A Phase II study of Atezolizumab and Bevacizumab in Child-Pugh B7 and B8 Hepatocellular Carcinoma (The AB7 Trial)

Big Ten Cancer Research Consortium BTCRC-GI20-457

Sponsor Investigator
Howard S. Hochster, MD
Rutgers Cancer Institute of New Jersey

Sub-Investigators
Kristen Spencer, DO, MPH
NYU Langone Health Perlmutter Cancer Center

Statistician
Dirk Moore, PhD

Trial Management Provided by
Big Ten CRC Administrative Headquarters at Hoosier Cancer Research Network, Inc.
7676 Interactive Way, Suite 120
Indianapolis, IN 46278

Trial Supported by
Genentech
(RO-IIS-2020-20529)

Investigational New Drug (IND) Number:
Exempted by the FDA on 16DEC2020

Initial Protocol Version Date: 05NOV2020

Protocol Amendment Version Date:
07JAN2021
08FEB2021
30AUG2022
09MAY2023 (current)

PROTOCOL SIGNATURE PAGE

Protocol title: A Phase II study of Atezolizumab and Bevacizumab in Child-Pugh B7 and B8 Hepatocellular Carcinoma (The AB7 Trial)

VERSION DATE: 09MAY2023

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

_____
Site Investigator Name (printed)

_____
Site Investigator Title

_____
Name of Facility

_____
Location of Facility (City and State)

PLEASE EMAIL COMPLETED FORM TO
BIG TEN CRC ADMINISTRATIVE HEADQUARTERS

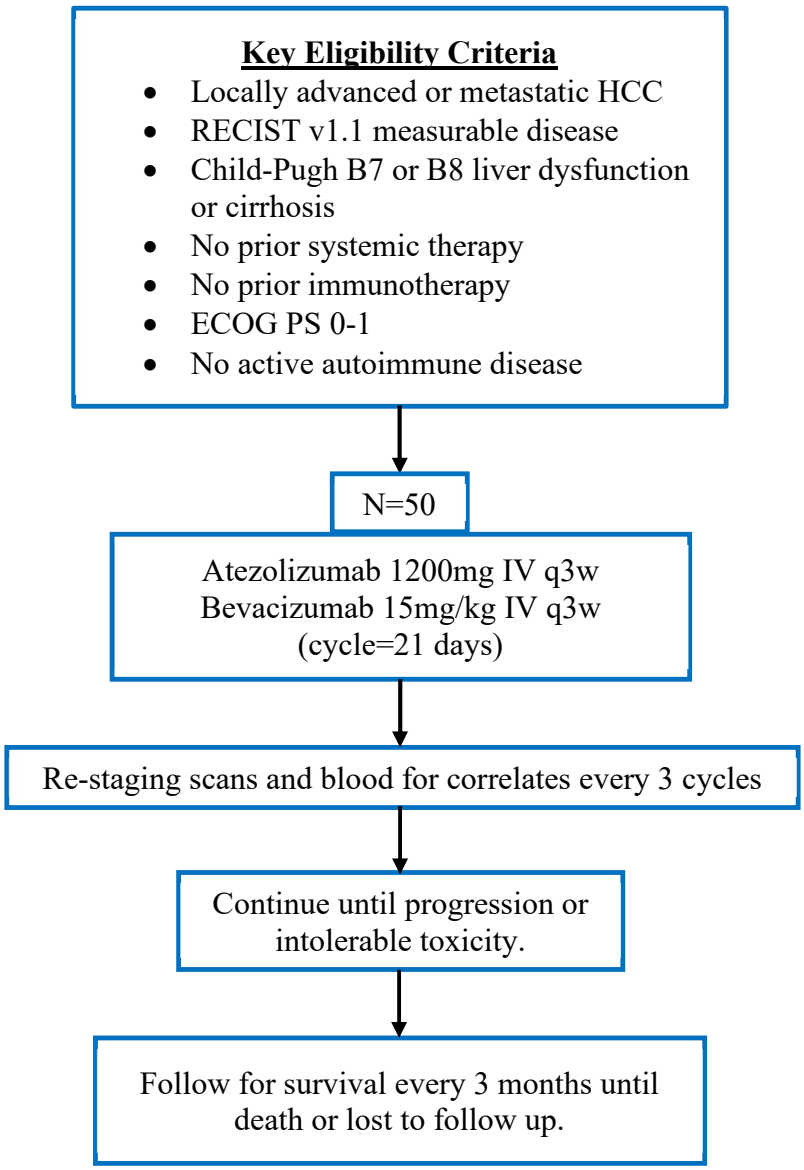
SYNOPSIS

TITLE	A Phase II study of Atezolizumab and Bevacizumab in Child-Pugh B7 and B8 Hepatocellular Carcinoma (The AB7 Trial)
PHASE	II
OBJECTIVES	Primary Objective: To estimate the safety of the combination of atezolizumab and bevacizumab in patients with advanced/metastatic HCC and Child-Pugh B7 and B8 liver dysfunction by grade 3-5 adverse event rate. Secondary Objectives: To estimate the efficacy of the combination in this patient population by overall response rate (ORR), disease control rate (DCR), duration of response (DOR), progression free survival (PFS), and overall survival (OS). Exploratory Objectives: 1) To correlate tumor molecular signature from NGS tissue analysis with clinical outcomes and treatment response. 2) To correlate tumor molecular signature from NGS tissue analysis with ctDNA. 3) To correlate levels of ctDNA with clinical outcomes and treatment response.
KEY ELIGIBILITY CRITERIA (See Section 3 for full eligibility criteria)	1) Age ≥ 18 years. 2) Eastern Cooperative Oncology Group (ECOG) PS 0-1. 3) Locally advanced, metastatic, or unresectable hepatocellular carcinoma that has not received prior systemic therapy. If no prior histologic diagnosis exists, prefer fresh biopsy if both safe and feasible. Imaging criteria per AASLD guidelines may be used for diagnosis if biopsy is not safe and feasible. 4) Child Pugh Class B7 or B8 liver dysfunction or cirrhosis. 5) No GI or esophageal variceal hemorrhage/perforation, hemoptysis, or intracranial hemorrhage within 3 months prior to treatment. 6) No prior systemic therapy for HCC. 7) No prior immunotherapy. 8) At least 1 untreated measurable lesion according to RECIST 1.1. 9) Willingness to undergo fresh tumor biopsy at baseline if indicated and safe and feasible. 10) Next generation sequencing analysis will be requested from archival tissue or fresh biopsy (if applicable), preferable Foundation One CDX if indicated. 11) Adequate bone marrow and organ function defined in the body of the protocol. 12) EGD demonstrating no signs of actively bleeding varices within 6 months prior to start of study therapy (documented varices should be treated appropriately).

	13) No clinically significant ascites or hepatic encephalopathy. (see exclusion 3.2.6 and 3.2.7) 14) No active autoimmune disease requiring systemic corticosteroids greater than the equivalent of prednisone 10 mg daily or other systemic immunosuppressive medications. 15) No untreated/uncontrolled CNS/leptomeningeal disease 16) No known concurrent malignancy that is expected to require active treatment within two years. 17) No prior chemotherapy, biological cancer therapy, or investigational agent/device within 21 days of first planned dose of study therapy (within 14 days for palliative radiation).
STATISTICAL CONSIDERATIONS	This will be a nonrandomized, single arm feasibility study with the primary goal of evaluating the safety profile of the combination of atezolizumab and bevacizumab in patients with advanced/metastatic HCC with Child-Pugh B7 and B8 liver disease. Based on the grade 3-5 event rate in the IMbrave 150 trial, we hypothesize that a grade 3-5 treatment-related adverse event rate less than 50% in patients with Child-Pugh B7 and B8 liver disease will be considered acceptable. We will use a Bayesian continuous monitoring approach for toxicity rate.
TOTAL NUMBER OF SUBJECTS	N = 50
ESTIMATED ENROLLMENT PERIOD	18-20 months after all participating institutions open to accrual
ESTIMATED STUDY DURATION	24-26 months after all participating institutions open to accrual

TABLE OF CONTENTS

SCHEMA


Key Eligibility Criteria
Locally advanced or metastatic HCC
RECIST v1.1 measurable disease
Child-Pugh B7 or B8 liver dysfunction or cirrhosis
No prior systemic therapy
No prior immunotherapy
ECOG PS 0-1
No active autoimmune disease
N=50
Atezolizumab 1200mg IV q3w
Bevacizumab 15mg/kg IV q3w
(cycle=21 days)
Re-staging scans and blood for correlates every 3 cycles
Continue until progression or intolerable toxicity.
Follow for survival every 3 months until death or lost to follow up.

