reactions over that listed in the protocol or Investigator Brochure
- Expected SAEs and AEs will be included in Annual Reports.

10.4.5 DSMC Reporting
Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting should occur within 24 hours of knowledge of the SAE occurring at our institution or affiliate sites.

10.4.6 Reporting to Drug Manufacturer by Sponsor-Investigator
Investigators must report single case reports as mentioned in **Section 10.4.1** adequately within the timelines described below. The completed Genentech approved reporting forms should be faxed/emailed immediately upon completion to Genentech at the following contacts:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints with an AE should be sent to:
Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

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

For questions related to safety reporting, please contact Genentech Drug Safety:
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

It is understood and agreed that the Sponsor will be responsible for the evaluation of AEs, SAEs, AESIs, Special Situation reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.

These single case reports will be exchanged between the parties as outlined below so that regulatory obligation are met. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

SADRs (Serious Adverse Drug Reaction)
Serious AE reports that are related to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

Other SAEs
Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

AESIs
AESIs requiring expedited reporting shall be forwarded to Genentech within thirty (30) calendar days of the awareness date.

Special Situation Reports
Pregnancy reports
While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

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

- Data related to 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

Product Complaints

All Product Complaints (with or without an AE) shall be forwarded to Genentech within thirty (30) 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.

Reporting to Regulatory Authorities, Ethics Committees and Investigators

Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations

The Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

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

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

Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via Sponsor Investigator (Columbia University Irving Medical Center) emailing Genentech a Quarterly line-listing documenting single case reports sent by Sponsor Investigator to Genentech in the preceding time period. The periodic line-listing will be exchanged within five (5) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Sponsor Investigator to Genentech within five (5) calendar

days from request by Genentech.

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

10.5 HICCC DSMC Reporting Process

All SAEs must be reported using the HICCC DSMC Serious Adverse Event Reporting Form and submitted to the central HICCC DSMC email at: HICCC_DSMC@lists.cumc.columbia.edu.
Affiliate sites will report all SAEs directly to the HICCC CPDM Multicenter Trials Core.
Any events that qualify for FDA reporting to the applicable IND/IDE, must be vetted through the CPDM IND officer, in collaboration with the applicable regulatory staff.

10.6 AGGREGATE REPORTS

Development Safety Update Report

The Sponsor of the Study, will be responsible for the preparation of their own Development Safety Update Report (DSUR) for the Study and for the submission of the report to the regulatory authorities and Ethics Committees of the concerned Member States, where applicable. The Sponsor agrees to share a copy of their own DSUR with Genentech as soon as reasonably possible after completion.

Genentech agrees to forward to *the Sponsor* an executive summary of the Genentech DSUR upon request. Furthermore, Genentech agrees that *Sponsor* may cross-reference the executive summary of the Genentech DSUR, as applicable.

Sponsor will forward a copy of the Final Study Report to Genentech upon completion of the Study.

STUDY CLOSE-OUT

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

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

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

QUERIES

Queries related to the Study will be answered by Columbia University Irving Medical Center (Sponsor Investigator). However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. Sponsor Investigator agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

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

SAFETY CRISIS MANAGEMENT

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

The Parties agree that Genentech shall have the final say and control over safety crisis management issues relating to the Product. Columbia University Irving Medical Center (Sponsor Investigator) agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech.

COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT / AUDIT

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

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

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

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

11 PHARMACEUTICAL INFORMATION

Study Drugs

11.1 Description

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

Atezolizumab, carboplatin and etoposide are commercially available and are considered to be non-Investigational Medicinal Products (NIMPs).

11.2 Treatment Regimen

Induction phase- four cycles of 21 days duration each will be administered as follows:

- Atezolizumab fixed dose of 1200 mg administered IV on day 1
- Carboplatin AUC=5 administered IV on day 1
- Etoposide 100 mg/m^2 on days 1, 2, and 3 of each cycle
- Stereotactic body radiation therapy administered to up to 3 liver lesions within +/-3 days of cycle 2 day 1.

Maintenance phase: atezolizumab 1200 mg administered on day 1 in 21 day cycles until withdrawal criteria are met as outlined in **Section 5.5**.

11.3 Method for Assigning Subjects to Treatment Groups

All patients enrolled in this study will receive the same study treatment protocol.

11.4 Preparation and Administration of Study Drug

Atezolizumab, carboplatin and etoposide are prepared according to the recommendations from the manufacturers' label. All drugs are obtained through standard commercial pharmacies.

Any overdose or incorrect administration of any of the study treatments should be noted in the patient's medical records and reported according to **Section 10.4** (Special Situations Reports). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded in the patient's medical records

Guidelines for dosage modification treatment interruption or discontinuation for patients who experience adverse events are provided in **Section 9**.

