A phase II study of Carboplatin plus Pemetrexed plus Atezolizumab plus Bevacizumab in chemotherapy and immunotherapy-naïve patients with stage IV non-squamous non-small cell lung cancer: Big Ten Cancer Research Consortium BTCRC-LUN17-139

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

_____ _____

Signature of Site Investigator Date

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Site Investigator Name (printed)

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Site Investigator Title

_____

Name of Facility

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Location of Facility (City and State)

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SYNOPSIS

TITLE	A phase II study of Carboplatin plus Pemetrexed plus Atezolizumab plus Bevacizumab in chemotherapy and immunotherapy-naïve patients with stage IV non-squamous non-small cell lung cancer
PHASE	Phase II
OBJECTIVES	Primary Objective: To estimate the progression free survival (PFS) of the combination of Carboplatin plus Pemetrexed plus Atezolizumab plus Bevacizumab for patients with stage IV non-squamous NSCLC who are chemotherapy and immunotherapy naïve. • Progression free survival (PFS) defined as the time from the initiation of treatment to the time when the criteria for disease progression is met as defined by RECIST v1.1 or death of any cause. • 1 year PFS will be estimated. Secondary Objectives: 1) To estimate the overall response rate (CR + PR), as well as the disease control rate (CR + PR + SD) of carboplatin plus pemetrexed plus atezolizumab plus bevacizumab in immunotherapy and chemotherapy-naïve patients with stage IV non-squamous non-small cell lung cancer. • Overall Response rate will include confirmed complete response (CR) + confirmed partial response (PR), as determined as per RECIST v1.1 criteria and assessed by the local investigator or designee. • disease control rate will include complete response (CR], partial response (PR), and stable disease (SD), as per RECIST v1.1 criteria. 2) To estimate the overall survival (OS) of carboplatin plus pemetrexed plus atezolizumab plus bevacizumab in immunotherapy and chemotherapy-naïve patients with stage IV non-squamous non-small cell lung cancer. 3) To characterize the toxicity of carboplatin plus pemetrexed plus atezolizumab plus bevacizumab in immunotherapy and chemotherapy-naïve patients with stage IV non-squamous non-small cell lung cancer • Toxicity as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5. Tertiary Objectives: To characterize the association of tissue and blood markers with efficacy and toxicity. These may include genomic, proteomic, methalomic, and immune markers
STUDY DESIGN	This is a multicenter single arm phase II clinical trial. All eligible patients will receive: Carboplatin (AUC 5) i.v. day 1 plus pemetrexed (500 mg/m^2) i.v. day 1 plus atezolizumab 1200 mg i.v. day 1 plus bevacizumab 15 mg/kg i.v. day 1 every 3 weeks for up to 4 cycles. Patients with non-PD after 4 cycles will be permitted to continue with maintenance therapy with pemetrexed plus atezolizumab plus

	bevacizumab every 3 weeks until the time of disease progression or intolerable toxicities.
KEY ELIGIBILITY CRITERIA	• Age ≥ 18 years at the time of consent. • ECOG Performance Status of 0-1 within 21 days prior to registration. • Histological or cytological confirmation of non-squamous cell non-small cell lung cancer • Patients with known EGFR mutations, BRAF mutations, ALK translocations or ROS1 translocations are eligible once they have received approved molecularly targeted therapy. A 1-week washout prior to enrollment is strongly encouraged (3 weeks preferred). • Must have PD-L1 IHC results available using the Dako 22C3 antibody ***OR*** must have at least 5 unstained slides to perform PD-L1 testing (results not required for eligibility). If tissue is not available, subjects may choose to have a standard of care biopsy to meet eligibility. • Measurable disease according to RECIST v1.1 criteria within 21 days prior to registration with either PET/CT scan, CT scan of chest and abdomen, or CT chest including upper abdomen and adrenal glands which define stage IV disease. • Patients who had disease progression greater than 1 year after completing prior adjuvant therapy for stage I – III are eligible as long as no systemic therapy was given at time of recurrence. • No prior immunotherapy or antiangiogenic therapy. Prior platinum or pemetrexed are permissible if previously given in the adjuvant setting for stage I-III disease and disease recurrence is > 1 year from completion of treatment. • If subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention. • A subject with CNS disease may be considered if they have completed their treatment for brain metastasis at least 2 weeks prior to study registration, have been off corticosteroids for ≥ 2 weeks, and are asymptomatic. Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan, if other specified eligibility criteria for CNS disease are met. • Demonstrate adequate organ function as defined in the body of the protocol.
STATISTICAL CONSIDERATIONS	The study will evaluate whether carboplatin plus pemetrexed plus atezolizumab plus bevacizumab will improve the PFS compared to the PFS of carboplatin plus pemetrexed plus bevacizumab as reported in the literature. According to the current knowledge as reported in the literature, the median PFS for patients treated with carboplatin plus pemetrexed plus bevacizumab is approximately 6 months. We hypothesize that carboplatin plus pemetrexed plus atezolizumab plus bevacizumab will improve the median PFS to 9.6 months.

	The total study duration is 30 months, where the accrual period for the trial is 18 months and each patient will have a pre-scheduled follow-up of 12 months except for reason due to death. The test statistic is the nonparametric one-sample log-rank test [28]. The sample size calculation was based on the assumptions of uniform accrual over time, no loss to follow-up, exponentially distributed PFS times. A sample size of 42 would detect the hypothesized PFS difference with an 87% power with 1-sided type I error of 0.05. To ensure the power of study, the study would require at least 42 patients to complete the 1-year follow-up or until death. Suppose a rate of loss to follow-up of 5%. Then we anticipate recruiting 46 patients. If all 46 patients finish their pre-scheduled follow-up, then the power of the study is 90%. We thus propose a total sample size of 46. Because of the short accrual period (1 year), no interim analysis is planned to avoid the interruption of the study flow.
TOTAL NUMBER OF SUBJECTS	N= 46
ESTIMATED ENROLLMENT PERIOD	18 months
ESTIMATED STUDY DURATION	30 months

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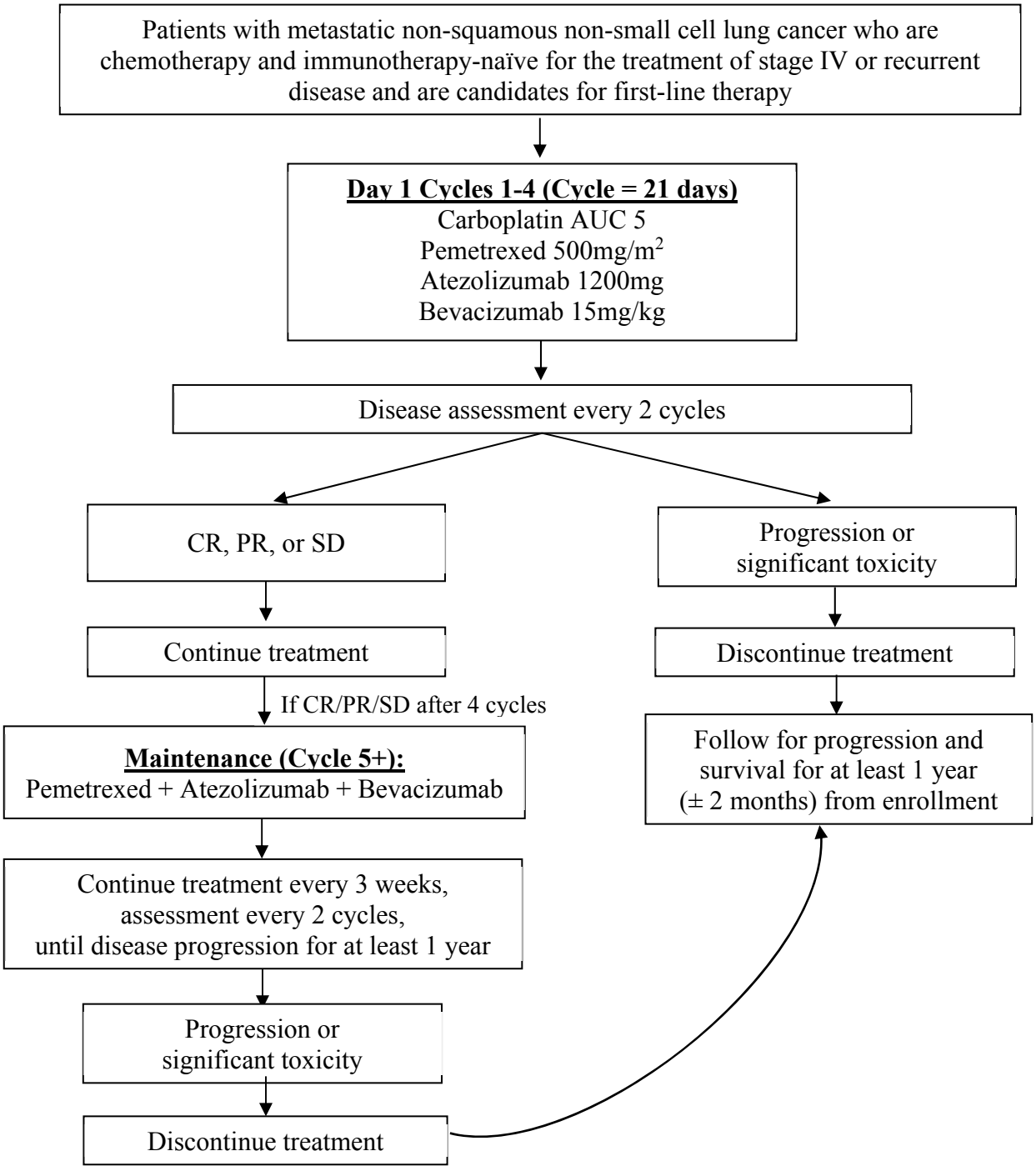
SCHEMA


Patients with metastatic non-squamous non-small cell lung cancer who are chemotherapy and immunotherapy-naïve for the treatment of stage IV or recurrent disease and are candidates for first-line therapy
Day 1 Cycles 1-4 (Cycle = 21 days)
Carboplatin AUC 5
Pemetrexed 500mg/m2
Atezolizumab 1200mg
Bevacizumab 15mg/kg
Disease assessment every 2 cycles
CR, PR, or SD
Progression or significant toxicity
Continue treatment
Discontinue treatment
If CR/PR/SD after 4 cycles
Maintenance (Cycle 5+):
Pemetrexed + Atezolizumab + Bevacizumab
Follow for progression and survival for at least 1 year (± 2 months) from enrollment
Continue treatment every 3 weeks, assessment every 2 cycles, until disease progression for at least 1 year
Progression or significant toxicity
Discontinue treatment

1. BACKGROUND AND RATIONALE

The hypothesis of this study is that the addition of Atezolizumab (an anti-PD-L1 antibody), to the combination of Carboplatin plus Pemetrexed plus Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, for the treatment of patients with stage IV non-squamous, non-small cell lung cancer (NSCLC) will improve progression free survival (PFS) compared with a historical control of carboplatin plus pemetrexed plus bevacizumab.

1.1 Non-Small Cell Lung Cancer

In 2015, there were about 220,000 new cases of lung cancer expected in the United States, and approximately 160,000 deaths. Lung cancer remains the leading cause of cancer death in the United States, being responsible for an estimated 27% of all cancer deaths in 2015[1]. The most common type of lung cancer is non-squamous non-small-cell lung cancer (NSCLC). At the time of diagnosis most patients will have stage IV disease. The majority of patients treated for earlier stage disease will also develop recurrent or metastatic disease [2]. Historically, patients with advanced stage NSCLC have been treated with a platinum-based doublet chemotherapy regimen in the first line setting [3].