1. BACKGROUND AND RATIONALE

1.1 Advanced/Metastatic Hepatocellular Carcinoma

While hepatocellular carcinoma (HCC) has been relatively rare in the United States, both the incidence and death rate have been on the rise over the last ten years. While the Hepatitis B virus (HBV) is the main risk factor for HCC in Asian and Africa, the overwhelming majority of cases in the United States are attributed to Hepatitis C (HCV), alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD). Unfortunately, HCC is currently the fastest-increasing cancer-related cause of death in the United States. While over 70% of patients present with localized or regional disease, only 18% of patients will be alive 5 years after their diagnosis, a particularly alarming statistic given the median age at diagnosis is only 64 [1-4].

1.2 Current Standard of Care

In patients with adequate performance status (PS) who have progressed on liver directed therapy (LDT) or have metastatic disease or extensive tumor burden, systemic therapy is recommended. Prior to the approval of sorafenib in the United States, there was no standard FDA approved treatment for unresectable advanced/metastatic HCC. Several cytotoxic chemotherapy combinations have been used in this setting, however none resulted in a demonstrable improvement in median overall survival (OS)[5-8].

Sorafenib, an oral multikinase inhibitor (TKI), was considered to be the first global standard of care for the first-line treatment of patients with advanced HCC after the SHARP trial demonstrated a survival benefit in patients with advanced/metastatic HCC over placebo[9]. The SHARP trial was a phase III, double-blind, placebo-controlled trial where patients were randomized to receive either sorafenib (400 mg twice daily) or placebo[9]. Sorafenib improved median OS from 7.9 months to 10.7 months, and median time to radiologic progression (5.5 vs 2.8 months), though the response rate was low (2%)[9]. This study led to the FDA approval of sorafenib in 2007. Despite the demonstrated overall survival benefit, efficacious use of sorafenib is limited by its toxicity profile.

Since the approval of sorafenib there have been several additional systemic therapy approvals in the first and second line settings for the treatment of advanced/metastatic HCC. Unfortunately, results in this setting are disappointing, with median overall survivals of 1 year or less with TKI therapies[10,11], and second line nivolumab or pembrolizumab showing promisingly durable responses (range 17 mos-NR) and improvements in OS (mOS 12-15 mos) but low response rates (15-17%)[12,13].

The cautiously optimistic results with checkpoint inhibitor (CPI) monotherapy have generated interest in novel combinations that may improve efficacy. Combinations with vascular endothelial growth factor (VEGF) inhibitors are of interest given the known immunomodulatory effects of VEGF in the tumor microenvironment, including promoting inhibitory immune cells, suppressing maturation of dendritic cells, decreasing cytotoxic T cell responses, and altering lymphocyte development and trafficking[14]. Increasing the efficacy of CPIs by combinations including VEGF inhibitors was shown to be active in phase 1b combination trials, and was bore out clinically in the phase III IMbrave150 trial where a combination of atezolizumab and bevacizumab resulted in impressive improvements in RR (27% vs 12%), PFS (HR 0.59), and OS (HR 0.58) over sorafenib[15] in first line therapy for unresectable, locally advanced, and metastatic HCC. The combination of atezolizumab and bevacizumab is now FDA approved for the treatment of advanced/metastatic HCC.

Unfortunately, patients with the clinically frequent Child-Pugh B classification have been systematically excluded in the above trials (1 patient in IMbrave150, technically not eligible), although they typically make up 20-30% of presenting first-line patients[16-18]. Thus, data driven treatment in these patients is limited to the available data with sorafenib, lenvatinib, and nivolumab[19-21], consequentially limiting the application of combinations with significant benefit to a subset of patients. As such, identifying an acceptable standard of care with a routinely clinically meaningful impact on OS with a tolerable toxicity profile in patients with advanced/metastatic HCC with B7 and B8 liver disease remains an ongoing unmet need. However, a recent study of nivolumab in Child-Pugh B7 patients demonstrated a similar safety profile and efficacy to Child-Pugh A patients[20], suggesting a role for further investigation of combinations in a broader patient population.

The combination of Atezolizumab and Bevacizumab was statistically and clinically superior to standard sorafenib in first line therapy of advanced/metastatic HCC, but this study was limited to C-P stage A patients. We propose to study the same regimen in the large subset of HCC patients with C-P stage B7 and B8 liver dysfunction to determine safety and efficacy.

1.3 Investigational Treatment (Atezolizumab + Bevacizumab)

1.3.1 Atezolizumab

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity[22,23]. Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy. Atezolizumab is approved in multiple countries in several indications. Refer to the atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.3.1.1 Clinical Development of Atezolizumab Monotherapy in Hepatocellular Carcinoma

1.3.1.1.1 *Study PCD4989g*

Study PCD4989g is a Phase Ia, multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion every 3 weeks (Q3W) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.

In the analysis of Study PCD4989g (clinical cutoff date of December 31, 2016) conducted in 15 patients with first- and later-line HCC, the median duration of treatment was 2.0 months (range: 0.7-6.3 months). At the time of the clinical cutoff date, 1 patient remained on treatment, 12 patients had discontinued treatment due to disease progression, 1 patient discontinued because of an adverse event, and 1 patient

was discontinued as per the physician's decision. Of the 15 response-evaluable patients, none had an objective response (confirmed complete response [CR] or partial response [PR] as assessed by investigator per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1). Four patients (33.3%) had stable disease (SD) < 24 weeks. No patients had SD ≥ 24 weeks. Median progression-free survival (PFS) per investigator assessment per RECIST v1.1 was 2.3 (95% CI: 1.3, 3.4) months and median OS was 5.3 (95% CI: 2.4, NE) months.

1.3.1.1.2 *Study YO29233*

Study YO29233 is a Phase I, open-label, multicenter study evaluating the pharmacokinetics, safety, and preliminary anti-tumor activity of atezolizumab as monotherapy in Chinese patients with locally advanced or metastatic gastric cancer, nasopharyngeal carcinoma, esophageal cancer, HCC and other solid tumors, and the safety and preliminary anti-tumor activity of atezolizumab in combination with gemcitabine and cisplatin in Chinese patients with Stage IV, treatment-naive NSCLC. For monotherapy cohorts, atezolizumab is administered as a single agent at a dose of 1200 mg IV Q3W. Based on a clinical cutoff date of 1 April 2018, 21 patients with HCC had received atezolizumab monotherapy. At the time of the clinical cutoff date, 7 patients remained on treatment (3 first-line HCC patients), while 7 patients had discontinued treatment due to disease progression, 2 patients discontinued treatment due to an adverse event, 2 patients discontinued treatment due to non-compliance with study drug, and 1 patient each discontinued treatment due to a protocol deviation, physician decision, and death due to progression of disease.

Of the 21 efficacy-evaluable patients (first-line and second-line or greater), 2 patients (9.5% [95% CI: 1.17%, 30.38%]) had a confirmed objective response and 11 patients (52.4% [95% CI: 29.78%, 74.29%]) had a best response of SD. Median PFS was
2.8 months (95% CI: 1.4, 7.8 months) and median OS was 11.1 months (95% CI: 4.7 months, NE).

1.3.2 Bevacizumab

Avastin (bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in in vitro and in vivo assay systems. Bevacizumab contains human framework
regions and the complementarity-determining regions of a murine antibody that binds to VEGF, and has an approximate molecular weight of 149 kD. Bevacizumab is produced in a mammalian Chinese hamster ovary cell line.

Bevacizumab was first granted marketing approval in the United States on 26 February 2004 (international birth date) in combination with IV 5-fluorouracil (5-FU)-based chemotherapy for the first-line treatment of patients with metastatic carcinoma of the colon or rectum (CRC). As of November 2016, bevacizumab has been approved for use in over a 100 countries worldwide in a variety of indications. Refer to the bevacizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.3.2.1 Clinical Development of Bevacizumab Monotherapy in Hepatocellular Carcinoma

1.3.2.1.1 *Phase II Study of Bevacizumab in Unresectable Hepatocellular Carcinoma*

This study was a Phase II, single center, single arm trial designed to evaluate the clinical and biological effects of bevacizumab in unresectable HCC[24]. Adult patients with organ-confined HCC, ECOG Performance Status of 0-2, and compensated liver function (Child-Pugh class A or B7), received

bevacizumab 5 mg/kg or 10 mg/kg every 2 weeks (Q2W) until disease progression or treatment-limiting toxicity. Of note, patients with extrahepatic disease, tumor invasion of the main portal vein or inferior vena cava were excluded. Given the known prognostic value of these factors, the study likely enrolled a population with a more favorable prognosis and treatment outcome compared with a population that would typically be enrolled in a first-line HCC study. The primary objective was to determine whether bevacizumab improved the 6-month PFS rate from 40% to at least 60%. Overall, 46 patents were enrolled, including 12 patients who received bevacizumab 5 mg/kg and 34 patients who received bevacizumab 10 mg/kg Q2W.