Atezolizumab Administration

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see **Appendix 21.2**. Atezolizumab infusions will be administered per the instructions outlined in **Table 5**.

Table 5 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (± 15) minutes. • If clinically indicated, vital signs should be measured every 15 (± 5) minutes during the infusion and at 30 (± 10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (± 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital

	signs should be measured during the infusion and at 30 (± 10) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in **Appendix 21.3**.

No dose modification for atezolizumab is allowed.

Carboplatin Administration

Carboplatin should be administered after completion of atezolizumab/placebo by IV infusion over 30−60 minutes to achieve an initial target AUC of 5 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines. 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 carboplatin dose of AUC 5 will be calculated using the Calvert formula (Calvert et al. 1989):

Calvert FormulaTotal dose (mg)=(target AUC)×(glomerular filtration rate [GFR]+25)
NOTE: The GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min.

For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance (CRCL). The CRCL is calculated by institutional guidelines or by the method of Cockcroft and Gault (1976) using the following formula:

$$\text{CRCL}=\frac{(\text{"\#\$\%\&'}()(*+)}{,-./01}(\times 0.85\ if\ female)$$

Where:

CRCL=creatinine clearance in mL/min
age=patient's age in years
wt=patient's weight in kg
Scr=serum creatinine in mg/dL

NOTE: For patients with an abnormally low serum creatinine level, estimate the GFR through use of a minimum creatinine level of 0.8 mg/dL or cap the estimated GFR at 125 mL/min.

If a patient's GFR is estimated based on serum creatinine measurements by the isotope dilution mass spectroscopy method, the FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. On the

basis of the Calvert formula described in the carboplatin label, the maximum doses can be calculated as follows:
Maximum carboplatin dose (mg)=target AUC (mg×min/mL)×(GFR+25 mL/min)
The maximum dose is based on a GFR estimate that is capped at 150 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC=5, the maximum dose is 5×150=750 mg.
For a target AUC=4, the maximum dose is 4×150=600 mg.

Refer to the FDA's communication regarding carboplatin dosing with use of the following Web site for more details:
http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm228974.htm

Etoposide Administration
During the induction phase (Cycles 1−4), on Day 1 of each cycle, etoposide (100 mg/m2) should be administered intravenously over 60 minutes following carboplatin administration. On Days 2 and 3 of each cycle, etoposide (100 mg/m2) should be administered intravenously over 60 minutes. Premedication should be administered according to local standard-of-care. 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.

11.5 Subject Compliance Monitoring
Compliance will be monitored by office visit documentation.

11.6 Prior and Concomitant Therapy
All history pertaining to prior and/or concomitant medical therapy will be collected at the time of study enrollment. See **Section 8.3** for details regarding which concomitant medications/therapies are permitted during the study.

11.7 Packaging
Atezolizumab, carboplatin and etoposide are considered non-Investigational Medicinal Products (NIMPs). Atezolizumab, carboplatin and etoposide will be used in the commercially available formulation. For information on the formulation, packaging, and handling of carboplatin and etoposide see the prescribing information for each drug.

11.8 Receiving, Storage, Dispensing and Return
11.8.1 Receipt of Drug Supplies
Atezolizumab, carboplatin and etoposide will be used in the commercially available formulation since they are NIMPs.

11.8.2 Storage
Storage conditions are described in the Manufacturer's Package Insert for atezolizumab, carboplatin and etoposide.

11.8.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug administration. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

12 STUDY CALENDAR

Procedure/Intervention[a]	Screening	Every 3 week cycles (±2 days) Induction Phase				Maintenance Phase	Treatment Discontinuation Visit	Survival Follow up
	Days -28 to -1	C1D1	C2D1	C3D1	C4D1	CXD1	<30 days after last dose	Every 3 months
Informed Consent	X							
Tumor Biopsy[b]	X							
Liver metastasis biopsy[c]	X							
Clinical Assessments								
Medical and Cancer History	X							
Physical Examination	X	X	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	
12 Lead ECG	X							
Concomitant Medications	X	X	X	X	X	X	X	
Adverse Events[d]			X	X	X	X	X	
Survival Status[e]								X
Treatment								
Atezolizumab[f]		X	X	X	X	X		
Carboplatin[g]		X	X	X	X			
Etoposide[g]		X	X	X	X			
Liver-directed radiation[h]			X					
Tumor Assessments								
Optional tumor biopsy		At time of progression						
Brain MRI or CT head w/ contrast	X							
CT chest and abdomen w/ contrast[i]	X[j]				X	X[k]	X	X[l]
PET/CT (if applicable)	X							
Laboratory Assessments[m]								
CBC	X	X	X	X	X	X	X	
Chemistry[n]	X	X	X	X	X	X	X	
PT/PTT	X							
TSH, free T3, free T4[o]	X	X			X	X	X	
Urinalysis	X						X	
Serum beta-HCG[p]	X	X						
EBV, HIV, HCV, HBV serology[q]	X							
Research bloods[r]	X[s,t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	