1.2 Squamous cell and non-squamous cell histology of NSCLC

The two most common histologies of NSCLC are squamous cell and adenocarcinoma. Large cell and adenocarcinoma are further categorized as non-squamous NSCLC, to distinguish it from squamous cell. In recent years multiple studies have demonstrated clear distinctions in biology and subsequently therapeutic approaches between stage IV squamous cell and non-squamous cell subtypes. The squamous cell subtype is most associated with a smoking history in a dose-dependent manner [4]. Non-squamous subtypes, specifically adenocarcinoma, are much more likely than squamous cell lung cancer to harbor driver mutations; examples include EGFR, ALK, ROS1, BRAF, MET and KRAS, and many of these driver mutations can now be targeted with molecular therapy [5]. There are also distinctions regarding therapeutic responses between squamous and non-squamous subtypes of NSCLC. Pemetrexed is an antifolate chemotherapy agent which targets thymidylate synthase (TS); as squamous cell cancers generally have very high levels of expression of TS, pemetrexed appears less efficacious in this subtype. Pemetrexed is only FDA approved to treat patients with non-squamous NSCLC. [6]. In addition, Bevacizumab is contraindicated in patients with squamous cell histology because of the increased risk of major life-threatening bleeding as demonstrated in a phase II clinical trial of bevacizumab plus carboplatin and paclitaxel [7]. Similar to pemetrexed, bevacizumab is also FDA approved to treat only patients with non-squamous NSCLC type.

1.3 Cisplatin + Pemetrexed

Up until 2008, the initial treatment of all subtypes of NSCLC consisted of doublet combinations including platinum (cisplatin or carboplatin) combined with gemcitabine, vinorelbine, or taxanes (paclitaxel or docetaxel). Comparator trials demonstrated similar efficacy among several regimens [3]. A study by Scagliotti et al compared cisplatin plus gemcitabine to cisplatin plus pemetrexed in patients with advanced NSCLC. Overall survival for cisplatin and pemetrexed was noninferior to cisplatin plus gemcitabine; however, a pre-planned subgroup analysis showed a statically superior overall survival for the cisplatin/pemetrexed arm in patients with non-squamous NSCLC. Patients with squamous cell histology had numerically better outcomes when randomized to the cisplatin/gemcitabine arm. This phase III study established the important distinction of squamous vs. non-squamous NSCLC when making therapeutic decisions. [8]. Furthermore, this study finding resulted in an FDA label change for

pemetrexed to be used in combination with cisplatin in the first-line treatment of advanced and metastatic NSCLC for only patients with non-squamous histology.

1.4 Maintenance Pemetrexed

The use of maintenance chemotherapy was not standard until the last several years. Maintenance pemetrexed had also been studied following platinum-based chemotherapy induction for advanced NSCLC in patients without disease progression, demonstrating improvement in overall survival and progression free survival [9]. The PARAMOUNT trial was a randomized phase III clinical trial investigating the effect of maintenance pemetrexed versus placebo after completing induction chemotherapy for advanced non-squamous NSCLC with 4 cycles of pemetrexed plus cisplatin. The results of this trial showed a significant risk reduction for progression-free survival and overall survival favoring maintenance pemetrexed over a placebo group with a hazard ratio (HR) of 0.62 [10]. This trial led to the FDA expansion allowing for maintenance pemetrexed after induction chemotherapy for patients with advanced non-squamous NSCLC.

1.5 Addition of VEGF inhibitor bevacizumab to chemotherapy

Vascular endothelial growth factor (VEGF) is an endothelial-cell–specific mitogen and has been found to be a major regulator of angiogenesis in tumors [11, 12]. Treatment with the VEGF inhibitor, bevacizumab, in combination with chemotherapy had shown improved survival when combined with standard chemotherapy alone in the treatment of patients with metastatic colon cancer [13]. A phase III study investigated the effect of adding Bevacizumab to carboplatin plus paclitaxel in patients with advanced non-squamous NSCLC. Patients treated on the bevacizumab arm experienced improved overall survival, progression free survival, and response rate [14]. This study established the combination of carboplatin plus paclitaxel plus bevacizumab as a standard treatment for patients with advanced non-squamous cell NSCLC.

1.6 Carboplatin plus pemetrexed plus bevacizumab

For patients with advanced non-squamous NSCLC, carboplatin plus pemetrexed had recently been established as an option for the initial systemic treatment. Previously, carboplatin, paclitaxel and bevacizumab had already been an established initial treatment[14]. The POINTBREAK study compared pemetrexed, carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab to paclitaxel, carboplatin, and bevacizumab followed by maintenance bevacizumab. Patients treated on the pemetrexed-containing arm experienced prolonged progression free survival but not overall survival compared with the paclitaxel containing regimen [15]. This trial established carboplatin, pemetrexed and bevacizumab followed by maintenance pemetrexed plus bevacizumab as an acceptable alternative to carboplatin, paclitaxel, and bevacizumab followed by maintenance bevacizumab for the treatment of patients with advanced non-squamous NSCLC in the first-line setting.

1.7 Carboplatin plus pemetrexed plus immunotherapy for NSCLC

There has been a great deal of interest in recent years in studying how the immune system interacts with neoplastic cells. T-cells express a certain regulatory receptor called programmed death 1 receptor (PD-1) and this receptor interacts with a ligand (PD-L1 and PD-L2) to downregulate T cell activity [16, 17]. Drugs targeting programmed death 1 (PD-1) and its ligand, PD-L1, have demonstrated a manageable safety profile and robust efficacy [18]. The KEYNOTE-021 study per Langer et al. analyzed the addition of pembrolizumab, an anti- PD-1 monoclonal antibody, to carboplatin plus pemetrexed. [19] This randomized phase II trial compared carboplatin plus pemetrexed with maintenance pemetrexed to

carboplatin, pemetrexed and pembrolizumab with maintenance pemetrexed and pembrolizumab in patients with advanced, non-squamous cell NSCLC. There was significant improvement in objective response in the carboplatin plus pemetrexed plus pembrolizumab group (55%) compared to the carboplatin plus pemetrexed alone group (29%). Progression free survival also favored the pembrolizumab group. This trial was the basis for accelerated FDA approval of pembrolizumab combined with carboplatin and pemetrexed for previously untreated metastatic non-squamous NSCLC, irrespective of PD-L1 level expression in tumor. A phase III trial by Ghandhi et al. reported improved OS for patients receiving pembrolizumab plus combination chemotherapy compared with chemotherapy alone in patients with metastatic non-squamous NSCLC (1-year OS 69.2% vs. 49.4%). Survival was improved with the addition of pembrolizumab, regardless of PD-L1 status [20].

1.8 VEGF inhibitors combined with PD-L1 inhibitors

There are no fully-published studies examining the addition of angiogenesis inhibitors with PD-1 or PD-L1 targeted immunotherapy in patients with lung cancer. There is a good deal of preclinical data suggesting the combination of immunotherapy with antiangiogenic agents may have synergistic effects **[21]**. Proangiogenic factors like VEGF can reduce T-cell infiltration, thereby lessening the immune response to cancer. Data from other malignancies reveals the close association with angiogenesis and immune response. In patients with metastatic renal cell carcinoma, measurement of PD-L1 expression revealed that a higher level of expression was significantly related to poor response to anti-VEGF treatment; this suggests the combination PD-1/PD-L1 blockade could potentially augment therapeutic benefit to anti-VEGF therapy **[22]**. Murine colon adenocarcinoma cancer models evaluating the combination of PD-1 and VEGFR2 inhibitors found the two agents induced a synergistic response, with significantly inhibited tumor growth; the combination also increased expression of CD4 cell infiltration into the tumor bed and elevated levels of tumor necrosis factor **[23]**. The toxicity profile of carboplatin plus pemetrexed plus bevacizumab as well as the combination of carboplatin plus pemetrexed plus atezolizumab are well characterized. Safety data has already been published evaluating the combination of the VEGF inhibitor, Ramucirumab, with pembrolizumab in a phase I study of patients with gastric adenocarcinoma, NSCLC, or urothelial carcinoma **[24]**. More recently, a phase II clinical trial in metastatic renal cell cancer patients evaluated the combination of the anti-PD-L1 inhibitor atezolizumab plus bevacizumab versus and following atezolizumab and sunitinib (a tyrosine kinase inhibitor used in first line setting for metastatic renal cell cancer). 101 subjects were in the experimental arm, and safety was comparable to the known individual profiles of atezolizumab and bevacizumab; for PD-L1+ patients, the PFS hazard ratio was 0.64 for the combination therapy, and this combined therapy is now being evaluated in a phase III study **[25]**.

1.9 Carboplatin plus paclitaxel plus atezolizumab or bevacizumab for metastatic NSCLC

Most recently data from a randomized phase III clinical trial evaluating the role of bevacizumab combined with carboplatin plus paclitaxel plus atezolizumab has been reported. This multicenter trial randomized patients with advanced non-squamous NSCLC to receive carboplatin plus paclitaxel plus atezolizumab versus carboplatin plus paclitaxel plus bevacizumab versus carboplatin plus paclitaxel plus atezolizumab plus bevacizumab. Results of this 3-arm phase III trial were recently presented by Reck et al at an international meeting. The co-primary objectives were 1. to compare investigator-assessed PFS in an ITT population and included the evaluation of T-effector high patients and 2. compare overall survival. The carboplatin plus paclitaxel plus bevacizumab arm served as the control. The 4-drug regimen of carboplatin plus paclitaxel plus bevacizumab plus atezolizumab resulted in superior PFS when compared with the carboplatin plus paclitaxel plus bevacizumab control arm (HR 0.617,

p<0.0001). The 1-year PFS was 37% vs. 18% and median PFS was 11.3 months vs. 6.8 months. The ORR also favored the 4-drug regimen (64%) vs. the control arm (48%). Preliminary OS also favored the 4-drug regimen (HR 0.7, p=0.0262) with a median OS of 19.2 months vs. 14.4 months. Furthermore, grade 3/4 toxicities were uncommon with the 4 drug regimen, and comparable to the control arm of carboplatin plus paclitaxel plus bevacizumab [26].

1.10 Rationale

Combination therapy of carboplatin plus pemetrexed plus bevacizumab, or carboplatin plus pemetrexed plus pembrolizumab or, carboplatin plus paclitaxel plus atezolizumab plus bevacizumab have demonstrated effectiveness in the treatment of patients with non-squamous NSCLC. The use of pemetrexed has several advantages over the use of paclitaxel, namely; pemetrexed can be given as maintenance therapy, which is proven to prolong overall survival (paclitaxel can't be given as maintenance due to dose-limiting neurotoxicity); pemetrexed does not require high dose of steroids [that may negate the effects of concomitant immunotherapy agents] to prevent major toxicities (paclitaxel requires corticosteroids to reduce infusion related reactions); pemetrexed is infused over 10 minutes (versus 3 hours for paclitaxel); pemetrexed has a more favorable side effect profile compared with paclitaxel.

Based on the landmark trials for treatment of non-squamous NSCLC, and promising recent clinical data combining immunotherapy and anti-VEGF therapy, we propose to study the combination of carboplatin plus pemetrexed plus atezolizumab plus bevacizumab in chemotherapy and immunotherapy-naïve patients with stage IV non-squamous NSCLC.

2. STUDY OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

1) To estimate the progression free survival (PFS) of the combination of Carboplatin plus Pemetrexed plus Atezolizumab plus Bevacizumab for patients with stage IV non-squamous NSCLC who are chemotherapy and immunotherapy naïve.
   - Progression free survival (PFS) defined as the time from the initiation of treatment to the time when the criteria for disease progression is met as defined by RECIST v1.1 or death of any cause.
   - 1-year PFS will be estimated.

2.1.2 Secondary Objectives

1) To estimate the overall response rate (CR + PR), as well as the disease control rate (CR + PR + SD) of carboplatin plus pemetrexed plus atezolizumab plus bevacizumab in immunotherapy and chemotherapy-naïve patients with stage IV non-squamous non-small cell lung cancer.
   - Overall Response rate will include confirmed complete response (CR) + confirmed partial response (PR), as determined as per RECIST v1.1 criteria and assessed by the local investigator or designee.
   - Disease control rate will include complete response (CR], partial response (PR), and stable disease (SD), as per RECIST v1.1 criteria.