Clinical activity of bevacizumab was observed in patients with nonmetastatic HCC. Of the 46 patients, 6 patients (13%) had objective responses (95% CI: 3%, 23%), and 65% (95% CI: 51%, 79%) of patients were progression free at 6 months. Median PFS was 6.9 months (95% CI: 6.5, 9.1) and median OS was 12.4 months (95% CI: 9.4, 19.9). No significant changes were seen with respect to dose and outcome. The response rates for the 5 mg/kg and 10 mg/kg groups were 8.3% and 14.7%, respectively ($p = 0.99$ by Fisher's exact test). Median OS times for patients receiving 5 mg/kg and 10 mg/kg were 15.1 months and 12.2 months, respectively ($p = 0.64$ by the log-rank test)[24].

1.3.2.1.2 *Phase II Study of Bevacizumab in Advanced Hepatocellular Carcinoma*

This study was a Phase II, single-center, single-arm trial designed to evaluate the efficacy, safety, and potential biomarkers of activity of bevacizumab in patients with advanced HCC[25]. Patients with histologically confirmed advanced HCC that was not amenable to curative-intent therapies (e.g., resection, liver transplantation, or percutaneous ablation) received bevacizumab 5 mg/kg or 10 mg/kg Q2W until disease progression or unacceptable toxicity. The primary objective was to determine the disease-control rate at 16 weeks (16W-DCR) defined as the proportion of patients with a CR, PR, or SD at 16 weeks after study entry, according to RECIST v1.0. Overall, 48 patients were enrolled, of which 25 patients were planned to receive bevacizumab 5 mg/kg and 23 patients were planned to receive bevacizumab 10 mg/kg, Q2W. Of the 48 patients enrolled, 43 patients received at least one dose of bevacizumab.

Among the 38 response-evaluable patients, six patients achieved a PR (intent-to-treat [ITT] objective response rate [ORR], 14%; 95% CI: 4%, 24%), median duration of response (DOR) was 148 days (range, 55-362 days), 18 patients had SD (DCR, 56%), including 12 patients who experienced SD for ≥ 16 weeks. The 16W-DCR was 42% (95% CI: 27%, 57%) in the overall population, 39% (95% CI: 19%, 59%) in patients treated with 5 mg/kg bevacizumab, and 45% (95% CI: 23%, 67%) in those treated at the 10 mg/kg dose. In the overall population (n = 43), median PFS was 3 months (95% CI: 2, 4); median OS was 8 months (95% CI: 4, 9)[25].

1.4 Rationale and Support for the Combination of Atezolizumab and Bevacizumab in HCC

Strong scientific rationale and emerging clinical data suggest that the combined VEGF/PD-L1 blockade may be clinically beneficial in a number of tumor types including HCC. It is known that HCC is a highly vascularized tumor, and that several proangiogenic factors play a role in HCC pathogenesis. For example, in HCC, increased VEGF correlates with vascular density, tumor invasiveness and metastasis, and poor prognosis[25,26]. The VEGF pathway also plays a crucial role in exerting and maintaining an immunosuppressive tumor microenvironment through several mechanisms. For instance, VEGF-A has been shown to induce FasL expression on endothelial cells, which have the ability to kill effector CD8+ T cells, but not T-reg cells. Administration of anti-VEGF-A attenuated tumor endothelial FasL expression and produced a significant increase in the influx of tumor-rejecting CD8+ over FoxP3+ T

cells, which was FasL-dependent, and led to CD8-dependent tumor growth suppression[27]. Furthermore, bevacizumab can restore and/or maintain the antigen presentation capacity of dendritic cells, leading to enhanced T-cell infiltration in tumors[28,29]. In addition to increased trafficking of T cells into tumors[30], several publications have illustrated that anti-VEGF therapies can also reduce frequency of myeloid-derived suppressor cells, decrease production of suppressive cytokines, and lower expression of inhibitory checkpoints on CD8+ T cells in tumors[31,32]. Therefore, the immunomodulatory effect of bevacizumab is expected to increase CD8-positive T-cell recruitment and relieve intratumoral immunosuppression, thereby boosting the effects of atezolizumab.

1.4.1 Clinical Support for the Combination in Hepatocellular Carcinoma

1.4.1.1 *Study GO30140*

Study GO30140 is a Phase Ib, multicenter study of atezolizumab in combination with bevacizumab and/or chemotherapy for first-line metastatic cancer patients[33]. Arm A is designed to test the combination of atezolizumab and bevacizumab in patients with locally advanced or metastatic HCC who have not received prior systemic therapy. Patients receive 1200 mg of atezolizumab plus 15 mg/kg of bevacizumab on Day 1 of every 21-day cycle (Q3W)[33]. In arm F patients were randomly assigned (1:1) to receive atezolizumab plus bevacizumab Q3W or atezolizumab alone.

Updated results published in 2020 reported 104 patients were enrolled onto arm A from July 20, 2016-July 31, 2018 and received atezolizumab + bevacizumab combination first-line therapy. At the time of data cutoff (June 14, 2019) the median duration of follow-up was 12.4 months. Confirmed objective responses were seen in 37 patients (36%, 95% CI 26-46), including 12 patients (12%) with a complete response. 28 patients (76%) had an ongoing response at the time of data cutoff, and the median duration of response had not been reached (95% CI 11.8-NE), with responses lasting ≥ 6 months in 24 patients (including 1 patient with a response ongoing for ≥ 31 months). Disease control rate by RECIST v1.1 criteria and independent review was 71%, with a mPFS of 7.3 months (R 5.4-9.9 mos). Median OS was 1.7 mos (95% CI 13.8-NE), with 57 patients (55%) alive at the time of data cutoff. Responses were consistent across all subgroups and clinical activity was observed regardless of PD-L1 status [33].

Additionally, 119 patients were enrolled onto arm F from May 18, 2018-March 7, 2019, 60 of which received atezolizumab + bevacizumab, and 59 received atezolizumab monotherapy. One patient in the atezolizumab monotherapy group withdrew from the study before receiving any treatment and was not included in the efficacy analysis. Further, 26 patients crossed over from the atezolizumab monotherapy group to the combination group and post-cross over safety and efficacy data were not reported. At the time of data cutoff (June 14, 2019), the median duration of follow up was 6.6 months in the combination group, and 6.7 months in the monotherapy group. Combination atezolizumab + bevacizumab resulted in a significant improvement in mPFS to 5.6 mos (95% CI 3.6-7.4) vs 3.4 mos (95% CI 1.9-5.2), for a stratified HR of 0.55 (80% CI 0.40-0.74, p = 0.011). The improvement in mPFS was seen across all subgroups. The confirmed ORR by RECIST v1.1 and independent review in the combination group was 20% (R 11-32%) vs 17% (R 8-29%) in the atezolizumab alone group. The disease control rate was 67% in the combination group, and 49% in the monotherapy group. The median DOR was not reached in either group, however the median time to radiographic progression was 5.6 mos (R 3.7-NE) in the combination group and 3.1 mos (R 1.9-5.5) in the monotherapy group. Median OS was not reached in either group (combination group 95% CI 8.3 mos-NE, monotherapy group CI 8.2 mos-NE). In the combination group 16 patient (27%) had died as compared to 18 patients (31%) in the monotherapy

group. The progression free survival benefit was seen regardless of PD-L1 status, although assessment in patients with PD-L1 positivity of at least 10% was not possible due to small sample size [33].

The median duration of treatment was 8.3 mos with atezolizumab and 8.2 mos with bevacizumab in arm A, and 5.2 mos with atezolizumab and 4.9 mos with bevacizumab in the combination group in arm F. The median duration of monotherapy treatment in arm F was 1.6 mos. In group A, grade 3-4 adverse events were reported in 55 patients (53%), with adverse events related to any treatment occurring in 91 patients (88%). The most common grade 3-4 treatment-related adverse events were hypertension (13%) and proteinuria (7%). Grade 5 adverse events of any cause were seen in 7 patients (7%) and attributed to hepatic cirrhosis, abnormal hepatic function, bacteremia, bacterial peritonitis, cardiac arrest, upper gastrointestinal hemorrhage, and pneumonitis, 3 of which (3%) were felt to be treatment related (abnormal hepatic function, hepatic cirrhosis, and pneumonitis). Serious adverse events were seen in 46 patients (44%), and treatment-related serious adverse events were seen in 25 patients (24%). The most common treatment-related serious adverse events were upper gastrointestinal hemorrhage, colitis, esophageal variceal hemorrhage, and pneumonitis (all occurring in 2% of patients). Fifty patients (48%) had adverse events that led to dose modification or interruption of study treatment, while 18 patients (17%) had adverse events that led to discontinuation of any study treatment (including 10 patients or 10% who discontinued both atezolizumab and bevacizumab concurrently). The most frequent adverse events leading to treatment discontinuation were esophageal variceal hemorrhage (2 patients, 2%) leading to discontinuation of bevacizumab only) [33].