1. Assessments should be performed prior to study drug infusion
2. Histologic confirmation of SCLC diagnosis
3. Liver biopsy must be obtained prior to pre-treatment for evaluation of exploratory biomarkers
4. All serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period, the investigator should report any serious adverse events or adverse events of special interest believed to be related prior to study drug treatment.
5. Survival visits are to occur every 4 to 6 months from the date of the 6 month Follow-up visit. Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits. Study staff may use a public information source (e.g., county records), when permissible, to obtain information about survival status only.
6. For atezolizumab, the initial dose will be delivered over 60 (± 15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes until loss of clinical benefit.
7. For carboplatin and etoposide, drug should be administered as described in **Section 11**
8. Liver directed radiation with three doses of 10Gy delivered on alternate days up to three liver lesions measuring no greater than 5 cm each should be started within 7 (+/-3) days of C2D1
9. CT scans (with oral/IV contrast unless contraindicated) or MRI scans of the chest and abdomen.
10. A CT scan of the pelvis is required at screening and as clinically indicated or as per local standard-of-care at subsequent response evaluations.
11. Perform every 6 weeks (±7 days) (approximately every two cycles) for 12 months following Cycle 1, Day 1 and then every 9 weeks (±7 days) thereafter, regardless of treatment delays, until radiographic disease progression, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will continue to undergo tumor assessments every 6 weeks (±7 days) or sooner if symptomatic deterioration occurs. For these patients, tumor assessments should continue every 6 weeks (±7 days), regardless of time on study, until study treatment is discontinued.
12. If the patient discontinued study treatment for any reason other than disease progression (e.g., toxicity), tumor assessments will continue at the same frequency as would have been followed if the patient had remained on study treatment until radiographic disease progression, withdrawal of consent, death, or study termination by the principal investigator, whichever occurs first, even if the patient starts another anti-cancer therapy after study treatment discontinuation, unless consent is withdrawn.
13. Laboratory assessments to be done within 2 days prior to study drug infusion.
14. Serum chemistries include Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, and magnesium.
15. Thyroid function testing (TSH, free T3, free T4) collected at Cycle 1, Day 1 and every fourth cycle thereafter.
16. Serum pregnancy test must be performed within 14 days prior to C1D1.
17. HBV DNA must be collected on or before Cycle 1, Day 1 in patients who have negative serology for hepatitis B surface antigen and positive serology for HBcAb. HCV RNA must be collected on

or before Cycle 1, Day 1 in patients who test positive for anti-HCV. Screening EBV serology samples will be collected, but tests will be performed only if patients subsequently experience an acute inflammatory event such as systemic inflammatory response syndrome while receiving study treatment.

18. Research Blood Samples are not to be collected on days when treatment is being delayed orheld.
19. At screening, research bloods will be drawn for a) germline sequencing as a companion to somatic tumor DNA sequencing , b) T-cell subsets, and c) HLA-typing (see **Laboratory Manual**)
20. PBMC isolation, serum and plasma (see **Laboratory Manual**)

13 MEASUREMENT OF EFFECT

13.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients will undergo a baseline scan during screening and should be re-evaluated for response every 6 weeks for 12 months beginning within -7d of Cycle 4, Day 1 and thereafter every 9 weeks.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[53]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

13.2 Definitions

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

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

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

13.3 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be $\geq$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.

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

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. The liver lesions that undergo SBRT will be excluded from the target lesions. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

13.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness

greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

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

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

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

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

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

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

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

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

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

13.5 Response Criteria

13.5.1 Evaluation 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 progression).

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.

13.5.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

13.5.3 Evaluation of Disease Control Relative to the Radiation Field

In-field local control will be assessed in patients with at least 6 months of follow-up imaging post-SBRT. Follow-up images will be compared (by using image fusion software) with the SBRT treatment plan to evaluate local control (LC).

In-field local progression: Defined as new or progression lesions that develop within or at the margin of the radiation planning target volume (PTV)

Out-of-field progression: Defined as the development of lesions outside the PTV as assessed by RECIST v1.1. criteria.

13.5.4 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (e.g., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**

PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST v1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint (not applicable to this study given PFS6 as primary endpoint).
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

13.6 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.7 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression as defined by RECIST v1.1 or death, whichever occurs first. The 6-month PFS (PFS6) is defined as the proportion of patients that are progression free and alive at 6 months from the start of treatment.