2) To estimate the overall survival (OS) of carboplatin plus pemetrexed plus atezolizumab plus bevacizumab in immunotherapy and chemotherapy-naïve patients with stage IV non-squamous non-small cell lung cancer.
3) To characterize the toxicity of carboplatin plus pemetrexed plus atezolizumab plus bevacizumab in immunotherapy and chemotherapy-naïve patients with stage IV non-squamous non-small cell lung cancer
   - Toxicity as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.

2.1.3 Tertiary, Correlative/Exploratory Objectives

To characterize the association of tissue and blood markers with efficacy and toxicity. These MAY include genomic, proteomic, methylomic, and immune markers. This protocol will collect archived tissue specimens for future analysis and blood samples at various time points for future analysis. These analyses MAY include:

1) To assess PD-L1 expression levels in the archival tumor samples of subjects and correlate with PFS, OS, and treatment toxicity.
2) To assess associations between cfDNA, DNA, RNA, microRNA, DNA methylation, protein expression, immune markers, protein biomarkers, cytokines, and other markers and efficacy and toxicity of treatment.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

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

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

2. Age ≥ 18 years at the time of consent.

3. ECOG Performance Status of 0-1 within 21 days prior to registration.

4. Must have life expectancy of ≥ 3 months at time of consent

5. Histological or cytological confirmation of non-squamous NSCLC.

6. Must have known PD-L1 status using the Dako 22C3 antibody (+ vs. -) ***OR*** must have at least 5 unstained slides to perform PD-L1 testing (results not required for eligibility). PD-L1 positive is defined as a tumor proportion score (TPS) ≥ 1%. PD-L1 negative is defined as a TPS <1%. If tissue is not available, subjects may choose to have a standard of care biopsy to meet eligibility.

7. Patients with known targetable mutations in EGFR or BRAF or known translocations in ALK or ROS1 are eligible if they have received FDA approved targeted therapy first. A 1-week washout prior to enrollment is strongly encouraged (3 weeks preferred).

8. Stage IV disease or recurrent disease

9. Measurable disease according to RECIST v1.1 criteria within 21 days prior to registration with either PET/CT scan, CT scan of chest and abdomen, or CT chest including upper abdomen and adrenal glands which define stage IV disease.

10. Patients who had disease progression greater than 1 year after completing prior adjuvant therapy for stage I – III are eligible as long as no systemic therapy was given for recurrence.

11. No prior immunotherapy or antiangiogenic therapy.

12. Prior platinum therapy or pemetrexed are permissible if previously given in the adjuvant setting for stage I-III disease and disease recurrence is > 1 year from completion of therapy.

13. If subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

14. Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained within 21 days prior to registration.

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	≥ 1.5 K/mm^3
Hemoglobin (Hgb)	≥ 9 g/dL
Platelets	≥ 100 K/mm^3
Renal	
Serum creatinine: Calculated creatinine clearance:	≤1.5 × upper limit of normal (ULN) OR ≥ 40 cc/min using the Cockcroft-Gault formula
Hepatic	
Bilirubin	≤ 1.5 × upper limit of normal (ULN)
Aspartate aminotransferase (AST)	≤ 1.5 × ULN or < 5x ULN if the transferase elevation was due to liver metastases
Alanine aminotransferase (ALT)	≤ 1.5 × ULN or <5x ULN if the transferase elevation was due to liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 × ULN (unless subjects is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended use of anticoagulants)

15. Females of childbearing potential must have a negative serum pregnancy test within 7 days prior to registration. **NOTE:** A woman is considered to be of childbearing potential if she is postmenarcheal, 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).

16. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two non-hormonal methods of contraception, including at least one method

with a failure rate of < 1% per year, during the treatment period and for 5 months after the last dose of atezolizumab or 120 days after the last dose of any study drug, whichever is later; examples of non-hormonal 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. Must use "estrogen-free" hormonal method if this is chosen contraception method.
A barrier method may be used as the second contraceptive method. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

17. Contraception method must begin starting from the time of informed consent until 120 days after treatment discontinuation.

18. 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 the treatment period and for 120 days after the last dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

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

3.2 Exclusion Criteria

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

1. Active infection requiring systemic therapy

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

3. Active secondary cancers.

4. Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases. Brain imaging with either MRI or CT with contrast must be performed on all subjects at screening to evaluate for the presence of brain metastases. Patients with a history of treated CNS lesions are eligible, provided that all of the following criteria are met:
    - Measurable disease, per RECIST v1.1, must be present outside the CNS.
    - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.

- Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
- The patient has not received stereotactic radiotherapy within 14 days prior to initiation of study treatment or whole-brain radiotherapy within 21 days prior to initiation of study treatment
- The patient has no ongoing requirement for corticosteroids as therapy for CNS disease and off steroid therapy for at least 14 days. Anticonvulsant therapy at a stable dose is permitted.
- Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.

5. Major surgery within 3 weeks of the first dose of trial treatment.

6. Completed palliative radiotherapy within 7 days of the first dose of trial treatment.

7. The patient had a history of uncontrolled hereditary or acquired thrombotic disorder.

8. Patients with a history of gross hemoptysis (defined as bright red blood or ≥1/2 teaspoon) within 2 months prior to enrollment.

9. The patient had clinically relevant congestive heart failure (CHF; NYHA II-IV) or symptomatic or poorly controlled cardiac arrhythmia.

10. The patient had experienced any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to enrollment.

11. The patient had uncontrolled arterial hypertension ≥150 / ≥90 mm Hg despite standard medical management.

12. The patient has had a serious or non-healing wound, ulcer, or bone fracture within 28 days prior to enrollment.

13. Patients with ≥ 2 + protein on dipstick urinalysis. All patients with ≥ 2 + protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection and must demonstrate ≤ 1 g of protein in 24 hours to be eligible.

14. Clear cavitation of pulmonary lesions seen on imaging.

15. The patient had significant bleeding disorders, vasculitis, or experienced Grade 3-4 gastrointestinal (GI) bleeding within 3 months prior to enrollment.

16. History of GI perforation and/or fistulae within 6 months prior to enrollment.

17. Evidence of tumor invading or abutting major blood vessels.

18. The patient had a bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection (hemicolectomy or extensive small intestine resection with chronic diarrhea), Crohn's disease, ulcerative colitis, or chronic diarrhea.

19. Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

20. Previously had a severe hypersensitivity reaction to treatment with another monoclonal antibody (mAb).

21. Has active autoimmune disease that has required systemic treatments in the past 2 years, including but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-α agents; chronic or occasional use of low-dose steroid therapy can be still be considered eligible as long as no greater than the daily equivalent of 5mg oral prednisone.

22. Exceptions to excluding patients with active autoimmune disease include the following:
    - Patients with a history of autoimmune-related hypothyroidism who are on thyroid replacement hormone are eligible for the study.
    - Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
    - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations are eligible for the study provided all of following conditions are met:
        - Rash must cover < 10% of body surface area
        - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
        - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months

23. Subjects with asthma that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study. Subjects on chronic systemic steroids would be excluded from the study.

24. Had prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies

25. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment

26. Treatment with systemic immunosuppressive medication (including, but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:

- Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.
- Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

27. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins

28. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

29. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

30. Has known active Hepatitis B or C. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay. For patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg), the patient is only eligible if they are negative for HBV DNA.

31. Active tuberculosis

32. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.

33. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

34. Has known interstitial lung disease or history of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan; history of radiation pneumonitis in the radiation field (fibrosis) is permitted. Lymphangitic spread of the NSCLC is not exclusionary.

4. SUBJECT REGISTRATION

All subjects must be registered through Big Ten Cancer Research Consortium (Big Ten CRC) Administrative Headquarters'(AHQ) electronic data capture (EDC) system. A subject is considered registered when an 'On Study' date is entered into the EDC system.

Subjects must be registered prior to starting protocol therapy. Subjects should begin therapy within **7 business days** of registration. Beginning therapy outside that timeframe will not be considered a deviation.

5. TREATMENT PLAN

Patients will be treated in 3 week (21 day) cycles for duration of the study, for both the induction and maintenance phases.

5.1 Initial therapy: Cycles 1-4

On Day 1 of each cycle, patients will be treated with Carboplatin AUC 5 IV, Pemetrexed 500mg/m^2 IV, Atezolizumab at fixed dose of 1200mg IV, and bevacizumab 15mg/kg IV. Treatment will continue for a maximum duration of 4 cycles in this phase.

If carboplatin is discontinued prior to completing 4 cycles, the patient may continue receiving the remaining study drugs.

5.2 Maintenance Therapy: Cycle 5+

After 4 cycles, the carboplatin will be stopped and subjects without progression (complete response [CR], partial response [PR], or stable disease [SD] as defined by RECIST v1.1 criteria) will continue the maintenance therapy at the same dosing and schedule as initial treatment:

- Patients will receive Pemetrexed 500mg/m^2 IV, Atezolizumab at fixed dose of 1200mg IV, and bevacizumab 15mg/kg IV every 3 weeks on D1 of each 21 day cycle.

Treatment will continue until disease progression or unacceptable toxicity. Should a single agent be discontinued secondary to unacceptable toxicity (as defined below), individual remaining agents from the maintenance phase can continue to be given. Drugs will be discontinued based upon attribution of toxicity. However, in the event that attribution of drug to toxicity can not be determined, the order of discontinuation will be as follows:

- 1st: Bevacizumab. 2nd: Atezolizumab. 3rd: Pemetrexed

5.3 Pre-medication and Hydration

Premedication and hydration will be administered as per institutional standards.

The administration of vitamin B12 and folic acid will be per institutional standards. The use of corticosteroids to prevent chemotherapy-related nausea/vomiting is discouraged but not disallowed. The use of a 5 HT3 antagonist plus neurokinin 1 antagonist (with or without olanzapine) can be considered as prophylaxis to prevent nausea/vomiting. The use of corticosteroids the day before, the day of, and the day after each pemetrexed infusion is left to the discretion of the treating physician and the institutional standards. Sites may follow institutional standards for the management of nausea/vomiting not otherwise addressed.

5.4 Study Drug Administration: Initial Therapy

Drug	Dose[1]	Route	Schedule[2]	Cycle Length
Carboplatin	AUC 5	Intravenously (IV) per institutional standards	Day 1	21 days
Pemetrexed	500 mg/m^2	IV per institutional standards	Day 1	
Atezolizumab	1200 mg fixed dose	IV over 60 minutes; subsequent infusions over 30 minutes[3]	Day 1	
Bevacizumab	15mg/kg	IV. 1st infusion=90 min 2nd infusion=60 min 3rd + infusions=30 min[4]	Day 1	

[1] Body surface area (BSA) should be recalculated when weight changes by ≥ 10% according to the Mosteller formula.
[2] A window of ± 7 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).
[3] For 1st infusion, atezolizumab (1200 mg in a 250 mL 0.9% NaCl IV bag) will be given over 60 mins ± 10 minutes. If no reaction occurs, subsequent infusions may be delivered over 30 minutes (-5/+ 10 minutes).
[4] The initial dose of bevacizumab will be delivered over 90 ± 10 minutes. If the 90-minute infusion is tolerated without infusion-associated adverse events (fever or chills), the second infusion may be delivered over 60 ± 10 minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes (-5/+ 10 minutes).

5.5 Study Drug Administration: Maintenance Therapy

Drug	Dose[1]	Route	Schedule[2]	Cycle Length
Pemetrexed	500 mg/m^2	IV per institutional standards	Day 1	Every 21 days
Atezolizumab	1200 mg fixed dose	IV over 30 minutes (-5/+ 10 minutes)	Day 1	
Bevacizumab	15mg/kg	IV over 30 minutes (-5/+ 10 minutes)	Day 1	

[1] Body surface area (BSA) should be recalculated when weight changes by ≥ 10% according to the Mosteller formula.
[2] A window of ± 7 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).

5.6 Concomitant Medications

5.6.1 Allowed Concomitant Medications

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

- Oral contraceptives
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated influenza vaccinations
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency.