In arm F, adverse events related to treatment occurred in 14 (68%) of patients in the atezolizumab + bevacizumab group, 20% of which were grade 3-4. Adverse events related to treatment occurred in 24 patients (41%) in the atezolizumab group, 5% of which were grade 3-4. The most common grade 3-4 adverse events in the combination group were hypertension (5% vs none in the monotherapy group), and proteinuria (3% vs none in the monotherapy group). There were no deaths due to adverse events. Serious adverse events were reported in 15 patients in the combination group (25%), and 6 patients in the monotherapy group (10%). Treatment-related serious adverse events were observed in 7 patients (12%) in the combination group and included diarrhea, duodenal ulcer hemorrhage, gastric hemorrhage, Guillain-Barre´ syndrome, pneumonia, epistaxis, pyrexia, and embolism). Treatment-related serious adverse events were observed in 2 patients (3%) in the monotherapy group and included Guillain-Barre´ syndrome and increased aminotransferases). No event occurred in more than one patient in either group. Adverse events leading to dose modification or interruption occurred in 9 patients (15%) in the combination group, and 5 patients (9%) in the monotherapy group. Adverse events leading to treatment discontinuation of either or both drug in the combination group occurred in six patients (10%) including 2 patient (3%) who discontinued both drugs simultaneously [33].

1.4.1.2 *IMBrave150*

IMBrave150 is a phase 3, open-label trial of atezolizumab in combination with bevacizumab compared to sorafenib in patients with unresectable/metastatic HCC who had not received prior systemic therapy[34]. Patients were randomized 2:1 to receive atezolizumab 1,200 mg plus bevacizumab 15 mg/kg IV every 3 weeks or sorafenib 400 mg orally twice daily. Patients continued treatment until unacceptable toxicity or loss of clinical benefit. Dose modifications were not permitted in the atezolizumab-bevacizumab group but were allowed in the sorafenib group. As of the date of clinical data cutoff (August 29, 2019) with a median duration of follow-up of 8.6 months, 501 patients at 111 sites in 17 countries had been enrolled (336 patients in the atezolizumab-bevacizumab group, 165 patients in the sorafenib group). Overall survival was significantly longer in the atezolizumab-bevacizumab group (estimated survival at 6

months 84.8% in the atezolizumab-bevacizumab group vs 72.2% in the sorafenib group, and at 6 months 67.2 vs 54.6%). Median PFS was also prolonged with the combination (6.8 months vs 4.3 months), as was objective response rate (27.3% vs 11.9% by independent assessment and 33.2% vs 13.3% by hepatocellular carcinoma-specific mRECIST). 18 patients in the atezolizumab-bevacizumab group had a complete response (CR) as compared to 0 in the sorafenib group. The disease control rate (DCR) was 73.6% with the combination and 55.3% with sorafenib[34].

A total of 485 patients received at least one dose of trial treatment (329 atezolizumab-bevacizumab, 156 sorafenib) and were included in the safety analyses. The median duration of treatment with atezolizumab was 7.4 months, 6.9 months for bevacizumab, and 2.8 months with sorafenib. Over three hundred patients (98.2%) who received the combination reported adverse events of any grade and any causality (as compared to 154 patients or 98.5% who received sorafenib). Grade 5 adverse events occurred in 15 patients (4.6%) in the combination group and in 9 patients (5.8%) in the sorafenib group). Serious adverse events occurred more frequently in the atezolizumab-bevacizumab group (38% or n = 125) than in the sorafenib group (30.8% or n = 48), however no specific adverse event was responsible for this difference. There was no serious adverse event with a between group difference of more than 2% noted. The most common grade 3 or 4 adverse events with the combination was hypertension (15.2%), and treatment-related adverse events that occurred in at least 10% of patients (or grade 3 or 4 events occurring in ≥ 2% of patients) were hypertension, proteinuria, fatigue, liver enzyme abnormalities, pruritus, infusion-reactions, diarrhea, anorexia, and thrombocytopenia in the combination group, and hypertension, fatigue, diarrhea, anorexia, rash, nausea, asthenia, alopecia, palmar-plantar erythrodysesthesia syndrome, and liver enzyme abnormalities in the sorafenib group. In the combination group 15.5% of patients discontinued treatment due to an adverse event, as compared to 10.3% in the sorafenib group. Adverse events requiring a dose modification/interruption occurred in 49.5% of patients in the combination group, and 60.9% in the sorafenib group[34].

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- To estimate the safety of the combination of atezolizumab and bevacizumab in patients with advanced/metastatic HCC and Child-Pugh B7 and B8 liver dysfunction by grade 3-5 adverse event rate.

2.1.2 Secondary Objectives

- To estimate the efficacy of the combination in this patient population by overall response rate (ORR), disease control rate (DCR), duration of response (DOR), progression free survival (PFS), and overall survival (OS).

2.1.3 Correlative/Exploratory Objectives

- To correlate tumor molecular signature from next generation sequencing (NGS) tissue analysis with clinical outcomes and treatment response.
- To correlate tumor molecular signature from NGS tissue analysis with ctDNA.
- To correlate levels of ctDNA with clinical outcomes and treatment response

2.2 Endpoints

2.2.1 Primary Endpoint

As the primary objective of this study is to determine safety, the primary endpoint of this study will be grade 3-5 treatment-related adverse event rate according to CTCAE v5.

2.2.2 Secondary Endpoints

As the secondary objective of this study is to determine efficacy, the secondary endpoints of this study will be:

- Overall response rate (ORR) defined as the proportion of patients who have a partial or complete response to therapy according to RECIST v1.1
- Disease control rate (DCR) defined as the proportion of patients who have a partial/complete response to therapy or stable disease for at least 16 weeks according to RECIST v1.1
- Duration of response (DOR) defined as the length of time from the first occurrence of an objective response to disease progression or death from any cause according to RECIST v1.1
- Median progression-free survival (PFS) defined as the median time from start of treatment to disease progression or death from any cause according to RECIST v1.1
- Median overall survival (OS) defined as the median time from start of treatment to death from any cause

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

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

3.1.1 Written informed consent and HIPAA authorization for release of personal health information must be obtained either from the subject or their representative. See 3.1.12. NOTE: HIPAA authorization may be included in the informed consent or obtained separately.

3.1.2 Age ≥ 18 years at the time of consent.

3.1.3 ECOG Performance Status of 0-1.

3.1.4 Locally advanced, metastatic, or unresectable hepatocellular carcinoma that has not received prior systemic therapy. Note: if no prior histologic diagnosis exists, prefer fresh biopsy if it is both safe and feasible. If fresh biopsy is not safe and feasible, imaging criteria may be used for diagnosis as per AASLD criteria in cirrhotic patients (please see www.aasld.org for up to date guidelines).

3.1.5 Child Pugh Class B7 or B8 liver dysfunction or cirrhosis with the following limitations:

- Bilirubin ≤ 3 mg/dL
- Albumin ≥ 2.8 g/dL
- INR ≤ 1.7
- Absent to slight [CP=1 to 2] (no moderate [CP=3]) ascites (also see Exclusion Criteria 3.2.6)
- No clinically significant encephalopathy (also see Exclusion Criteria 3.2.7)

3.1.6 At least 1 untreated measurable lesion according to RECIST 1.1.

3.1.7 Willingness to undergo fresh tumor biopsy at baseline if safe and feasible. Note: archival tissue may be used at baseline provided histologic diagnosis was made and sufficient tissue is available for NGS analysis.

3.1.8 NGS analysis must be requested from archival tissue or fresh biopsy (if applicable) as per standard of care. Foundation One CDX is the preferred platform. Prior NGS sequencing results (including from another platform) will be accepted if NGS sequencing was previously obtained (please see 3.1.4 and Study Calendar).