13.8 Exploratory Biomarkers

An exploratory objective of this study is to identify potential biomarkers of response to the study treatment. Such blood and tissue biomarkers may provide evidence for the synergistic benefit of radiation with chemoimmunotherapy and may inform selection of patients most likely to benefit from this treatment. Biomarker analysis may include PBMC and tumor analyses including but not limited to TCR sequencing, flow cytometry, CITE-SEQ and CyTOF. Tumor specific analyses may

include, but not be limited to, whole exome and RNA sequencing, TCR sequencing, multiplex immunoflourescence analyses.

14 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 14.3.

14.1 Data Collection

The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system (CTMS) that will be used for data collection. CRFs for the study will be built into the CTMS for data entry. The system has full auditing capabilities which is web-based and housed on a server in a fully HIPAA compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity of patients via an interface with the electronic medical patient index. Staff with the appropriate IRB defined roles can run reports within the system for reporting purposes.

14.2 Data Reporting

Case Report Forms will be completed for each subject enrolled into the clinical study through the CTMS. It is the investigator's responsibility for ensuring that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate and authentic.

14.3 Data and Safety Monitoring Committee

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUIMC-IRB policy and guidelines. The committee is chair is appointed by the HICCC Director. The committee consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUIMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

For multicenter research, the principal investigator will assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. The report will document that a review of data and outcomes across all centers took place on a given date. It will summarize the DSMC's review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It will also inform site investigators of the study the DSMC's conclusion with respect to progress or need for modification of the protocol.

14.4 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures. The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings.

Internal On-site Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).

- The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.

- The Compliance Coordinator will communicate with the site coordinator/Site Principal Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.

- The assigned Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source

documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

14.5 Confidentiality

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

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

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Genentech representatives and collaborators, and the IRB/Ethics Committee (EC) for each study site, if appropriate.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

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

The subject binders will be maintained with in the CPDM offices, a secured floor within the Herbert Irving Pavilion and only the investigator and study staff will have access to the file.

14.6 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches,

photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

14.7 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

14.8 Records Retention

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

This minimum retention period applies whether or not any subjects were enrolled in the study.

Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least seven years, per CUIMC and NYP policy which is based on state law.

15 STATISTICAL CONSIDERATIONS

15.1 Study Design

This is a single-arm, open-label phase II study to assess the efficacy of liver-directed SBRT added to first-line atezolizumab, carboplatin, and etoposide in ES-SCLC patients as measured by 6-month PFS (primary endpoint). We hypothesize that the addition of SBRT will increase the 6-month PFS from 20% (historical control rate) to 45%. A single-stage design based on one-sided exact binomial test will be used, with a type I error of 0.10 and a power of 80%. This design requires a total of 16 evaluable patients. If at least 6 out of 16 patients have not experienced progression at 6 months, this combination therapy will be considered worthy of further study. In order to account for an estimated 10% dropout rate, 18 patients will be accrued to this study.

Primary endpoint:

- 6-month PFS rate will be defined as the proportion of patients that are progression free and alive at 6 months from the start of treatment.

Secondary endpoints:

- Overall survival (OS) will be defined as the time from treatment start to date of death or last follow up. Patients lost to follow-up at the cut-off date will be censored in the analysis.

- Overall response rate (ORR) will be defined as the proportion of patients who have a partial (PR) or complete response (CR) after beginning study treatment. Only patients who have received at least one cycle of therapy and have had their disease re-evaluated will be considered evaluable for response (see **Section 13.5.2**).
- Disease control rate (DCR) will be defined as the proportion of patients who have a partial (PR) or complete response (CR) or stable disease (SD) after beginning study treatment. Only patients who have received at least one cycle of therapy and have had their disease re-evaluated will be considered evaluable for response (see **Section 13.5.3**).
- Best overall response (BOR) will be defined as the best response recorded from the start of the treatment until disease progression (see **Section 13.5.4**).
- Duration of response will be defined as measured from the time measurement criteria are met for CR or PR until the first date that recurrent or progressive disease is objectively documented (see **Section 13.6**)
- The safety and tolerability of liver-directed SBRT will be determined by reported AEs, physical examinations and laboratory tests. Frequencies of toxicities by grade according to NCI CTCAE (version 5.0) will be tabulated.
- In-field local control will be defined as the absence of disease progression within the planning target volume (PTV) as per RECIST v1.1 on CT at 6 months following radiation treatment
- Out of field disease progression will be defined as the development of lesions outside the PTV as assessed by RECIST v1.1 criteria at 6 months following radiation treatment

15.2 Analytical Plan

Descriptive statistics will be used to describe all the study endpoints. Mean (standard deviation) and/or median (interquartile range) will be used to summarize the continuous variables. Frequencies and percentages will be used to describe categorical variables.