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

Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in subjects with Grade 3-4 febrile neutropenia.

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

5.6.2 Cautionary Therapy for Atezolizumab-Treated patients

Corticosteroids and Tumor Necrosis Factor-α Inhibitors
Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator (except that systemic corticosteroids may not be given as premedication to patients with an allergy to contrast agents used for tumor scans).

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to the Atezolizumab Investigator's Brochure for details).

5.6.3 Prohibited Concomitant Medications

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer outside of the design parameters of this study (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited prior to starting study treatment, and during study treatment, until disease progression is documented and the patient has discontinued study treatment
- Investigational therapy (other than protocol-mandated study treatment) is prohibited during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.
- Systemic corticosteroids may not be administered as premedication to patients with an allergy to contrast agents used for tumor scans

5.7 Atezolizumab Related Assessment of Safety

5.7.1 Safety Plan

The safety plan for patients in this study is based on clinical experience with atezolizumab, bevacizumab, pemetrexed, and carboplatin in completed and ongoing studies. The anticipated important safety risks are outlined below

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab, carboplatin, and pemetrexed, and bevacizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below. Refer to on safety reporting (e.g., adverse events, pregnancies) for this study.

5.7.1.1 Risks associated with Atezolizumab

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

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when atezolizumab is given in combination with other immunomodulating agents.

As detailed in this protocol, there will NOT be combination of other immunomodulating agents with Atezolizumab in this clinical trial, however, systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation of those patients should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

5.7.2 Management of Patients who experience Adverse Events with Atezolizumab

5.7.2.1 Dose Modifications

There will be no dose modifications of atezolizumab in this study; management of adverse events are outlined below.

5.7.2.2 Treatment Interruption for Atezolizumab

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 105 days from the last dose, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for >105 days to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >105 days if the Investigator believes that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The investigator will determine the acceptable length of treatment interruption.

5.7.2.3 Management Guidelines for Atezolizumab Related Adverse Events

Guidelines for the management of patients who experience specific adverse events related to Atezolizumab are provided in detail in Appendix at end of protocol, "Management of Atezolizumab-Specific Adverse Events".

Grade events are detailed in NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

All dose reductions of chemotherapy are considered permanent. Once a dose of chemotherapy is reduced, it will not be increased to previous level, even if toxicity has resolved.

Subjects who miss a treatment of chemotherapy and/or atezolizumab for a reason unrelated to toxicity need to resume therapy ≤ 14 days of the originally planned treatment. If a delay of more than 14 days occurs, the subject will be taken off treatment.

6.1 Dose Delays/Dose Modifications

Unless otherwise noted in the dose modification tables below, treatment may be delayed ≤ 2 weeks from the expected day of the next treatment for any reason. If treatment is delayed ≤ 2 weeks, subjects will proceed with the next cycle of treatment at the dose level recommended according to the tables below.

6.2 Dose Levels for Dose Reductions

Dose level	Carboplatin	Pemetrexed
Starting Dose	AUC 5	500mg/m^2
Dose level (-1)	AUC 3.75 (25% reduction)	375mg/m^2
Dose level (-2)	AUC 2.5 (50% reduction)	250mg/m^2

***** No adjustments in fixed dose of atezolizumab or bevacizumab; toxicity, treatment delay or discontinuation of therapy handled as outlined below.

6.3 Bevacizumab

Dose modifications for fluctuations from baseline body weight of ≥ 10% are permitted for bevacizumab according to standard practice. If AEs that require omitting bevacizumab occur, the dose will remain the same once treatment resumes.

Any toxicities associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Omission of bevacizumab will have no immediate therapeutic effect. Bevacizumab has a terminal half-life of 21 days.

Patients should be clinically assessed for toxicity before, during, and after each infusion of bevacizumab. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be permanently discontinued, however the patient may remain on study.

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed.
Specific toxicities and treatment schedule:

Infusion reaction:

- Patients who experience an infusion–associated adverse event may be premedicated for the next infusion, but the infusion time may not be decreased for that infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 ± 10 minutes as long as the patient continues to be premedicated.
- If a patient experiences an infusion associated adverse event with the 60 minute infusion despite premedication, all subsequent doses should be delivered over 90 ± 10 minutes. Similarly, if a patient experiences an infusion associated adverse event with the 30 minute infusion despite premedication, all subsequent doses should be delivered over 60 ± 10 minutes.
- Reduce the infusion rate by 50% for grade 1 or 2; add dexamethasone (or equivalent) and acetaminophen to diphenhydramine premedication regimen before each bevacizumab dose
- Permanently discontinue for grade 3 or 4

Hypertension:

- Interrupt therapy for severe hypertension until controlled with medical management
- Permanently discontinue for severe hypertension that cannot be controlled with antihypertensive therapy

Proteinuria:

- Interrupt therapy for urine protein levels ≥2 g/24 hr; reinitiate treatment at previous fixed dose of 15 mg/kg when urine protein level returns to <2 g/24 hr
- Permanently discontinue for urine protein level >3 g/24 hr, or if there are 3 separate occurrences of protein level ≥ 2g/24hr, or in the setting of nephrotic syndrome

Arterial thrombotic events:

- Permanently discontinue

Bleeding, grade 3 or 4:

- Permanently discontinue

Gastrointestinal perforation:

- Permanently discontinue

Reversible posterior leukoencephalopathy syndrome (RPLS):
- Permanently discontinue for confirmed diagnosis

Wound healing complications:
- Withhold treatment prior to surgery; do not reinitiate until the surgical wound is fully healed. If wound healing complications develop during treatment, withhold until the wound is fully healed.

Fistula (any type), grade 4
- permanently discontinue

Tracheooesophageal fistula (any grade)
- permanently discontinue

Venous thrombosis, grade 3
- withhold Bevacizumab until stable on anti-coagulation,

Recurrent VTE, grade 3
- permanently discontinue

VTE, grade 4
- permanently discontinue

Congestive Heart Failure (any grade)
- permanently discontinue

6.4 Atezolizumab Dose Modifications

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

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

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

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

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

For subjects Hepatotoxicity events of Grade 3-4, patients are to permanently discontinue Atezolizumab, with the exception of patients with liver metastasis who began treatment with Grade 2 AST or ALT; if

AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then subjects should be discontinued.

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

6.5 Pemetrexed and Carboplatin Dose Modifications

Standard previously established dose modifications will apply to use of chemotherapy agents pemetrexed and carboplatin.

For Grade 3 or 4 diarrhea or any diarrhea requiring hospitalization, there will be dose reduction to 75% of prior dose (as established above in dose adjustment table), and subsequent episodes will have further dose reduction to 50% for both pemetrexed and carboplatin.

Grade 3 or 4 mucositis: Pemetrexed dose should be reduced to 50% of the previous dose (continue the carboplatin at prior dose). If pemetrexed has already been dose reduced secondary to prior toxicity, further dose reductions will not be allowed unless based on the investigator discretion.

6.6 Dose modifications for hematologic toxicities

- CBC with differential is obtained on Day 1 of each cycle.
- Day 1 carboplatin, pemetrexed, bevacizumab, and atezolizumab may only be given if the platelets count $\geq 100 \times 10^9$/L and ANC $\geq 1.5 \times 10^9$/L.
- Filgrastim support per FDA labeled guidelines may be utilized on or after the 2nd cycle if warranted by neutropenic fever or neutrophil count causing delay or dose reduction in chemotherapy, per standard guidelines.

Hematologic toxicities requiring dose modifications of carboplatin and pemetrexed are as follows:

- Grade 4 hematologic toxicity: Lasting ≥ 7 days OR
- Febrile neutropenia Grade 3 or Grade 4:
  - Grade 3 is defined as ANC < 1000/mm^3 with a single temperature of > 38.3 degrees C (101° F) or a sustained temperature of ≥ 38 degrees C (100.4° degrees F) for > 1 hour.
  - Grade 4 is defined as ANC < 1000/mm^3 with a single temperature of > 38.3 degrees C (101° F) or a sustained temperature of ≥ 38 degrees C (100.4° F) for more > 1 hour, with life-threatening consequences and urgent intervention indicated
- Grade 3 or Grade 4 thrombocytopenia if associated with:
  - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
  - life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit

For Day 1 hematologic toxicities occurring for cycles 1-4, the current cycle should be delayed by 1 week. A CBC with differential should be checked at least once a week if treatment is not given on Day 1. Study treatment may be resumed after a 1 week delay if the platelet count is $\geq 100 \times 10^9$/L and ANC is $\geq 1.5 \times 10^9$/L. Continuation at the same dose or at a reduced dose is based on investigator discretion

unless the above criteria requiring dose reduction is met. If chemotherapy is delayed more than 1 week, dose reductions should occur.

6.7 Dose Modifications for Renal Toxicity

Glomerular filtration rate (GFR) as calculated by the standard Cockcroft and Gault formula must be used to calculate creatinine clearance (CrCl) prior to each dose of carboplatin on Day 1 of each cycle. Only subjects with a CrCl of ≥ 30 mL/min will be treated.

- If CrCl < 30 mL/min, carboplatin, pemetrexed and atezolizumab should be held;
- If CrCl < 40 mL/min, pemetrexed should be held
- If a Grade 3 or Grade 4 toxicity (as below, per CTCAE grading) occurs, carboplatin, and atezolizumab should be held.

	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine increased	> ULN* - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN

*ULN, upper limit of normal

If medications are held, a serum chemistry should be checked and CrCl calculated at least once a week. Carboplatin may be resumed at one dose level lower (per dose level reductions) once the CrCl returns to ≥ 30 mL/min or returns to Grade 1 toxicity level. Atezolizumab can be resumed at standard dose.

Pemetrexed may be resumed one dose level lower (per dose level reductions) once the CrCl returns to ≥ 40 mL/min OR ≤1.5 × ULN

- If CrCl remains < 30 mL/min or > Grade 1 toxicity for ≥ 3 weeks after last dose of carboplatin, atezolizumab, or pemetrexed, these therapies should be discontinued.
- Patient will have the option of proceeding with single agent bevacizumab at this time. No dose adjustments are necessary for the bevacizumab in setting of renal failure.

6.8 Dose reductions for Hepatic Toxicity

- Hepatic function labs should be assessed on Day 1 of each cycle.
- Toxicity evaluated per CTCAE grading.
- If any medications are required to be held, hepatic function labs should be repeated once a week. Treatment can be resumed once liver function tests return to acceptable levels.
- For Grade 3 (5.1 - 20 times ULN) or 4 (>20 times ULN) transaminase elevation during treatment, after returning to acceptable levels, reduce the pemetrexed dose 1 level reduction, or by 25%.
- If liver function tests remain elevated in Grade 3-4 range for ≥ 3 weeks after last dose of atezolizumab, atezolizumab should be discontinued,

6.9 Dose Modifications for sensory peripheral neuropathy toxicity

Sensory neuropathy assessment will be screened for with history and graded by CTCAE v5.

- Withhold carboplatin for Grade 3-4 sensory peripheral neuropathy.
- Resume the carboplatin at reduced dose levels, with AUC 3.75 and AUC 2.5 for first and second occurrence, respectively, when sensory peripheral neuropathy improves to Grade 1 or completely resolves.

- Discontinue the carboplatin if there is third occurrence.

6.10 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined in section 6.1, a subject will also be discontinued from protocol therapy and followed up per protocol under the circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

- Documented disease progression
- The treating physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant
- If protocol therapy is interrupted for ≥ 14 days for events unrelated to toxicity. See section 6.