3.1.9 Demonstrate adequate bone marrow and organ function as defined in the table below:

Hematologic	
Absolute neutrophil count (ANC)	≥ 1,000/mcL
Lymphocyte count	≥ 0.5×10^9/L (500/μL)
Hemoglobin	≥ 90 g/L (9 g/dL) *Patients may be transfused to meet this criterion*
Platelet count	≥ 70,000/mcL
Renal	
Serum creatinine OR calculated* serum creatinine clearance (GFR can be used in place of creatinine or creatinine clearance)	≤ 1.5x upper limit of normal (ULN) OR ≥ 30 mL/min for participants with creatinine levels > 1.5x institutional ULN *Calculate serum creatinine clearance using the standard Cockcroft-Gault formula.
Urine protein	Urine dipstick for proteinuria < 2+ within 7 days prior to start of study treatment *Patients with ≥ 2+ proteinuria on dipstick analysis at baseline should undergo a 24-hour urine collection which must demonstrate < 1g of protein in 24 hours
Hepatic	
AST (SGOT) and ALT (SGPT)	≤ 8x ULN
Alkaline phosphatase (ALP)	≤ 8x ULN

3.1.10 For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab, or 6 months after the last dose of bevacizumab. See also section 5.5 for definition of childbearing potential.

3.1.11 For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use effective contraceptive measures. Men with female partners of childbearing potential must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 6 months after the last dose of bevacizumab. With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of bevacizumab to avoid exposing the embryo. See also section 5.5 for additional information.

3.1.12 As determined by the enrolling physician or protocol designee, ability of the subject to understand a written informed consent document, and ability and willingness to comply with study procedures for the entire length of the study. Patients with impaired decision-making capacity (IDMC) who have a close caregiver or legally authorized representative (LAR) and/or family member available are also eligible.

3.2 Exclusion Criteria

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

3.2.1 Histologic diagnosis of fibrolamellar or sarcomatoid HCC or mixed cholangiocarcinoma-HCC.

3.2.2 Patients who have had chemotherapy, definitive radiation, biological cancer therapy, or investigational agent/device within 21 days of first planned dose of study therapy (within 14 days for palliative radiation). Patients who have had major surgery within 4 weeks of start of study therapy or anticipation of need for a major surgical procedure during the study.

3.2.3 Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > CTCAE Grade 1) with the exception of alopecia or neuropathy.

3.2.4 Patients who have received prior systemic therapy for HCC.

3.2.5 Patients who have received prior immunotherapy.

3.2.6 Patients with clinically meaningful ascites, defined as ascites requiring non-pharmacologic intervention (e.g. paracentesis) to maintain symptomatic control within 3 months prior to the first dose of study treatment. Note: Patients with ascites meeting eligibility criteria who require pharmacologic intervention (e.g. diuretics) to maintain symptomatic control and who have been on stable doses of diuretics for 2 months prior to the first dose of study treatment are eligible.

3.2.7 Patients with clinically meaningful encephalopathy, defined as a history of hepatic encephalopathy within 6 months prior to first dose of study treatment or requirement for medications to prevent or control encephalopathy (e.g. lactulose, rifaximin).

3.2.8 Any of the following additional high-risk features:

- Patients with untreated or incompletely treated esophageal and/or gastric varices with bleeding or high risk for bleeding. Note: Patients must undergo an esophagogastroduodenoscopy (EGD), and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment. Patients who have undergone an EGD with appropriate management of varices (if applicable) within 6 months of prior to initiation of study treatment do not need to repeat the procedure.
- History of esophageal and/or gastric hemorrhage within 3 months prior to study treatment.
- History of hemoptysis (< 2.5 mL of bright red blood per episode) within 1 month prior to study treatment.
- History of intracranial hemorrhage within 1 month prior to study treatment.
- History of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment. Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure.
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture within 30 days prior to start of study treatment.
- Metastatic disease that involves major airways or blood vessels. Patients with vascular invasion of the portal or hepatic veins may be enrolled.
- Significant vascular disease (e.g. aortic aneurysm requiring surgical repair) or vasculitis within 6 months prior to initiation of study treatment.

- History of arterial thrombotic event (e.g. myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack) within 6 months prior to initiation of study treatment.
- Chronic or recent (within 10 days of first dose of study treatment) use of aspirin > 325 mg/day, dipyramidaole, ticlopidine, clopidogrel, or dilostazol. Note: Use of aspirin < 325 mg/day is allowed.
- Patients with a history of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism, portal vein thrombosis, or any other significant thromboembolism) must be on a stable dose of anticoagulation for 1 month prior to initiation of study treatment and must have completely treated varices
- Use of Coumadin-like products or full dose oral or parenteral anticoagulants. Use of prophylactic low dose anticoagulation, unfractionated heparin or LMWH is allowed.
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Core biopsy or other minor surgical procedure within 3 days prior to the first dose of bevacizumab.
- History of intestinal obstruction. Note: Patients with previous intestinal obstruction may be enrolled if they have received definitive treatment for symptom resolution.
- History of inflammatory process within 6 months prior to start of study treatment including but not limited to active peptic ulcer disease, diverticulitis or colitis.
- Significant traumatic injury within 4 weeks prior to start of study treatment.
- Uncontrolled pleural effusion or pericardial effusion requiring frequent drainage procedures (> once monthly). Patients with indwelling catheters (e.g. PleurX®) are allowed.
- History of nephrotic or nephritic syndrome.
- Uncontrolled hypertension defined as systolic pressure ≥ 150/90 in spite of maximum anti-hypertensive therapy

3.2.9 Patients with untreated/uncontrolled CNS/leptomeningeal disease. Note: Patients with asymptomatic, treated CNS disease are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy and the following criteria are met:

- No evidence of interim progression between the completion of CNS-directed therapy and the start of study enrollment.
- No stereotactic radiation or whole-brain radiation within 28 days prior to randomization.
- No evidence of intracranial hemorrhage or spinal cord hemorrhage.

3.2.10 Patients with active autoimmune disease requiring systemic corticosteroids greater than the equivalent of prednisone 10 mg daily or other systemic immunosuppressive medications including but not limited to: systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, colitis, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis, with the following exceptions:

- Patients with a history of autoimmune hypothyroidism on thyroid replacement hormone are eligible.
- Patients with Type 1 diabetes mellitus on an insulin regimen are eligible.

- Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only are eligible provided: 1) rash covers < 10% of body surface area (BSA), 2) disease is well controlled at baseline and requires only low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%).
- See Appendix 4 for a more comprehensive list of autoimmune diseases and immune deficiencies.

3.2.11 Patients receiving treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [TNF] agents) within 6 weeks must discontinue these medications prior to starting protocol therapy, with the exception of:

- Patients with active autoimmune disease managed with systemic corticosteroids less than the equivalent of prednisone 10 mg daily.
- Patients who have received acute, low dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea).
- The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension and adrenocortical insufficiency.

3.2.12 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. Note: History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

3.2.13 Patients who have undergone prior solid organ or bone marrow transplant with the exception of patients with prior renal transplant for whom dialysis may be employed in the event of graft rejection.

3.2.14 Patients with serious active infection within 2 weeks prior to enrollment (e.g. requiring hospitalization and/or intravenous [IV] antibiotics) infection within 2 weeks prior to enrollment, or currently receiving oral or IV antibiotics for the treatment of infection. Patients receiving prophylactic antibiotics are eligible.

3.2.15 Patients must have documented hepatitis virology status.

- Patients with active hepatitis B virus (HBV) infection must have a viral load < 500 IU/mL within 28 days prior to start of study treatment and be on suppressive therapy (per local standard of care) for a minimum of 14 days prior to start of study treatment and for the length of the study.
- Patients with co-infection with HBV and hepatitis C virus (HCV) are excluded. Patients with a history of HCV infection but with negative HCV RNA by PCR are considered non-infected with HCV.

3.2.16 Patients with known human immunodeficiency virus (HIV) are allowed on study provided they have:

- A stable regimen of highly active anti-retroviral therapy (HAART)
- No requirement for concurrent concurrent antibiotics or antifungal agents for the prevention of opportunistic infection
- A CD4 count above 250 cells/mcL
- An undetectable HIV viral load on standard PCR-based testing

3.2.17 Patients with uncontrolled intercurrent illness (e.g., including but not limited to uncontrolled HTN [systolic BP ≥ 150, diastolic BP ≥ 100 despite optimal medical management or history of hypertensive crisis or hypertensive encephalopathy], symptomatic congestive heart failure [CHF], uncontrolled cardiac arrhythmia, or other within 3 months prior to start of study treatment or psychiatric illness/social situations or other conditions that would limit compliance with study requirements or substantially increase risk of incurring AEs in the opinion of the treating investigator.