The primary efficacy analysis will be based on the treated, response-evaluable . All patients who meet eligibility criteria, receive at least one dose of the study drug, and have evaluable 6-month outcomes will be included in the analysis of the primary and secondary endpoints, even if there are subsequent protocol deviations. Patients who withdraw from the study before on-treatment study effects can be assessed will be replaced

Analysis of Primary Endpoints

The 6-month PFS rate and its exact two-sided 95% confidence interval (CI) will be calculated. The primary analysis will be conducted after patients have been on treatment for 6 months. As secondary analysis, we will also evaluate the 6-month PFS as a time-to-event outcome using a non-parametric (Kaplan-Meier) or parametric Weibull model, based on the distribution of the survival function.

Analysis of Secondary Endpoints

The overall survival and progression free survival probabilities will be estimated using Kaplan-Meier method. The median survival and the corresponding 95% CI will also be provided.

The estimates of the overall response rate (ORR), disease control rate (DCR), best overall response (BOR), duration of response, rate of in-field local control and out of field disease progression will be provided with the corresponding 95% CIs.

15.3 Size/Accrual Rate
The total sample of 18 patients is expected to be accrued over the course of two years (approximately 1 patient/month).

15.4 Stratification Factors
No stratification factors are applicable to this study.

15.5 Continuous Monitoring for Toxicity
Sequential boundaries will be used to monitor the toxicity rate throughout the trial. If an excessive number of dose-limiting toxicities are seen the DSMC will have the option of halting study accrual. The boundaries at which the study is halted are listed in Table 6. This is a Pocock-type boundary that yields at most a 5% probability of crossing the boundary when the rate of dose-limiting toxicity is equal to the acceptable rate 30%. The trial will be stopped if the number of dose limiting toxicities is equal to or exceeds b_n out of n patients with completed follow-up. This boundary is equivalent to testing the null hypothesis, after each patient, that the toxicity rate is equal to 0.3, using a one-sided level 0.023 test[54].

Table 6. Continuous monitoring of toxicity using Pocock-type boundary

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Boundary, b_n	-	-	-	4	5	5	6	6	7	7	7	8	8	9	9	10	10	10

15.6 Reporting and Exclusions
Evaluation of toxicity
All patients will be evaluable for toxicity from the time of their first treatment with the study drug.

16 PROTECTION OF HUMAN SUBJECTS [MULTI CENTER STUDIES]

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be obtained before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this

study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, as outlined in the IRB approved protocol, and the investigator-designated research professional obtaining the consent.

17 STUDY FINANCES

17.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Columbia University Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All CUIMC investigators will follow the University conflict of interest policy.

18 GUIDELINES FOR AFFILIATE INSTITUTIONS IN MULTICENTER STUDIES

18.1 Multi-Site Communication

The CPDM Office at CUIMC provides administration, data management, and organizational support for the affiliate sites in the conduct of a multicenter clinical trial. The CPDM Office will coordinate, at minimum, regularly scheduled conference calls with affiliate sites.
The following issues will be discussed, as appropriate:

- Enrollment information
- Cohort updates (e.g., DLTs)
- Adverse events (e.g., new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

18.2 New Protocol Distribution, IRB Submission, Modifications, and Annual Renewals

- Protocol specific documents are distributed to affiliate sites once CUIMC IRB approval has been obtained.
- The affiliate site must submit a draft of site specific revisions to protocol and/or consent form documents for review and approval by the sponsor-investigator prior to submission to the local IRB. Draft documents should be sent to the study specific email address. The site will be provided confirmation that they are approved to submit to their local IRB.
- Protocol amendments must be approved by the affiliate site's local IRB within 90 days of distribution to the site by the sponsor-investigator.

18.3 Regulatory Documents

Prior to Site Initiation:
Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected, prior to the initiation of an affiliate site.

- CV of PI, Co-I's and other research staff listed on FDA 1572 (signed and dated copy within 2 years)
- Medical Licenses of PI and Co-I's (current copy)
- Human subjects training certificates for PI and Co-I's
- CLIA/Laboratory Certifications for Local Laboratories listed on FDA 1572
- Local Laboratory Director's CV and License
- Local Laboratory Reference Ranges
- IRB roster or statement of compliance
- FDA Form 1572, if applicable (wet ink originals required)
- Financial Disclosure forms for all members listed on FDA 1572 (wet ink originals required)

Ongoing Regulatory Documentation: Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected throughout the course of the study.

- IRB approval letters for all protocol modifications and all renewals
- IRB-approved consent forms
- Current IRB roster, if statement of compliance is not provided as part of site initiation
- FDA Form 1572, if applicable as updates are required
- Updated investigator and site information where relevant (e.g., CV, medical licensure and Financial Disclosure for new sub-investigator, local laboratory information)

Regulatory documents may be sent to AAAT0174@lists.cumc.columbia.edu or to the following address if wet ink originals are required:

Clinical Protocol & Data Management Office
161 Fort Washington Ave.
Herbert Irving Pavilion
Mezzanine Level, M-203
New York, NY 10032

18.4 Site Activation

Columbia University will schedule a site initiation visit once IRB approval has been submitted from the affiliate site, if applicable.