6.11 Protocol Discontinuation

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete the final study assessments. The site study team should contact the subject by telephone or through a clinic visit to determine the reason for the study withdrawal. If the reason for withdrawal is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Cycle = 21 days	Screen	Initial Therapy		Maintenance Therapy	Safety follow up	Long-term Follow up[5]
		Cycle 1[2]	Cycle 2-4 [2]	Cycles 5+		
	-21 days[1]	Day 1	Day 1	Day 1	30 days post Tx[2,4]	Q 3months (±14 days)
REQUIRED ASSESSMENTS						
Medical history, smoking history, trial awareness[7]	X					
Diagnosis and Staging[6]	X					
Physical exam	X	X	X	X	X	
Vital signs, ECOG Performance status[8]	X	X	X	X	X	
AEs & concomitant medications	X	X	X	X	30, 90[4]	
LABORATORY ASSESSMENTS						
Complete Blood Cell Count with diff (CBC)	X	X	X	X	X	
Comprehensive Metabolic Profile (CMP)[9]	X	X	X	X	X	
PT/INR and aPTT	X					
Thyroid Function (TSH, T4, free T3), Amylase, Lipase	X	X	Cycle 3	Q2 cycles	X	
Pregnancy test (serum or urine) WOCBP	-7days[10]					
Urinalysis	X[10]					
DISEASE ASSESSMENT[3,11]						
CT of chest[11] or CT chest and CT abdomen	X		Q2 cycles[11]	Q2 cycles[11]	X[11]	X[5]
MRI or CT Brain[11]	X					
TREATMENT EXPOSURE						
Carboplatin		X	X			
Pemetrexed		X	X	X		
Atezolizumab		X	X	X		
Bevacizumab		X	X	X		
CORRELATIVE STUDIES (SPECIMEN COLLECTION)						
PD-L1 results; Prior genetic analyses	PD-L1[12]	Genetic[12]				
Archival tumor tissue[13]	X					
Blood, serum, plasma, and PBMCs[14]		X	Cycle 2		X	
BANKING SAMPLES (SPECIMEN COLLECTION)						
Whole Blood[15]		X				
Serum, Plasma[16]		X			X	
FOLLOW-UP						
Survival status, subsequent therapies						X

Key to Footnotes

[1]If screening (baseline) testing was performed within 10 days of D1 of treatment, these do not need to be repeated.

[2]A window of 7 days will be applied to all treatment study visits; for the long-term follow up visits, a 14-day window will apply.

[3]**Tumor imaging** to continue every odd numbered cycle until progression, starting with cycle 3.

[4]A **safety follow-up** visit will occur 30 days (±10 days) after the last dose of treatment. AESIs and SAEs will be collected for 90 days after the end of treatment. See Section 11.2.

[5]Subjects without documented disease progression will be followed for disease progression every 3 months (±14 days) for 1 year. Once disease progression is documented, subjects will enter a survival follow up period every 3 months (±14 days) for 1 year from the time of documented progression. Follow up for may be accomplished via email, phone or other means as appropriate.

[6]**Diagnosis and staging** to include pathology report and Tumor Node Metastasis (TNM) staging

[7]**Medical history** to include smoking history and trial awareness question.

[8]**Vital signs** to include blood pressure, weight, and height (screening only) and ECOG performance status

[9]**CMP** to include AST, ALT, total bilirubin, creatinine

[10]**Pregnancy test**: For women of childbearing potential (WOCBP): urine or serum βhCG, within 7 days prior to study registration. If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. **Urinalysis**: All patients with ≥ 2 + protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection and must demonstrate ≤ 1 g of protein in 24 hours.

[11]**Tumor response assessment** will be performed every odd numbered cycle starting with cycle 3; tumor imaging to be done at treatment discontinuation at discretion of investigator. CT scan of chest alone for imaging is acceptable only if instructed to include the upper abdomen in field, specifically must include the liver and bilateral adrenal glands. Brain imaging with either MRI or CT with contrast will be performed on all subjects at screening to evaluate for the presence of brain metastases. A 21 day window may be applied to screening scans and ±14 day window may be applied to all subsequent scans.

[12]**PD-L1**: Prior PD-L1 IHC testing must have been performed using the Dako 22C3 antibody. All other subjects must have at least 5 unstained slides available to perform PD-L1 testing. **Prior genetic testing**: If subjects have prior genetic sequencing analyses results available, those results should be submitted at C1D1.

[13]Fixed paraffin-embedded blocks/slides will be requested, if available, for future evaluation (up to 20-25 unstained slides preferred). See CLM.

[14]Serial blood samples will be collected at Pre-Treatment Cycle 1 Day 1, Cycle 2 Day 1, and progression / follow up period: whole blood; plasma; plasma and peripheral blood mononuclear cells (PBMC); and serum. See CLM for additional details including collection, processing, labeling and shipping.

[15]Whole blood for banking is to be collected at Pre-Treatment Cycle 1 Day 1. See CLM.

[16]Serum and plasma for banking is to be collected at Pre-Treatment Cycle 1 Day 1 and at the 30-Day Safety Follow up visit. See CLM.

7.1 Safety Follow-up Evaluations

A safety follow-up visit should occur when subjects permanently stop study treatment for whatever reason (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (±10 days) after the last dose of treatment. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, is deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier. AESIs and SAEs will be collected for 90 days after the end of treatment. See Section 11.2.

7.2 Long Term Follow-up Evaluations

All subjects will be followed until documented disease progression. Subjects who discontinue treatment for any reason without documented disease progression will be followed for disease progression every 3 months (±14 days) for 1 year.

Once disease progression is documented, subjects will enter a survival follow up period every 3 months (±14 days) for 1 year from the time of documented progression. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

8. BIOSPECIMEN STUDIES AND PROCEDURES

For archival tumor specimens or blood collected in the protocol, please see the Correlative Laboratory Manual (CLM) for additional information regarding collection, labeling and shipping.

8.1 Source and Timing of Biospecimen Collections

8.1.1 PD-L1 results

Prior PD-L1 IHC testing must have been performed using the Dako 22C3 antibody. All other subjects must have at least 5 unstained slides available to perform PD-L1 testing. See CLM for details.

8.1.2 Prior Genetic Sequencing Results

If subjects have prior genetic sequencing analyses results available, those results should be submitted at C1D1. In particular, markers such as EGFR mutation status, ALK, ROS-1, BRAF, KRAS, HER-2, MET, RET, NTRK, tumor mutational burden, PD-L1 will be noted in the database.

8.1.3 Archival Tumor Tissue

Mandatory submission of formalin-fixed, paraffin-embedded archival tumor tissue block for biomarker evaluation are requested, if available. A new biopsy is not required if archival tissue is not available. Tissue should be identified and requested before registration; submission to BTCRC AHQ will occur after subject is successfully registered. Excisional, incisional, punch or core needle samples are preferred. Fine needle aspirates with sufficient number of cells for testing are allowable if fixed in paraffin; alcohol fixation not suitable for PD-L1 IHC. Please see CLM for sample specifications.

PD-L1 analyses using the Dako 22C3 antibody will be performed for all subjects except those who have prior Dako 22C3 PD-L1 results. For those without prior Dako 22C3 results, submission of tissue for PD-L1 analysis is required.

Additional archival tumor tissue is requested if available. Tissue *MAY* also be macro-dissected and the nucleic acids extracted for genetic analyses such as (but not limited to) whole exome sequencing, Next Generation Sequencing, and/or DNA methylation analyses. Any residual nucleic acids remaining after analyses will be banked for future research with subject consent.

8.1.4 Mandatory Whole Blood Collection for Somatic Baseline

Whole blood samples will be collected prior to C1D1 treatment.

8.1.5 Mandatory Whole Blood Collection for gene expression/RNA

Whole blood specimens will be submitted prior to C1D1 treatment, prior to C2D1 treatment, and at Safety Follow-Up Visit.

RNA *MAY* be isolated for gene expression profiling using techniques such as (but not limited to) RNA-Seq.

8.1.6 Mandatory Plasma Collection for cfDNA and microRNA Analyses

Plasma specimens will be submitted prior to C1D1 treatment, prior to C2D1 treatment, and at Safety Follow-Up Visit.

miRNA *MAY* be isolated from plasma samples and reverse transcribed prior to quantitative PCR analyses.

cfDNA *MAY* be isolated from plasma samples and analyzed with appropriate platform such as (but not limited to) quantitative PCR, digital PCR, or next-generation sequencing.

8.1.7 Mandatory Serum Collection for Proteomic Analyses, Lipidomic Analyses, and Cytokine Analyses

Serum specimens will be submitted prior to C1D1 treatment, prior to C2D1 treatment, and at Safety Follow-Up Visit.

Proteomic analyses *MAY* be performed and could include ELISA (or multiplex assay system) with specific antibodies and/or LC-MS/MS proteomic analyses. These samples may also provide data for metabolomics guided by functional groups. Pre-treatment serum samples *MAY* also be used to explore the association of proteomic and lipidomic tests at baseline with measures of response.

Cytokine analyses *MAY* be performed and may include assessment of pre- and post-treatment serum cytokine markers of interest, such as (but not limited to) Interferon gamma, Interleukin-10, Interleukin-18, Interleukin-2, Interleukin-4, Interleukin-6, Interleukin-8, Macrophage Inflammatory Protein-1 beta, Tumor Necrosis Factor alpha, Tumor Necrosis Factor beta.

8.1.8 Mandatory PBMCs & Plasma Collection for Flow Cytometry of PBMCs and Banking of Plasma

Blood will be collected and processed for PBMCs and plasma prior to C1D1 treatment, prior to C2D1 treatment, and at Safety Follow-Up Visit.

Flow cytometry *MAY* be performed to analyze expression on human peripheral blood mononuclear cells stained with antibodies such as (but not limited to) CTLA-4 and CD28.

8.2 Banking of Leftover Biospecimens

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

8.3 Banking Samples for Future Unspecified Research

Subject consent will be obtained to collect additional samples for future unspecified Big Ten Cancer Research Consortium studies. HCRN will manage the banked samples. Samples will be banked indefinitely in the HCRN Biorepository.

This includes:

- Whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1.
- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit.

Please refer to the Correlative Laboratory Manual (CLM) for all sample collection, processing, labeling, and shipping instructions.

8.4 Confidentiality of Biospecimens

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

9. CRITERIA FOR DISEASE EVALUATION

Disease response will be evaluated as per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [27]. Refer to the RECIST v1.1 publication for complete details on these criteria.

9.1 Measurable Disease

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

9.1.1 Malignant Lymph Nodes

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

9.2 Non-measurable Lesions

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

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

9.3 Target Lesions

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

9.4 Non-target Lesions

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

9.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also

	demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.6 Evaluation of Non-target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.7 Evaluation of Best Overall Response

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

Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

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

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

9.8 Definitions for Response Evaluation – RECIST v1.1

9.8.1 First Documentation of Response

The time between initiation of therapy and first documentation of PR or CR.

9.8.2 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

9.8.3 Duration of Response

Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

9.8.4 Duration of Overall Complete Response

The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

9.8.5 Objective Response Rate

The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST v1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.8.6 Disease Control Rate

The disease control rate is the proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST v1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.8.7 Time to Progression

A measurement from the date of the initiation of treatment to the time when the criteria for disease progression is met as defined by RECIST v1.1. Subjects who have not progressed will be right-censored at the date of the last disease evaluation. Death due to any cause will be considered as a competing risk.

9.8.8 Progression Free Survival

A measurement from the date of registration until the criteria for disease progression is met as defined by RECIST v1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

9.8.9 Overall Survival

Overall survival is defined by the date of registration to date of death from any cause.

10. DRUG INFORMATION

10.1 Carboplatin

Please see product package insert for complete details regarding carboplatin.

10.1.1 Supplier/How Supplied

Carboplatin is available as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol.

Commercial supplies of carboplatin will be used in this study and billed to third party payers or the subject.

10.1.2 Preparation

As per institutional standards.

10.1.3 Storage and Stability

Intact vials are stored at room temperature protected from light. The reconstituted solution is stable for at least 24 hours. When further diluted in glass or polyvinyl plastic to a concentration of 10mg/mL with normal saline or 5% dextrose carboplatin is stable for 8 hours at 25 degrees C. Stability with further dilution to 0.5mg/mL has been reported for up to 8 hours. Other stability data indicate that carboplatin is stable for up to 24 hours and may be refrigerated; however, the manufacturer recommends that reconstituted solutions be discarded after 8 hours due to the lack of preservative in drug formulation.