3.2.18 Patients with known concurrent malignancy that is expected to require active treatment within two years or may interfere with the interpretation of the efficacy and safety outcomes of this study in the opinion of the treating investigator. Note: Superficial bladder cancer, nonmelanoma skin cancers, and low-grade prostate cancer not requiring cytotoxic therapy should not exclude participation in this trial. Patients with CLL may be enrolled if they do not require active chemotherapy and their hematologic, renal and hepatic function meets criteria previously mentioned.

3.2.19 Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications in the opinion of the treating investigator.

3.2.20 Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment.

3.2.21 History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins or know hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or bevacizumab infusion.

3.2.22 Uncontrolled tumor-related pain
NOTE: Patients requiring pain medication must be on a stable regimen at study entry. Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

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

3.2.24 Active tuberculosis

3.2.25 Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies

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 must begin therapy within 28 business days of registration.

5. TREATMENT PLAN

This will be a nonrandomized, single arm feasibility study with the primary goal of evaluating the safety profile of the combination of atezolizumab and bevacizumab in patients with advanced/metastatic HCC with Child-Pugh B7 and B8 liver disease who have received no prior systemic therapy.

Eligible consented patients will receive atezolizumab 1,200 mg IV and bevacizumab 15 mg/kg IV every 3 weeks (on day 1 of each 21-day cycle). Treatment will continue until disease progression or development of unacceptable toxicity. All patients will undergo baseline peripheral blood sampling, imaging assessment (e.g. CT chest, abdomen, and pelvis), and tumor biopsy for correlates (+ histologic diagnosis if not already obtained). Archival tissue may be used for correlates at baseline provided sufficient tissue is available for NGS analysis. Prior NGS sequencing results will be accepted if both histologic diagnosis and NGS sequencing were previously obtained. Peripheral blood sampling and imaging response assessment will then be repeated every 3 cycles (or every 9 weeks) (see study schema). Following disease progression, patients will be followed for survival and subsequent anti-cancer therapies until death, loss to follow-up, withdrawal of consent, or study termination, whichever occurs first. For a full schedule of activities please see the Study Calendar.

5.1 Pre-medication and Hydration

5.1.1 Atezolizumab

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. No premedication for the first infusion is permitted.

5.1.2 Bevacizumab

Administration of bevacizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. No premedication for the first infusion is permitted.

5.2 Atezolizumab and Bevacizumab Administration

Atezolizumab will be administered first, followed by bevacizumab, with a minimum of 5 minutes between dosing. Refer to the IB or prescribing information for detailed instructions on drug preparation, storage, and administration.

Sequence of Treatment Administration:

Drug	Dose	Route[1]	Schedule[2]	Cycle Length
Atezolizumab	1,200 mg	**First infusion:** Intravenously (IV) over 60 (± 15) minutes	Day 1	21 days
		Subsequent infusions (if tolerated): IV over 30 (± 10) minutes		
Bevacizumab	15 mg/kg	**First infusion**: IV over 90 (± 15) minutes		
		Subsequent infusions (if tolerated): IV over 60 and then 30 (± 10) minutes		

[1] Drug administration times performed outside the above recommended windows will not be considered as protocol deviations.
[2] A window of ± 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).

5.2.1 Atezolizumab

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

5.2.2 Bevacizumab

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the infusion. • Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Bevacizumab should be infused over 90 (±15) minutes. • Vital signs should be at the end of infusion and 2 (±1) hours after the infusion. Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. Bevacizumab should be infused over 60 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 90 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (±10) minutes thereafter. • Vital signs should be at the end of infusion and 2 (±1) hours after the infusion.

5.3 Concomitant Medications

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered more than 30 days after the last dose of trial treatment should be recorded for serious adverse events (SAE).

5.3.1 Permitted Therapy

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

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Megestrol acetate administered as an appetite stimulant

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

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see below) 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 3.

5.3.2 Cautionary Therapy

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

5.3.3 Prohibited Concomitant Medications

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

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 21 days prior to initiation of study treatment and during study treatment.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy [see below]), whether FDA approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Inclusion/Exclusion), and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy, local therapy and medications under the circumstances below:
  - Inactivated vaccinations (such as influenza, SARS-CoV-2)
  - Mineralocorticoids (e.g. fludrocortisone)
  - Inhaled corticosteroids administered for COPD or asthma
  - Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
  - Palliative radiotherapy provided it does not interfere with the assessment of the tumor target lesion.
    - Treatment with atezolizumab may be continued during palliative radiotherapy.
  - Cranial radiotherapy (either stereotactic radiosurgery or whole-brain radiation therapy) in patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have 3 or fewer brain metastases provided that:
    - There is no evidence of progression or hemorrhage after completion of CNS-directed therapy
    - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease (for more than 7 days after completion of radiotherapy)
    - Anti-convulsant therapy, if required, is at a stable dose
    - Treatment with atezolizumab and bevacizumab should be withheld during CNS-directed radiotherapy
  - Other local therapy (e.g. surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) in patients experiencing a mixed response requiring local therapy for control of 3 or

fewer non-target lesions may still be eligible to continue study treatment after sponsor investigator approval

- Concomitant use of herbal therapies/traditional Chinese medicine with anti-cancer activity included in the label is prohibited.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, 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 5 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.
- Anti-platelets and anti-coagulants except as expressly stated in inclusion/exclusion criteria or in section 5.3.1. Note: For the symptomatic relief of medical conditions (e.g., headache, fever) intermittent or short-term intake of oral NSAIDs is allowed
- Use of warfarin or Coumadin-like products (includes for prophylactic use) or full dose oral or parenteral anticoagulants is prohibited. Note: Use of prophylactic low dose anticoagulation, unfractionated heparin or LMWH is allowed.

5.4 Supportive Care

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies as clinically indicated, per local standard practice.

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated.

5.5 Reproductive Information

Participants of childbearing potential who are sexually active and their partners must agree to (1) abstain from heterosexual activity or (2) use an effective method(s) of contraception: two barrier methods, or a barrier method plus a hormonal method as described below.

5.5.1 Females

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Women must refrain from donating eggs during this same period.

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab or 6 months after the last dose of bevacizumab.

Note: "Female of childbearing potential" is defined as any female who has experienced menarche and who has not undergone surgical sterilization hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL to be considered of non-childbearing potential.

5.5.2 Males

Male patients will be instructed to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of bevacizumab. Note: 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. Men must refrain from donating sperm during these same time periods.

5.5.3 Highly Effective Methods of Contraception

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone-based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence which is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs.

5.5.4 Less Effective Methods of Contraception

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Female Condom. A male and female condom must not be used together
- Progestin only pills by WOCBP subject or male subject's WOCBP partner

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

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. The

NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0 will be used to grade adverse events.

6.1 Dose Delays/Dose Modifications

There will be no dose modifications for atezolizumab or bevacizumab in this study.

Please see Appendix 1 and 2 for Guidelines for Management of Atezolizumab and Bevacizumab in Patients Who Experience Treatment-Related Adverse Events.

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 to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 90 days after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 90 days to allow for patients to taper off corticosteroids prior to resuming treatment if they are otherwise eligible to resume therapy if the treating physician determines that the patient is likely to derive clinical benefit after discussion with the study PI.

Bevacizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. If bevacizumab is delayed due to toxicity for > 90 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab. Bevacizumab can be resumed after being withheld for > 90 days if they are otherwise eligible to resume therapy if the treating physician determines that the patient is likely to derive clinical benefit after discussion with the study PI.

Atezolizumab or bevacizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures), with Sponsor Investigator approval. The local investigator and the Sponsor Investigator will determine the acceptable length of treatment interruption.

If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule. If treatment was postponed for ≤ 3 days, the patient can resume the original schedule. After two complete cycles, one of three cycles may be delayed by 1 week (28 days instead of 21 days for one cycle) to allow for vacations/holidays. Following the delay, the next cycle visit must be 21 days from the previous Day 1 visit. Two consecutive 28-day cycles are not permitted.

If either study drug is withheld or discontinued, the other study drug can be continued as long as the patient is experiencing clinical benefit, as determined by the investigator per medical judgment.

If a cycle is held or missed and resumption of therapy is allowed as per guidelines above, treatment should resume with the cycle missed.

6.2 Dose Levels for Dose Reductions

There will be no dose modifications for atezolizumab or bevacizumab in this study.

6.3 Discontinuation from Protocol Therapy

Patients must permanently discontinue study treatment if they experience any of the following:

- Documented disease progression per RECIST v 1.1
- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Local Investigator or Sponsor Investigator determines it is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy of a female participant
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, and clinical status (e.g., symptomatic deterioration such as pain secondary to disease)

If one component of study treatment is discontinued permanently because of tolerability concerns, the patient may continue with the other components of study treatment until loss of clinical benefit as long as the patients are experiencing clinical benefit in the opinion of the investigator and after discussion with the PI and sponsor if agreed upon by the sub-investigator and patient.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit ≤ 30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities).