18.5 Central Registration Procedures- Affiliate Institution Research Participant Registration Process:

All Affiliate Institutions **must** register subjects with the coordinating center (CUIMC) **prior** to any administration of study drug/intervention/local institution registration. Please see instructions below:

1. Within 48 hours of obtaining consent (excluding holidays and weekends), the Affiliate Institution CRN and/or CRC is required to submit the following documents to the CPDM Multicenter Trials Core at AAAT0174@lists.cumc.columbia.edu. The coordinating center's designee will review the documents for accurateness, and subsequently submit the documents to the CPDM Central Registration Office via email with a request to register the patient "pending eligibility." The title of the email should read, "AAAT0174 Pending Subject Registration Request (PHI)". The following documents should be submitted with the pending registration request, as applicable:
    a. Redacted Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable
    b. Redacted Signed HIPAA (or institutional equivalent)
    c. MCT CPDM Velos Note to File form
2. The Affiliate Institution's investigator/research nurse/data manager/coordinator must contact the coordinating center's designee (CUIMC's study specific Clinical Research Coordinatoror Clinical Research Nurse) via telephone or email to communicate the following:
    - Notify of pending registration request
    - Confirm method of registration request submission (email or fax)
    - Communicate expected timeline of registration request submission (e.g., same day, next day, within the hour, etc.)
3. To complete registration, the Affiliate Institution's investigator/research nurse/data manager/coordinator should then submit the following documents to the CUIMC CPDM Multicenter Trials Core at the study listserv AAAT0174@lists.cumc.columbia.edu:
    - A signed Affiliate Site Eligibility Checklist (signed by the investigator)
    - Copies of redacted source documentation necessary for each item to be verified on the CUIMC specific Eligibility Checklist, including but not limited to:
        - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
        - Copy of pathology and surgical reports
        - Copy of clinic note(s) capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms. (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)

- Protocol deviation/waiver approvals (if applicable)

- **Please note**: subject line of email or fax should include the following: "AAAT0174 Complete Subject Registration Request (PHI)".

4. Upon receipt of the abovementioned documents, the designated study specific Clinical Research Coordinator will review all documents and verify patient eligibility. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable affiliate site study team personnel for clarification prior to enrollment. Upon verification, the CUIMC study specific designee will then forward all documents to the CPDM Central Registration Office for central registration (as described above). The CPDM Central Registration Registrar will review all applicable documents and communicate to the CUIMC study specific designee in order to clarify any items. The CUIMC study specific designee will communicate with the applicable site study team personnel for additional clarifications necessary prior to enrollment.
5. Upon receipt of the subject registration notification email, the CUIMC study specific designee will forward the notification email (which will include the study specific patient ID) to the affiliate site's Principal Investigator, Consenting Professional, and applicable research personnel. This notification should be filed in the patient research binder accordingly. Protocol therapy **may not** be initiated prior to receipt of this notification from the coordinating center.
6. All screenfail/ineligible subjects, as well as subjects who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration Office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

18.6 Protocol Deviation/Subject Waiver request for Affiliate Sites:

The Affiliate site MUST submit a prospective deviation request to the CUIMC lead PI for review and submission to the HICCC DSMC and CUIMC IRB. Approvals must be obtained from all entities prior to implementation at the Affiliate site. If a prospective protocol deviation request is submitted for review (from an Affiliate site), the PI/site memo(s), HICCC DSMC approval(s) and correspondence and CUIMC IRB eligibility deviation approval letter(s) should be forwarded to the Affiliate site for documentation. The Affiliate site is also required to obtain prospective local IRB approval as per institutional policies/procedures prior to implementing the proposed deviation and registering/enrolling the subject via CUIMC Central Registration. All documents and determinations must be clearly documented in the study subject's medical record, research chart and regulatory binder, as described. Please note that the HICCC DSMC will no longer be approving deviations to eligibility criteria.

18.7 Guidelines for Affiliate Site Monitoring

On-Site MCT Monitoring:

1. Initial, recurrent, and close-out on-site monitoring visits will also be conducted at Affiliate sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).

a. The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.

2. The Compliance Coordinator will communicate with the Affiliate site coordinator/Site Principal Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.
3. The Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled at the Affiliate site and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the participating site PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to Coordinating Center, local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.
4. An SIV (or) teleconference will be scheduled and conducted prior to study drug being made available (if applicable) and before any subjects are enrolled on a study at the Affiliate site.