10.1.4 Handling and Disposal

Caution should be exercised in handling and preparing carboplatin injection. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing carboplatin injection. If carboplatin injection contacts the skin, immediately wash the skin thoroughly with soap and water. If carboplatin injection contacts mucous membranes, the membranes should be flushed immediately and thoroughly with water.

10.1.5 Incompatibilities

Aluminum displaces platinum from the carboplatin molecule, resulting in the formation of a black precipitate and loss of potency. Carboplatin solutions should not be prepared or administered with

needles, syringes, catheters, or IV administration sets containing aluminum parts that might be in contact with the drug.

10.1.6 Adverse Events

Incidence rates of adverse events associated with carboplatin are provided in the product package insert. Some of the expected adverse events with carboplatin treatment are listed below.

- Hematologic: Thrombocytopenia (dose limiting), neutropenia, leukopenia, anemia.
- GI: Nausea and vomiting (frequent but less severe than with cisplatin), treatable with appropriate antiemetic prophylaxis. Anorexia, diarrhea, and constipation have also been reported.
- Dermatologic: Rash, urticaria. Rarer reactions include alopecia, mucositis, and hypersensitivity reactions.
- Hepatic: Abnormal liver function tests, usually reversible with standard doses.
- Neurologic: Rarely peripheral neuropathy is seen. May be more common in subjects greater than 65 years of age. May also be cumulative, especially in subjects with prior cisplatin treatment. Ototoxicity (rare).
- Renal: Elevations in serum creatinine, BUN; electrolyte loss (Mg, K, Na, Ca).
- Miscellaneous: Pain, asthenia, flu-like syndrome.

10.1.7 Drug Interactions

Concomitant myelosuppressive drugs or radiation therapy may potentiate the hematologic toxicity of carboplatin.

Concomitant nephrotoxic drugs may potentiate the nephrotoxicity of carboplatin, particularly when carboplatin is given in high-dose chemotherapy regimens.

10.2 Pemetrexed

Please refer to the current package insert for complete prescribing and toxicity information.

10.2.1 Supplier/How Supplied

Pemetrexed is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Pemetrexed is supplied in 100mg and 500 mg vials. Each 500-mg vial of pemetrexed contains pemetrexed disodium equivalent to 500 mg pemetrexed and 500 mg of mannitol. Each 100-mg vial of pemetrexed disodium contains equivalent to 100mg pemetrexed and 106mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

Commercial supplies of pemetrexed will be used in this study and billed to third party payers or the subject.

10.2.2 Preparation

As per institutional standards.

10.2.3 Storage and Stability

Pemetrexed for injection, should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Chemical and physical stability of reconstituted and infusion solutions of pemetrexed were

demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated, 2-8°C (36-46°F), or at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). When prepared as directed, reconstituted and infusion solutions of Pemetrexed contain no antimicrobial preservatives. Discard unused portion. Pemetrexed is not light sensitive.

10.2.4 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

After final drug reconciliation, unused pemetrexed vials should be disposed at the site following procedures for the disposal of anticancer drugs.

10.2.5 Incompatibilities and Potential Drug Interactions

Ibuprofen — Daily ibuprofen doses of 400 mg QID reduce pemetrexed's clearance by about 20% (and increase AUC by 20%) in patients with normal renal function. The effect of greater doses of ibuprofen on pemetrexed PK is unknown. Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of pemetrexed. Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially result in delayed clearance of pemetrexed. Although ibuprofen (400 mg QID) can be administered with pemetrexed in patients with normal renal function (creatinine clearance (80 mL/min), caution should be used when administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following pemetrexed administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

10.2.6 Adverse Events

Renal: creatinine elevation (10%)
Neurologic: neuropathy-sensory (9%), taste disturbance (8%)
Hematologic: anemia (33%), neutropenia (29%), leucopenia (18%), thrombocytopenia (10%)
Gastrointestinal: nausea (56%), vomiting (40%), anorexia (27%), constipation (21%), stomatitis/pharyngitis (14%), diarrhea (12%), dyspepsia/heartburn (5%)
Dermatology/skin: alopecia (12%), rash/desquamation (7%)
Other: fatigue, febrile neutropenia, infection, pyrexia, dehydration, increased AST, increased ALT, creatinine clearance decrease, renal failure, conjunctivitis, arrhythmia, chest pain, increased GGT, motor neuropathy

10.3 Atezolizumab

Please refer to the current package insert for complete prescribing and toxicity information.

10.3.1 Supplier/How Supplied

Genentech will provide atezolizumab at no charge to subjects participating in this clinical trial.

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

10.3.2 Preparation

Please refer to the package insert and local guidelines for atezolizumab preparation.

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

Prepare the solution for infusion as follows:

- Withdraw 20mLof TECENTRIQ from the vial.
- Dilute into a250mLpolyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% Sodium Chloride Injection, USP.
- Dilute with 0.9% Sodium Chloride Injection only.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard used or empty vials of TECENTRIQ.

Storage of Infusion Solution
Administer immediately once prepared. If diluted TECENTRIQ infusion solution is not used immediately, store solution either:

- At room temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration of the infusion, or
- Under refrigeration at 2°Cto 8°C (36°F to 46°F) for no more than 24 hours from time of preparation.

10.3.3 Storage and Stability

Clinical supplies must be stored in a secure, limited-access location. Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

10.3.4 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

After final drug reconciliation, unused atezolizumab vials should be disposed at the site following procedures for the disposal of anticancer drugs.

10.3.5 Dispensing

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

10.3.6 Adverse Events

Please refer to the current version of the Investigator's Brochure for a complete list of AEs.

Atezolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Atezolizumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events are of primary concern. Important identified risks for atezolizumab are of an immune mediate nature, including: pneumonitis, colitis, hepatitis, nephritis, endocrinopathies that include hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorder (hypothyroidism, hyperthyroidism), Type I diabetes mellitis, uveitis, myositis, Guillain-Barré syndrome, pancreatitis, myocarditis, severe skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome; and "solid organ transplant rejection following atezolizumab treatment in donor organ recipients"

The majority of immune-mediated adverse events were mild to moderate in severity, were manageable with appropriate care, and rarely required discontinuation of therapy.

The risk profile for atezolizumab also includes 2 important potential risks – i.e. myasthenic syndrome and increased risk of severe complications (such as early severe graft versus host disease and veno-occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors.

Further details around frequency, reporting, and management of immune-related adverse events (irAEs) can be found in the current version of the Investigator's Brochure.

In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated; these are also further described in the current IB.

10.4 Bevacizumab

Please refer to the current package insert for additional information regarding this drug.

10.4.1 Supplier/How Supplied

Bevacizumab is supplied as US commercial Avastin 400 mg per 16 mL single use vials with either clinical or commercial secondary packaging

Genentech will provide bevacizumab at no charge to subjects for their first year of participating in this clinical trial. After one year, subjects will receive commercial supplies of bevacizumab which will be billed to third party payers or the subject.

10.4.2 Preparation and Administration

As per institutional standards.

- Do not administer as an intravenous push or bolus. Administer only as an intravenous (IV) infusion.
- Do not initiate bevacizumab until at least 28 days following major surgery.
- Administer bevacizumab after the surgical incision has fully healed.
- First infusion and subsequent infusions duration as per institutional standards.

10.4.3 Storage and Stability

Unopened vials of bevacizumab are stable until the expiration date indicated on the package when stored at 2° to 8ºC (36° to 46ºF). Bevacizumab vials should be protected from light. **Do not freeze or shake.** Diluted bevacizumab solutions may be stored at 2° to 8ºC (36° to 46ºF) for up to 8 hours. Store in the original carton until time of use. No incompatibilities between bevacizumab and polyvinylchloride or polyolefin bags have been observed.

10.4.4 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

After final drug reconciliation, unused bevacizumab vials should be disposed at the site following procedures for the disposal of anticancer drugs.

10.4.5 Adverse Events

Please refer to the current version of the package insert for a complete list of AEs.

Gastrointestinal Perforations

Serious and sometimes fatal gastrointestinal perforation occurs at a higher incidence in bevacizumab treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.3 to 2.4% across clinical studies.

The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever. Perforation can be complicated by intra-abdominal abscess and fistula formation. The majority of cases occurred within the first 50 days of initiation of bevacizumab.

Discontinue bevacizumab in subjects with gastrointestinal perforation.

Surgery and Wound Healing Complications

Bevacizumab impairs wound healing in animal models. In clinical trials, administration of bevacizumab was not allowed until at least 28 days after surgery. In a controlled clinical trial, the incidence of wound healing complications, including serious and fatal complications, in patients with mCRC who underwent surgery during the course of bevacizumab treatment was 15% and in patients who did not receive bevacizumab, was 4%.

Bevacizumab should not be initiated for at least 28 days following surgery and until the surgical wound is fully healed. Discontinue bevacizumab in subjects with wound healing complications requiring medical intervention.

The appropriate interval between the last dose of bevacizumab and elective surgery is unknown; however, the half-life of bevacizumab is estimated to be 20 days. Suspend bevacizumab for at least 28 days prior to elective surgery. Do not administer bevacizumab until the wound is fully healed.

Necrotizing fasciitis, including fatal cases, has been reported in patients treated with bevacizumab, usually secondary to wound healing complications, gastrointestinal perforation, or fistula formation. Discontinue bevacizumab therapy in subjects who develop necrotizing fasciitis.

Hemorrhage
Bevacizumab can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving bevacizumab compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3 hemorrhagic events among patients receiving bevacizumab ranged from 1.2 to 4.6%.

Serious or fatal pulmonary hemorrhage occurred in four of 13 (31%) patients with squamous cell histology and two of 53 (4%) patients with non-squamous non-small cell lung cancer receiving bevacizumab and chemotherapy compared to none of the 32 (0%) patients receiving chemotherapy alone.

In clinical studies in non–small cell lung cancer where patients with CNS metastases who completed radiation and surgery more than 4 weeks prior to the start of bevacizumab were evaluated with serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of 83 bevacizumab - treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

Intracranial hemorrhage occurred in 8 of 163 patients with previously treated glioblastoma; two patients had Grade 3–4 hemorrhage.

Do not administer bevacizumab to subjects with recent history of hemoptysis of ≥ 1/2 teaspoon of red blood. Discontinue bevacizumab in subjects with hemorrhage.

Non-Gastrointestinal Fistula Formation
Serious and sometimes fatal non-gastrointestinal fistula formation involving tracheoesophageal, bronchopleural, biliary, vaginal, renal, and bladder sites occurs at a higher incidence in bevacizumab - treated patients compared to controls. The incidence of non-gastrointestinal perforation was ≤ 0.3% in clinical studies. Most events occurred within the first 6 months of bevacizumab therapy.

Discontinue bevacizumab in subjects with fistula formation involving an internal organ.

Arterial Thromboembolic Events
Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a higher incidence in patients receiving bevacizumab compared to those in the control arm. Across indications, the incidence of Grade ≥ 3 ATE in the bevacizumab containing arms was 2.6% compared to 0.8% in the control arms. Among patients receiving bevacizumab in combination with chemotherapy, the risk of developing ATE during therapy was increased in patients with a history of arterial thromboembolism, diabetes, or age greater than 65 years.

The safety of resumption of bevacizumab therapy after resolution of an ATE has not been studied. Discontinue bevacizumab in subjects who experience a severe ATE.

Hypertension
The incidence of severe hypertension is increased in patients receiving bevacizumab as compared to controls. Across clinical studies, the incidence of Grade 3 or 4 hypertension ranged from 5-18%.

Monitor blood pressure every two to three weeks during treatment with bevacizumab. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in subjects with bevacizumab -induced or -exacerbated hypertension after discontinuation of bevacizumab.