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

6.4 Discontinuation from Protocol Activities

6.4.1 Patient Discontinuation

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

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

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a

patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

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

6.4.2 Study Discontinuation

The Sponsor Investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor Investigator will notify participating institutions if such a decision is made.

6.4.3 Site Discontinuation

The Sponsor Investigator has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonization (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

7. STUDY CALENDAR & EVALUATIONS

	Screen	Treatment Phase [18] (Cycle = 21 days)		Safety Follow up[3]	Long-term Follow up
	-28 days	Cycle 1 Day 1	Cycle 2+ Day 1	30 Days after Last Dose (± 7)	Q 3 months (±21 days)[21]
REQUIRED ASSESSMENTS[1, 2]					
Informed Consent	X				
Medical & surgical history, trial awareness[4]	X				
Tissue sent for NGS testing if available and not previously done[13]	X				
Physical exam, Vital signs, ECOG Performance status[5]	X	X[19]	X	X	
ECG	X	As clinically indicated			
EGD[6]	X				
AEs & concomitant medications		X	X	X	
LABORATORY ASSESSMENTS					
Complete Blood Cell Count with diff (CBC)	X	X[19]	X	X	
Comprehensive Metabolic Profile (CMP), Mg, Phos[7]	X	X[19]	X	X	
PT/INR and aPTT, Thyroid Function (TSH, T4, free T3)	X	X[19, 20]	Every odd cycle[20]	X	
Pregnancy test (serum or urine) WOCBP[8]	X	X[19]	X		
Urinalysis[9]	X	X[19]	X		
HBV, HCV serology[10]	X				
Alphafetoprotein (AFP)	X	X[19, 20]	Every odd cycle[20]	X	
DISEASE ASSESSMENT					
CT of chest; CT or MRI of abdomen and pelvis[11]	X		Q3 cycles	X	X
TREATMENT EXPOSURE					
Atezolizumab		X	X		
Bevacizumab[12]		X	X		
CORRELATIVE STUDIES (SPECIMEN COLLECTION)					
Archival tumor tissue or fresh biopsy[13]	X				
Whole blood for somatic baseline		X			
Plasma and buffy coat samples[14]		X	Q3 cycles	X	
BANKING SAMPLES (SPECIMEN COLLECTION)					
Whole Blood[15]		X			
Unstained Slides (if available)[16]	X				
Serum and Plasma[17]		X		X	
FOLLOW-UP					
Survival status, subsequent therapy					X

Key to Footnotes

1- C1D1 within 28 business days of consent.

2- With the exception of screening labs (see below), results of standard-of-care tests or examinations performed prior to obtaining informed consent but within 28 business days of C1D1 may be used for screening assessments rather than repeating such tests.

3- A safety follow-up visit will occur 30 days (±7 days) after the last dose of treatment or before the first dose of a new anti-cancer therapy, whichever occurs first. AESIs and SAEs will be collected for 90 days after the end of treatment. See Section 11.2. All AE (SAE) considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, is deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.

4- Medical history to include smoking history and trial awareness question. Medical history will also include diagnosis and staging such as pathology report and Tumor Node Metastasis (TNM) staging and any prior NGS analysis.

5- Vital signs to include blood pressure, weight, and height (screening only) and ECOG performance status. Vital signs should also be measured throughout atezolizumab and bevacizumab infusions as directed in the Treatment Administration section of the protocol.

6- All patients must undergo an EGD and all size of varices (small to large) must be assessed and treated per local standard of care prior to start of study treatment.

7- CMP to include albumin, sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase. Magnesium and phosphorus will also be evaluated.

8- For women of childbearing potential (WOCBP): urine or serum βhCG, within 7 days prior to C1D1, then day 1 of every cycle thereafter. If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

9- Urine dipstick includes specific gravity, pH, glucose, protein, ketones, and blood and should be repeated before every cycle during treatment. Urine dipstick for proteinuria must be <2+ within 7 days prior to initiation of study treatment. Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection prior to start of study treatment and must demonstrate < 1 g of protein in 24 hours.

10- All patients will be tested for HBV and HCV locally prior to inclusion into the study and if not in contraindication with local legislation. HBsAg, HBcAb, and HBsAb, anti-HCV, HBV DNA, and HCV RNA should be collected as needed to document subject virology status.

11- Tumor response assessment will be performed at baseline, then every 3 cycles thereafter until treatment discontinuation. Tumor imaging performed within 6 weeks prior to the treatment discontinuation visit do not need to be repeated. In the absence of disease progression, tumor assessments should continue regardless of whether patients discontinue study treatment, unless the patient dies, withdraws consent, initiates subsequent anti-cancer therapy, or the study is terminated. During the survival follow up period, records of tumor imaging done at an outside facility are acceptable.

12- The dose of bevacizumab will be based on the patient's weight (in kilograms) measured within 14 days of C1D1 (or on C1D1), and will remain the same throughout the study unless there is a weight change of > 10% from baseline.

13- Fresh biopsy with fixed paraffin-embedded blocks/slides is requested for correlates + histologic diagnosis if no histologic diagnosis exists and biopsy is safe and feasible. If a biopsy for histologic diagnosis and NGS is NOT safe or feasible, imaging criteria may be used for diagnosis (NGS will be foregone in these cases). Foundation One CDX is the preferred platform for tissue NGS analysis. Archival tissue may be used for correlates at baseline provided there is likely to be sufficient tissue is available for NGS analysis in the opinion of the treating investigator. Prior NGS sequencing results will be accepted if NGS sequencing was previously obtained. Patients with elevated coagulation studies who still meet

eligibility criteria may be given fresh frozen plasma (FFP) or other agent prior to baseline biopsy if indicated and biopsy is otherwise safe and feasible per institutional guidelines. If baseline biopsy is performed, tissue for correlates is requested.

14- Plasma to be collected for liquid biopsy (ctDNA) at baseline, with each tumor imaging assessment, and at treatment discontinuation. Buffy coat also collected at C1D1 for somatic baseline.

15- Whole blood for banking is to be collected at Pre-Treatment Cycle 1 Day 1. See CLM for collection, processing, labeling and shipping instructions.

16- Submission of unstained slides for banking from an archived FFPE tumor block (if available). See CLM for collection, labeling, and shipping instructions.

17- Serum and plasma for banking are to be collected at Pre-Treatment Cycle 1 Day 1 and at the 30-Day Safety Follow up visit. See CLM for collection, labeling, processing, and shipping instructions.

18- A window of +/- 3 days will be applied to all treatment study visits; for safety follow-up visit and tumor imaging, a 7-day window will apply.

19- If screening (baseline) PE, vitals, ECOG or labs were performed within 7 days of C1D1, these do not need to be repeated, otherwise they should be repeated within 7 days of C1D1.

20- Laboratory assessments to be done during screening, C1D1 (unless performed within 7 days of C1D1), every other cycle thereafter, and at treatment discontinuation visit.

21- Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 21 days) until death, loss to follow-up, or until study termination. All patients will be followed for survival and new anti-cancer therapy (including targeted therapy and immunotherapy) information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

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 (±7 days) after the last dose of treatment. All AEs (SAEs) considered related to atezolizumab or bevacizumab will be followed until resolution to ≤ Grade 1 or baseline, is deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first. All other AEs (SAEs) will be followed according to the subject's clinical needs according to standard of care.

7.2 Long Term Follow-up Evaluations

Once disease progression is documented, subjects will enter a survival follow up period every 3 months (+/- 21 days) until death, loss to follow-up, study termination, or the patient requests to be withdrawn from follow-up. Subjects who discontinue treatment for any reason without documented disease progression will enter a survival follow up, including following for disease progression, every 3 months (+/- 21 days) until death, loss to follow-up, study termination, or the patient requests to be withdrawn from follow-up. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate. Request to withdraw from study follow-up should be documented and signed by the investigator.