MCT Remote Monitoring:

- When necessary (due to logistical constraints), Affiliate sites will be monitored remotely by a designated Compliance Coordinator. Sites will be informed of this remote monitoring process on a site-by-site basis.
- Affiliate sites will be monitored by the Compliance Coordinator on both a regulatory level, as well as a clinical data/source documentation review level.
- Redacted source documents (applicable to supporting the protocol specific CRF data requirements) will be sent to the designated Compliance Coordinator via fax or secure email for all subjects enrolled at Affiliate sites. Timelines for submission procedures will be defined on a case-by-case basis.
- The Compliance Coordinator will review all submitted redacted source documents against the data entered on the protocol specific CRFs. The Compliance Coordinator will issue queries when/if necessary.
- The Affiliate site research staff will respond to queries within 30 days. If queries remain outstanding, the Compliance Coordinator will send a delinquent query reminder for the outstanding items.

- The remote monitoring procedures will include review of applicable redacted source documentation and supporting applicable documents to determine compliance regarding:
    a. Informed consent procedures
    b. Eligibility criteria
    c. Protocol specific treatment compliance
    d. Protocol specific toxicity/outcome documentation/compliance
    e. Protocol specific schedule of events (e.g., baseline visits, pre-treatment, on study, follow-up)
    f. Participating site IRB documents (e.g., IRB amendment approvals, annual renewals, SAE/UP submissions, violation/deviation submissions, INDSR submissions, etc.).
    g. Required specimen submissions (e.g., tissue specimens, research bloodspecimens, etc.)
    h. Pharmacy accountability records
    i. Adherence to the CRF submission timeframes to CUIMC (within the protocol specified timeframes)
- Affiliate site remote monitoring reports will be sent to the lead PI, HICCC DSMC, and Affiliate sites after each remote monitoring review. Reports will include information regarding data submission timeliness/accuracy, protocol adherence items, query resolution status, regulatory status, and overall Affiliate site performance. These reports will be generated by the Compliance Coordinator and reviewed with the Compliance Core Manager prior to dissemination.

18.8 Adverse event reporting

Sponsor reporting: Notifying participating investigators at affiliate sites of adverse events
It is the responsibility of the study sponsor to notify all affiliate sites, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Serious Adverse Event Reporting
Each participating investigator is required to abide by the reporting requirements set by Columbia University Medical Center. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.
Participating investigators must report each serious adverse event to the Columbia University Medical Center Overall Principal Investigator and the CPDM Multicenter Trials Core **within 24 hours** of learning of the occurrence using the HICCC DSMC SAE Report Form.The CPDM Multicenter Trials Core will report the event to the HICCC DSMC and Genentech on the subsite's behalf. In the event that the participating investigator does not become aware of the serious adverse

event **immediately** (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Brian Henick, MD
Fax: 646-317-6321
bh2682@cumc.columbia.edu
AAAT0174@lists.cumc.columbia.edu

The participating investigator must provide follow-up information on the serious adverse event until resolution of the event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow- up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression ofthe original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject **continued** or withdrew from study participation or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the Investigator's Brochure for the study drug (new occurrence) and is thought to be related to the investigational agent, the sponsor-investigator may urgently require further information from the investigator for reporting to Health Authorities.

Non-Serious Adverse Event Reporting
Non-serious adverse events will be reported to the Columbia University Medical Center Overall Principal Investigator on the toxicity Case Report Forms.

Reporting to the Institutional Review Board (IRB) and the Data and Safety Monitoring Committee:
All Unanticipated Problems (UPs) will be reported to the CUIMC IRB. SAEs not constituting UPs will reported to the HICCC DSMC.

Each affiliate site will be responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 7 calendar days following the occurrence of the UP or the Principal's Investigator's acquiring knowledge of the UP. Copies of each report and documentation of IRB notification and receipt must be included in the regulatory binder.
Expected AEs must be reported at the time of continuing review of a protocol.

Reporting to Hospital Risk Management
Affiliate Site investigators will report to their local Risk Management Office any subject safety reports or sentinel events that require reporting according to institutional policy.

18.9 Confidentiality

Each affiliate site will be assigned a site number. Each subject that signs consent should be assigned a unique code number consisting of site number followed by a number with each new subject being assigned the next sequential number (e.g., 04-10). All sites will be required to enter their data in the Velos eResearch, the Clinical Trial Management System used for all Cancer-related clinical research at CUIMC. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials.

Subject confidentiality must be maintained according to HIPAA regulations and GCP recommendations.

Except when required by law, study information shared with persons and organizations outside of Columbia University Medical Center must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier.

If the results of this research project are published or presented at a scientific or medical meeting, the patient not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

18.10 Data Reporting Plan

Columbia University Irving Medical Center (CUIMC) is deeply committed to research integrity and strong credibility when it comes to the discovery of new treatment concepts, implementation of new clinical research techniques, and acceptance of its researcher's findings by the medical establishment. In accord with these ethics, CUIMC encourages and supports its investigators in the sharing of final research data and/or details of newly developed clinical treatments.