Temporarily suspend bevacizumab in subjects with severe hypertension that is not controlled with medical management. Discontinue bevacizumab in subjects with hypertensive crisis or hypertensive encephalopathy.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
RPLS has been reported with an incidence of < 0.1% in clinical studies. The onset of symptoms occurred from 16 hours to 1 year after initiation of bevacizumab. RPLS is a neurological disorder, which can present with headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of RPLS.

Discontinue bevacizumab in subjects developing RPLS. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known.

Proteinuria
The incidence and severity of proteinuria is increased in patients receiving bevacizumab as compared to controls. Nephrotic syndrome occurred in < 1% of patients receiving bevacizumab in clinical trials, in some instances with fatal outcome. In a published case series, kidney biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy.

Subjects with a 2 + or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. Suspend bevacizumab administration for ≥ 2 grams of proteinuria/24 hours and resume when proteinuria is < 2 gm/24 hours. Continue to monitor until 24-hr protein demonstrates < 1 g of protein. Discontinue bevacizumab in subjects with nephrotic syndrome. Data from a post-marketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24 hour urine protein (Pearson Correlation 0.39 (95% CI 0.17, 0.57).

Infusion Reactions
Infusion reactions reported in the clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion reactions with the first dose of bevacizumab were uncommon (< 3%) and severe reactions occurred in

0.2% of subjects.

Stop infusion if a severe infusion reaction occurs and administer appropriate medical therapy.

Ovarian Failure
The incidence of ovarian failure was higher (34% vs. 2%) in premenopausal women receiving bevacizumab in combination with mFOLFOX chemotherapy as compared to those receiving mFOLFOX chemotherapy alone for adjuvant treatment for colorectal cancer, a use for which bevacizumab is not approved. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with bevacizumab.

11. ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

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

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

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

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

11.1.2 Laboratory Test Abnormalities

Asymptomatic laboratory abnormalities that do not require treatment will not be collected as adverse events.

However, the following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE or Drug Induced Liver Injury (DILI)
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

Wherever possible, the clinical rather than laboratory term should be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

11.1.3 Serious Adverse Event (SAE)

An SAE is an adverse event that:

- Results in death. **NOTE**: Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Results in a congenital anomaly or birth defect in a neonate/infant born to a mother exposed to the investigational medicinal product.
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.
    - Potential drug induced liver injury (DILI) is also considered an important medical event.
    - Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.
    - Although pregnancy is not always serious by regulatory definition, it must be handled as an SAE.
    - Bevacizumab and/or atezolizumab overdose. For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for bevacizumab and/or atezolizumab by 20%.
    - Any venous or arterial event leading to discontinuation of bevacizumab will be considered serious and should be reported per SAE guidelines.
    - Cases of RPLS must be reported per SAE guidelines.

11.1.4 Pregnancy

If a female subject or a female partner of a male subject becomes pregnant while receiving the study drug or within 5 months after the last dose of study drug, an SAE report should be completed and submitted to Big Ten CRC AHQ according to the SAE reporting timelines described in 11.3.1. 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.

11.1.5 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, package insert, or when it is not included in the informed consent document as a potential risk. For example, under this definition, hepatic necrosis would be unexpected if the prescribing information or Investigator's Brochure only referred to elevated hepatic

enzymes or hepatitis. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.6 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

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

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

Yes
There is a plausible temporal relationship between the onset of the AE and administration of Atezolizumab, and the AE cannot be readily explained by the subject's clinical state, inter-current illness, or concomitant therapies; and/or the AE follows a known pattern of response to Atezolizumab; and/or the AE abates or resolves upon discontinuation of atezolizumab or dose reduction and, if applicable, reappears upon re- challenge.

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

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

11.1.7 AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the local investigator to Big Ten CRC AHQ 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 Big Ten CRC AHQ to other parties (e.g., Regulatory Authorities) may also be warranted.

The site will submit a completed SAE Submission Form (see Documents/ Info tab of the EDC) to Big Ten CRC AHQ within **3 business days** of discovery of the event to safety@hoosiercancer.org. Big Ten CRC AHQ will forward AESIs to Genentech **within fifteen (15) calendar days** of the awareness date.

Non-Drug Specific AESIs are:

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
  - Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 x ULN
  - Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice
- Suspected transmission of an infectious agent by Atezolizumab and Bevacizumab, 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.

The Atezolizumab Events of Special Interest are:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 × ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness and systemic inflammatory response syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

The Bevacizumab Adverse Events of Special Interest are:

- Hypertension ≥ grade 3
- Proteinuria ≥ grade 3
- GI perforation, abscesses and fistulae (any grade)
- Wound healing complications ≥ grade 3
- Haemorrhage ≥ grade 3 (any grade CNS bleeding; > grade 2 haemoptysis)
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events ≥ grade 3
- Posterior reversible encephalopathy syndrome (PRES - any grade)
- CHF ≥ grade 3

- Non-GI fistula or abscess ≥ grade 2

11.2 Adverse Events Recording

- AEs will be recorded from time of signed informed consent until 90 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.
- Asymptomatic laboratory abnormalities that do not require treatment will not be collected as adverse events.

11.2.1 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

A. 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.

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

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

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

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

E. 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. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (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

11.3 Serious Adverse Event (SAEs) Reporting

11.3.1 Site Requirements for Reporting SAEs to Big Ten CRC Administrative Headquarters

- SAEs will be reported from time of signed informed consent until 90 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs will be reported on the SAE Submission Form and entered in the SAE tab in the EDC system **within 1 business day** of discovery of the event.

- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.
- All Product Complaints (with or without an AE) shall be forwarded within fifteen (15) calendar days of the awareness date.
- 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 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.

The site will submit the completed SAE Submission Form (see Documents/ Info tab of the EDC) to Big Ten CRC AHQ within **1 business day** of discovery of the event. The form will be sent electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies of the SAE as per local requirements.

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

Once the SAE has resolved, sites must submit a follow up SAE Submission Form within a reasonable timeframe to Big Ten CRC AHQ electronically to safety@hoosiercancer.org.

11.3.2 Big Ten CRC AHQ Requirements for Reporting SAEs to Genentech (GNE)

Big Ten CRC AHQ will report all SAEs to GNE within 1 business day of receipt of the SAE Submission Form from a site. Follow-up information will be provided to GNE as it is received from site.

Please refer to the Genentech Safety Data Exchange Agreement (SDEA) for contact information.

11.3.3 Sponsor-Investigator Responsibilities

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

11.3.4 Big Ten CRC AHQ Responsibilities for Reporting SAEs to FDA

Big Ten CRC AHQ has been designated to manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. Big Ten CRC AHQ will cross-reference this submission to Genentech's parent IND at the time of submission. Additionally, Big Ten CRC AHQ will submit a copy of these documents to Genentech at the time of submission to FDA.

Big Ten CRC AHQ will be responsible for all communication with the FDA in accordance with 21CFR312 which includes but is not limited to the 7 and 15 Day Reports, as well as an Annual

Progress Report. Additionally, Big Ten CRC AHQ will submit a copy of these reports to Genentech at the time of submission to FDA.

11.3.5 IND Safety Reports Unrelated to this Trial

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

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

12. STATISTICAL CONSIDERATIONS

Statistical analysis will be performed at the Department of Biostatistics at Indiana University School of Medicine. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol; however all changes from the original analysis plan will be documented in the final study report. The statistical analysis methods are outline below.

12.1 Study Design

This is a multicenter single arm phase II clinical trial.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

Progression free survival (PFS) is defined as the time from the initiation of treatment to the time when the criteria for disease progression is met as defined by RECIST v1.1 OR death due to any cause. The PFS is subject to right censoring due to loss to follow-up or at the end of study duration. For patients who have not progressed and are alive at the last contact, the censoring time is defined as the time from the initiation of treatment to the time of the last disease evaluation.

12.2.2 Definition of Secondary Endpoints

Secondary objectives include the overall response rate (CR + PR), as well as the disease control rate (CR + PR + SD), toxicity, and overall survival.

- Response rate is defined as the number of confirmed complete response (CR) + confirmed partial response (PR) divided by the total number evaluable for response, as determined as per RECIST v1.1 criteria and assessed by the local investigator or designee.
- Disease Control Rate is defined as the number of confirmed complete response (CR) + confirmed partial response (PR) + stable disease (SD) divided by the total number evaluable for response, as determined as per RECIST v1.1 criteria.

- Toxicities will be defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.
- Overall survival will be defined as the time from the initiation of treatment until death from any cause.

12.3 Sample Size and Accrual

The study will evaluate whether carboplatin plus pemetrexed plus atezolizumab plus bevacizumab will improve the PFS compared to the PFS of carboplatin plus pemetrexed plus bevacizumab as reported in the literature. According to the current knowledge as reported in the literature, the median PFS for patients treated with carboplatin plus pemetrexed plus bevacizumab is approximately 6 months. We hypothesize that carboplatin plus pemetrexed plus atezolizumab plus bevacizumab will improve the median PFS to 9.6 months.

The total study duration is 30 months, where the accrual period for the trial is 18 months and each patient will have a pre-scheduled follow-up of 12 months except for reason due to death. The test statistic is the nonparametric one-sample log-rank test [28]. The sample size was calculated using the PASS sample size software, one-sample log-rank tests procedure. The assumptions are uniform accrual over time, no loss to follow-up, exponentially distributed PFS times. A sample size of 42 patients would detect the hypothesized PFS difference with 83.5% power with 1-sided type I error of 0.05. To ensure the power of study, the study would require all accrued patients to complete the 1-year follow-up or until death. The expected number of events is 32. Suppose a rate of loss to follow-up of 5%. Then we anticipate recruiting 46 patients. If all 46 patients finish their pre-scheduled follow-up, then the power of the study is 86.3%. We thus propose a total sample size of 46 patients. The expected number of events is 35.

Because of the short accrual period (18 months), no interim analysis is planned to avoid the interruption of the study flow. The primary analysis will start when the last accrued patient finishes the 1-year follow-up.

12.4 Analysis Datasets

Population	Definition
Enrolled	This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
Full analysis set for efficacy	The efficacy population will comprise all registered subjects who have received at least one dose of the treatment.
Safety	The safety population will comprise all subjects who received at least one dose of study medication. This population will be used for safety analysis.

12.5 Assessment of Safety

Patients that have received at least one dose of study medication will be assessed for safety. Toxicities according to CTCAE v5 will be summarized by frequencies and rates calculated as the proportion of patients in the safety population experiencing SAEs, discontinuations due to AEs, and AEs.

12.6 Assessment of Efficacy

Response Rate, disease control rate, and PFS will be assessed with RECIST v1.1. All registered subjects will be evaluable for efficacy.

12.7 Data Analysis Plans

12.7.1 Analysis Plans for Primary Objective

The hypothesis on PFS will be tested using the nonparametric one-sample log-rank test[28]. PFS will estimated with a Kaplan-Meier curve and 1-year PFS will be calculated with a 95% confidence interval.

12.7.2 Analysis Plans for Secondary Objectives

Response rate will be summarized as a rate measured as a proportion of patients in the efficacy population who achieved CR or PR during the study along with a 95% exact confidence interval. Disease control rate will be summarized as the proportion of patients who achieve CR or PR or SD with a 95% exact confidence interval. OS will be estimated with a Kaplan-Meier curve and 1-year OS will be calculated with a 95% confidence interval.

12.7.3 Analysis Plans for Exploratory Objectives

Tissue samples will be collected at baseline and blood markers will be collected at baseline, after cycle 1 and at end of study. Markers will be correlated with clinical outcomes and specific toxicities using logistic and Cox regression methods, which will include important covariates such as age, gender, and genotypes. Changes over time for blood markers will be analyzed with paired t-tests.

12.7.4 Subgroup Analyses

No pre-specified subgroup analyses are planned.

12.7.5 Other Planned Analyses

Subject characteristics, significant protocol violations, concomitant medication, exposure and compliance will be described.

12.8 Interim Analysis/Criteria for Stopping Study

Because of the short accrual period (1 year), no interim analysis is planned to avoid the interruption of the study flow.