CUIMC's policies that pertain to patient data sharing conform to CUIMC IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the Principal Investigator, Statistician, Data Safety and Monitoring Board (DSMC), and, in other instances, the CUIMC IRB. Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the CUIMC's guidelines for Protecting the Rights and Privacy of Human Subjects.

18.11 Data Acquisition and Submission

Informed consent, including HIPPA authorization, must be obtained on all subjects prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. Velos eResearch will be used as the electronic clinical trials and data management system. Affiliate sites will enter data directly into Velos eResearch via customized case report forms for the study. The research staff will generate reports from Velos eResearch to ensure timely submission of data by affiliate sites. This resource allows for the timely analysis of particular data sets for safety analysis.

18.12 Record Keeping and Record Retention

The Sponsor is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Sponsor is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study. Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. In accordance with FDA regulations, the investigator shall retain records for a period of 2 years after the investigation is discontinued and FDA is notified.

19 PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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21 APPENDICES

21.1 Appendix Preexisting Autoimmune Diseases and Immune Deficiencies

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

Autoimmune Diseases and Immune Deficiencies

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

21.2 Appendix Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

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

21.3 VA lung Study Group's (VALG) 2 stage SCLC classification scheme
Limited stage disease: confined to the ipsilateral hemithorax, which can be safely encompassed within a radiation field. Contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy falls within the category of limited stage disease.
Extensive stage disease: disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases

22 ATTACHMENTS

Appendix
Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

GENENTECH SUPPORTED RESEARCH

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

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

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

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

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

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

MANAGEMENT GUIDELINES

PULMONARY EVENTS

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

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

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

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

BAL = bronchoscopic alveolar lavage.

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or appropriate delegate).

HEPATIC EVENTS

Immune-related hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

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

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

Table 2 Management Guidelines for Hepatic Events

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

LFT = liver function test.

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
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 corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function test.

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

GASTROINTESTINAL EVENTS

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

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

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

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

GI = gastrointestinal.

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

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

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

GI = gastrointestinal.

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

ENDOCRINE EVENTS

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

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

Table 4 Management Guidelines for Endocrine Events

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

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

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

Table 4 Management Guidelines for Endocrine Events (cont.)

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

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

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

Table 4 Management Guidelines for Endocrine Events (cont.)

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

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

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

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

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

IMMUNE-RELATED MYOCARDITIS

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

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

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

Table 6 Management Guidelines for Immune-Related Myocarditis

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

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

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

1. 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 cyndrome (CRS) with atezolizumab may receive medication with antihistamines, antipyretics and/or analgesics (e.g., acetaminophen). 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 [58]. 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 [59, 60], including atezolizumab.

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

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

Event	Management
Grade 1[a] Fever[b] with or without constitutional symptoms	● Immediately interrupt infusion. ● Upon symptom resolution, wait 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 atezolizumab 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. ● If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. ● If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the sponsor-investigator.
Grade 3[a] Fever[b] with hypotension requiring a vasopressor (with	● Permanently discontinue atezolizumab.[f] ● 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.

or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	● Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. ● 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.
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.[f] ● 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.[e] For patients who are refractory to anti-cytokine therapy, experimental treatments[g] may be considered at the discretion of the investigator. ● Hospitalize patient until complete resolution of symptoms.

ASTCT= American Society for Transplantation and Cellular Therapy; BiPAP= bi-level positive airway pressure; CAR= chimeric antigen receptor; CPAP= continuous positive airway pressure; CRS= cytokine-release syndrome; HLH= hemophagocytic lymphohistiocytosis; IRR = infusion-related reaction; MAS= macrophage activation syndrome.

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

a. Grading system for 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 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. There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
f. 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 according to institutional guidelines and the above table. 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 considering the benefit-risk ratio.

g. Refer to Riegler et al. [61] for information on experimental treatments for CRS.

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 7.

Table 7 Management Guidelines for Pancreatic Events, Including Pancreatitis

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

GI = gastrointestinal.

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate).

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

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

GI = gastrointestinal.

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limited, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 8.

Table 8 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab. [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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 9.

Table 9 Management Guidelines for Neurologic Disorders

Event	Management
Immune-related neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-related neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Immune-related neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • 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 corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

IMMUNE-RELATED MENINGOENCEPHALITIS

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 10.

Table 10 Management Guidelines for Immune-Related Meningoencephalitis

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

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

RENAL EVENTS

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

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

Table 11 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab 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. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

IMMUNE-MEDIATED MYOSITIS

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

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

Table 12 Management Guidelines for Immune-Mediated Myositis

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

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

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

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

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

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

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

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

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

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

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

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

- Fever ≥38.5°C

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

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

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

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

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

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

References

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