Toxicities will be continuously monitored to determine if, in the first 10 subjects treated with at least one dose of study drug and observed for a minimum of 3 months after first dose of study therapy, two or more patients experience unacceptable toxicities warranting early closure of the trial, defined as: a) any treatment death; or b) any unexpected grade 3 or 4 toxicity lasting more than 2 weeks. If such events are observed as described above, the DSMC will discuss and provide recommendations to the sponsor-investigator whether to terminate the study.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted with guidance from the Indiana University Melvin and Bren Simon Cancer Center's (IUSCC) DSMP for High Risk Phase II Trials.

BTCRC AHQ facilitated oversight activities for High Risk Phase II Trials include:

- Review and processing of all AEs requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator, including a weekly update of aggregate AE data. For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the sponsor investigator will notify Big Ten CRC AHQ who will notify the DSMC Chair and Compliance Officer immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.
- Notify of participating sites of adverse events potentially requiring expedited reporting and subsequent DSMC recommendations for study modifications.
- Investigators will conduct continuous review of data and patient safety.
- BTCRC AHQ will coordinate monthly (Phase II) meetings which will include representation from each accruing site.
    - These meetings should include review of data, the number of subjects, and significant toxicities as described in the protocol. Big Ten CRC AHQ will maintain meeting minutes and attendance for submission to the DSMC upon request.
- Conduct the trial across all participating sites in accordance with the requirements set forth in the IUSCC DSMP.
- Submit data summary reports to the lead institution Data Safety Monitoring Committee for review as per their DSMP

13.2 IUSCC Data Safety Monitoring Committee Oversight

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study to assess toxicity, compliance, data integrity, and accrual per the Institutional DSMP. Trials managed by Big Ten CRC AHQ are not routinely audited or monitored by IUSCC; however, the IUSCC DSMC retains the right to audit Big Ten CRC AHQ trials on a for cause basis.

The IUSCC DSMC will review study data semi-annually during the active treatment and safety follow-up portion of the trial per the IUSCC DSMP.

In preparation for the IUSCC DSMC review, Big Ten CRC AHQ will provide the IUSCC DSMC with the following:

- Monthly Summary Reports
- Reports of the following, if not already included in the Monthly Summary Report:
    - Adverse event summary report (including serious adverse events)
    - Study accrual patterns
    - Protocol deviations
- Audit and/or monitoring results, if applicable

- Data related to stopping/ dose decision rules described in study design
- Big Ten CRC AHQ monthly (Phase II) meeting minutes/ attendance

Documentation of DSMC reviews will be provided to the sponsor-investigator and Big Ten CRC AHQ. The IUSCC DSMC will notify the sponsor-investigator and other regulatory bodies, as appropriate, for issues of immediate concern. The sponsor-investigator will work with Big Ten CRC AHQ to address the DSMC's concerns as appropriate.

At any time during the conduct of the trial, if it is the opinion of the sponsor-investigator that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the DSMC Chair and Compliance Officer. Alternatively, the DSMC may initiate suspension or early closure of the study at any time based on its review of the investigator reports.

13.3 IND Annual Reports

For trials with an IND held locally by the IU principal investigator or university, the IND Annual Report will be prepared and submitted to the Compliance Team. This report will be reviewed by the DSMC at the time of FDA submission.

13.4 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

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

13.5 Compliance with Trial Registration and Results Posting Requirements

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

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

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

14.2 Case Report Forms and Submission

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

The completed dataset is housed at Big Ten CRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and Big Ten CRC AHQ. After the initial publication, the complete data set will be available to all Big Ten CRC institutions.

14.3 Record Retention

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

14.4 Confidentiality

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

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

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

14.5 Aggregate Reports

The sponsor-investigator (Nasser Hanna) will forward a copy of the Final Study Report to Genentech/Roche upon completion of the study.

14.6 Study Close-out

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

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

15. ETHICS

15.1 Institutional Review Board (IRB) Approval

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

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

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

15.2 Ethical Conduct of the Study

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

15.3 Informed Consent Process

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

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

16. REFERENCES

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2015.* CA Cancer J Clin, 2015. **65**(1): p. 5-29.
2. *American Cancer Society. Cancer Facts & Figures 2017. Atlanta: American Cancer Society; 2017.*
3. Schiller, J.H., et al., *Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer.* N Engl J Med, 2002. **346**(2): p. 92-8.
4. Derman, B.A., et al., *Treatment of advanced squamous cell carcinoma of the lung: a review.* Translational Lung Cancer Research, 2015. **4**(5): p. 524-532.
5. Pao, W. and N. Girard, *New driver mutations in non-small-cell lung cancer.* The Lancet Oncology. **12**(2): p. 175-180.
6. Al-Saleh, K., C. Quinton, and P.M. Ellis, *Role of pemetrexed in advanced non-small-cell lung cancer: meta-analysis of randomized controlled trials, with histology subgroup analysis.* Current Oncology, 2012. **19**(1): p. e9-e15.
7. Johnson, D.H., et al., *Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer.* J Clin Oncol, 2004. **22**(11): p. 2184-91.
8. Scagliotti, G.V., et al., *Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer.* J Clin Oncol, 2008. **26**(21): p. 3543-51.
9. Ciuleanu, T., et al., *Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study.* Lancet, 2009. **374**(9699): p. 1432-40.
10. Paz-Ares, L., et al., *Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial.* Lancet Oncol, 2012. **13**(3): p. 247-55.
11. Ferrara, N., *The role of vascular endothelial growth factor in pathological angiogenesis.* Breast Cancer Res Treat, 1995. **36**(2): p. 127-37.
12. Folkman, J., *What Is the Evidence That Tumors Are Angiogenesis Dependent?* JNCI: Journal of the National Cancer Institute, 1990. **82**(1): p. 4-7.
13. Hurwitz , H., et al., *Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer.* New England Journal of Medicine, 2004. **350**(23): p. 2335-2342.
14. Sandler , A., et al., *Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer.* New England Journal of Medicine, 2006. **355**(24): p. 2542-2550.
15. Patel, J.D., et al., *PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer.* J Clin Oncol, 2013. **31**(34): p. 4349-57.
16. Okazaki, T., et al., *PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine.* Proc Natl Acad Sci U S A, 2001. **98**(24): p. 13866-71.
17. Greenwald, R.J., G.J. Freeman, and A.H. Sharpe, *The B7 family revisited.* Annu Rev Immunol, 2005. **23**: p. 515-48.

18. Garon, E.B., et al., *Pembrolizumab for the treatment of non-small-cell lung cancer.* N Engl J Med, 2015. **372**(21): p. 2018-28.
19. Langer, C.J., et al., *Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study.* Lancet Oncol, 2016. **17**(11): p. 1497-1508.
20. Gandhi, L., et al., *Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer.* New England Journal of Medicine. **378**(22): p. 2078-2092.
21. Manegold, C., et al., *The Potential of Combined Immunotherapy and Antiangiogenesis for the Synergistic Treatment of Advanced NSCLC.* J Thorac Oncol, 2017. **12**(2): p. 194-207.
22. Shin, S.J., et al., *The Association Between PD-L1 Expression and the Clinical Outcomes to Vascular Endothelial Growth Factor-Targeted Therapy in Patients With Metastatic Clear Cell Renal Cell Carcinoma.* Oncologist, 2015. **20**(11): p. 1253-60.
23. Yasuda, S., et al., *Simultaneous blockade of programmed death 1 and vascular endothelial growth factor receptor 2 (VEGFR2) induces synergistic anti-tumour effect in vivo.* Clin Exp Immunol, 2013. **172**(3): p. 500-6.
24. Herbst RS, B.J., Isambert N, et al., *A phase 1 study of ramucirumab (R) plus pembrolizumab (P) in patients with advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma, nonsmall cell lung cancer (NSCLC), or urothelial carcinoma (UC): phase 1a results [abstract].* J Clin Oncol, 2016.
25. Michael B. Atkins, D.F.M., Thomas Powles, Robert J. Motzer, Brian I. Rini, Lawrence Fong, Richard Wayne Joseph, Sumanta K. Pal, Mario Sznol, John D. Hainsworth, Walter Michael Stadler, Thomas E. Hutson, Alain Ravaud, Sergio Bracarda, Cristina Suarez, Toni K. Choueiri, Jiaheng Qiu, Mahrukh A. Huseni, Christina Schiff, Bernard J. Escudier; , *IMmotion150: A phase II trial in untreated metastatic renal cell carcinoma patients of atezolizumab and bevacizumab vs and following atezolizumab or sunitinib.* 2017 ASCO Annual Meeting. Abstract 4505. . .
26. Reck, M., et al., *LBA1_PRPrimary PFS and safety analyses of a randomized phase III study of carboplatin + paclitaxel +/− bevacizumab, with or without atezolizumab in 1L non-squamous metastatic nsclc (IMPOWER150).* Annals of Oncology, 2017. **28**(suppl_11): p. mdx760.002-mdx760.002.
27. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.
28. Kwak MJ, Jung SH. Phase II clinical trials with time-to-event endpoints: Optimal two-stage designs with one-sample log-rank test. Statistics in Medicine. 2014;33:2004–2016.
29. Lee DW, Santomasso BD, Locke FL et al. *ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells*. Biol Blood Marrow Transplant. 2019 Apr;**25**(4):625-638.
30. Rotz SJ, Leino D, Szabo S, et al. *Severe cytokine release syndrome in a patient receiving PD-1-directed therapy*. Pediatr Blood Cancer 2017;**64**:e26642.
31. Adashek ML, Feldman M. *Cytokine release syndrome resulting from anti-programmed death-1 antibody: raising awareness among community oncologist*. J Oncol Practice 2019;**15**:502-4.
32. Riegler LL, Jones GP, Lee DW. *Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy*. Ther Clin Risk Manag 2019;**15**:323-35.

17. APPENDIX I: 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.

18. APPENDIX II: MANAGEMENT OF ATEZOLIZUMAB-SPECIFIC ADVERSE EVENTS

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

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

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate)

PULMONARY EVENTS

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

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events 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 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. • For recurrent events, 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 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

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

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

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

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 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function tests.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully

recovered from the immune-related event. 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 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. 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 for life-threatening immune-related hyperthyroidism. c
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent

Event	Management
	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 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.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

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 ≤ 10 mg/day oral prednisone or equivalent. 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 ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. 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 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. 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, 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 GI illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

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

Table 6 Management Guidelines for Immune-Related Myocarditis

Event	Management
Immune-related myocarditis, Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
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 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. [a] • 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 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. [a,b] • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

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

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

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 premedication with antihistamines, antipyretics and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with

atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction [29]. 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 [30, 31], 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.

Table 7 Management Guidelines for Infusion-Related Reactions

Event	Management
Grade 1[a] Fever[b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait 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 Medical Monitor.
Grade 3[a] Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	• Permanently discontinue atezolizumab.[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. • 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 only after approval has been documented by the investigator (or an appropriate delegate). 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. [32] 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 work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

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

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

GI = gastrointestinal.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. 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. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist. • 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. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b]

Event	Management
	• 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]

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time will be determined by the investigator.
[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. 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 work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be determined by the investigator.
[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. 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 11.

Table 11 Management Guidelines for Immune-Related Meningoencephalitis

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

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

IMMUNE-RELATED NEPHRITIS

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

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

Table 12 Management Guidelines for Immune-Related Nephritis

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 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator.
b. If corticosteroids have been initiated, they must be tapered over 1 month to 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

IMMUNE-RELATED MYOSITIS

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

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

Table 13 Management Guidelines for Immune-Related Myositis

Event	Management
Immune-related myositis, Grade 1	• Continue atezolizumab • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-related myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset (a) • 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

Event	Management
	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. (c)
Immune-related myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. (a) • 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 prednisolone 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. (c) • For recurrent events, treat as a Grade 4 event.
Immune-related myositis, Grade 4	• Permanently discontinue atezolizumab. (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 limiting 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.

d. Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator.
e. If corticosteroids have been initiated, they must be tapered over 1 month to 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
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 only after approval has been documented by the investigator (or an appropriate delegate).