All patients will be followed for survival and new anti-cancer therapy (including targeted therapy and immunotherapy). Survival follow-up information may be collected via telephone calls, patient medical records, and/or clinic visits. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

8. BIOSPECIMEN STUDIES AND PROCEDURES

The issue of core biopsies of HCC lesions presents an ongoing challenge for clinicians in the age of precision medicine given both the unique ability to diagnose HCC without a biopsy by imaging criteria, and the risk of bleeding and potential seeding of malignant cells after a diagnostic biopsy. However, while not necessary for diagnosis, molecular information about an HCC lesion may guide choices for targeted and immune-based therapies, thus the ability to analyze DNA derived from these tumors without the need for an invasive biopsy could have transformative clinical applications. Additionally, circulating tumor DNA may better capture the molecular heterogeneity of a tumor than a core biopsy, and though early studies in small numbers of patients suggested low concordance between tumor genomics and plasma ctDNA samples, larger more recent studies that have obtained plasma and tissue samples simultaneously have reported concordance rates of 80-90%[35]. Further, the short half-life of ctDNA as compared to standard tumor markers used in clinical practice (e.g. alphafetoprotein or AFP) translates into ctDNA levels being better real-time gauges of tumor burden, and thus response to treatment, potentially preceding radiographic responses and/or progression of disease by weeks to months[35]. Thus, ctDNA has the potential to offer early evidence of response or progression that, if validated, may prove meaningful for clinical management.

We propose to examine these hypotheses through ctDNA analysis at baseline as compared to comprehensive genomic profiling, and in conjunction with regular imaging time points for assessment of tumor response.

8.1 Source and Timing of Biospecimen Collections

Refer the Correlative Laboratory Manual for details on sample collection, processing, and shipping.

8.1.1 NGS Testing

Comprehensive genomic profiling analysis will be performed on tumor tissue preferably by Foundation Medicine using their FoundationOne® CDX platform per standard of care when possible if not already performed. Prior clinical report will be provided and specific genes of interest, such as (but not limited to) TERT, TP53, CTNNB1, and ARID1A, will be entered into the EDC. When not possible, tissue will be collected for genetic analysis upon receipt of funding.

8.1.2 ctDNA Testing

Plasma samples for ctDNA analysis will be collected at baseline, at the time of each tumor imaging (every 3 cycles), and at the discontinuation of treatment visit.

Circulating tumor DNA (ctDNA) analysis will be performed using a platform such as (but not limited to) the FoundationOne® Liquid biopsy platform. The ctDNA analysis will be performed upon receipt of funding.

Additional pre-treatment tissue (archival or biopsy) will be collected for potential sequencing for tissue-informed patient-specific ctDNA analysis.

8.1.3 Germline Testing

Whole blood samples for germline analysis (somatic baseline) will be collected at baseline. In addition, buffy coat will be stored upon collection of the baseline plasma for ctDNA.

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

8.2 Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples that were 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.
- Unstained slides: Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample.

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

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.

9.2.1 Cystic Lesions

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.

9.2.2 Bone Lesions

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

9.2.3 Lesions with Prior Local Treatment

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

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

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.			

Patients with radiologic evidence of progression who are felt to otherwise be deriving clinical benefit in the opinion of the treating investigator may continue on study treatment after discussion with the study PI.

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 1.1

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 1.1, 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 16 weeks, or partial response (PR), or complete response (CR) according to RECIST 1.1, 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 Progression Free Survival

A measurement from the date of treatment initiation until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

9.8.8 Overall Survival

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

10. DRUG INFORMATION

The investigational medicinal products (IMPs) for this study are atezolizumab and bevacizumab. Please refer to the latest version of the prescribing information that can be found at *http://www.accessdata.fda.gov/scripts/cder/drugsatfda/*, and/or on the manufacturer's website.

10.1 Atezolizumab

Atezolizumab is indicated for the following: Urothelial Carcinoma, Non-Small Cell Lung Cancer (NSCLC), Triple-Negative Breast Cancer (TNBC), unresectable or metastatic hepatocellular carcinoma (HCC), and BRAF V600 mutation-positive unresectable or metastatic melanoma. Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody dependent cellular cytotoxicity. Refer to the atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

10.1.1 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.

Atezolizumab will be supplied as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1,200 mg) of atezolizumab solution.

10.1.2 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 atezolizumab 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 atezolizumab.

Storage of Infusion Solution
Administer immediately once prepared. If diluted atezolizumab infusion solution is not used immediately, store solution either:
- At room temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration of the infusion, or
- Under refrigeration at 2°Cto 8°C (36°F to 46°F) for no more than 24 hours from time of preparation.

10.1.3 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.

10.1.4 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.

10.1.5 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.

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

Atezolizumab has been associated with risks such as the following: IIRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis and severe cutaneous adverse reactions. In addition, immune−mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH).

Further details around frequency, reporting, and management of adverse events can be found in the current version of the Investigator's Brochure and in Appendix 2 of this protocol.

10.2 Bevacizumab

Bevacizumab is a vascular endothelial growth factor inhibitor indicated for the treatment of metastatic colorectal cancer, first-line non-squamous non−small cell lung cancer, recurrent glioblastoma metastatic renal cell carcinoma persistent, recurrent, or metastatic cervical cancer, epithelial ovarian, fallopian tube, or primary peritoneal cancer hepatocellular carcinoma. Refer to the bevacizumab Investigator's Brochure for details on nonclinical and clinical studies.

10.2.1 Supplier/How Supplied

Genentech will provide bevacizumab 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.

Bevacizumab will be supplied as a sterile liquid in single-use 400 mg preservative-free glass vials to deliver 16 mL bevacizumab (25 mg/mL). The vial contains approximately 16 mL of bevacizumab solution.

10.2.2 Preparation

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

10.2.3 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.

10.2.4 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 bevacizumab vials should be disposed at the site following procedures for the disposal of anticancer drugs.

10.2.5 Dispensing

Bevacizumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Bevacizumab 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.

10.2.6 Adverse Events

The most common adverse events due to bevacizumab (incidence > 10%) are listed below. For a comprehensive list of adverse events please see the bevacizumab Investigator's Brochure.

- Epistaxis
- Headache
- Hypertension
- Rhinitis
- Proteinuria
- Taste alteration
- Dry skin
- Hemorrhage
- Lacrimation disorder
- Back pain
- Exfoliative dermatitis

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
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with hepatocellular carcinoma that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

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

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

11.1.2 Serious Adverse Event (SAE)

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

11.1.3 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. The table below 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), 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

11.1.4 Expected and Unexpected Adverse Event(s)

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. 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.

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

11.1.5 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 (definite, probable, possible)
There is a plausible temporal relationship between the onset of the AE and administration of atezolizumab and/or bevacizumab, 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 bevacizumab; and/or the AE abates or resolves upon discontinuation of atezolizumab and/or bevacizumab or dose reduction and, if applicable, reappears upon re- challenge.

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

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

11.1.6 Pregnancy

If a female subject or a female partner of a male subject becomes pregnant while receiving the study drug or within **6** 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 11.2.2. 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.

11.1.7 AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product. AESIs shall be forwarded to Big Ten CRC AHQ according to the SAE reporting timelines described in 11.2.2. Big Ten CRC AHQ will forward them to Genentech as described in the Genentech Safety Data Exchange Agreement (SDEA).

<u>The Atezolizumab and/or Bevacizumab Events of Special Interest are:</u>

- 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. The patient population for this study consists of patients with decreased hepatic function who may exhibit abnormal liver function test results, some of which may meet Hy's law criteria prior to enrollment in the trial. The following modified Hy's law criteria are for the purpose of determining what may constitute a drug-induced liver injury for this trial population and define those cases which require expedited reporting to the health authorities in relation to Hy's law:
  - Treatment-emergent ALT or AST > 3 × baseline value in combination with total bilirubin > 2 x ULN
  - Treatment-emergent ALT or AST > 3 × baseline value in combination with clinical jaundice
- Suspected transmission of an infectious agent by Atezolizumab and/or 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 <u>only</u> when a contamination of the study drug is suspected.

Adverse events of special interest specific to atezolizumab are:

- Systemic lupus erythematosus
- Nephritis

- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, macrophage activating syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH).
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

Selected Adverse Events for HCC studies with Atezolizumab and Bevacizumab are:

- Hemorrhage
  - Any grade CNS bleeding
  - Grade ≥ 2 hemoptysis
  - Other Grade ≥ 3 hemorrhagic event

11.1.8 Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Big Ten CRC AHQ:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

11.1.9 Product complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial. Product complaints shall be transmitted to Big Ten CRC AHQ who will forward them to Genentech as described in the Genentech Safety Data Exchange Agreement (SDEA).

11.1.10Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior atezolizumab and bevacizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject (including pregnancy occurring in the partner of a male study subject) who participated in the study, this should be reported as an SAE to Big Ten CRC AHQ during follow up period.

11.2 Reporting

11.2.1 Adverse Events

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies,

discontinuation of medications) should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, investigators should only report SAEs that are attributed to prior study treatment.

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 atezolizumab or bevacizumab 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.

11.2.2 Serious Adverse Events (SAEs)

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

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported.

- After initiation of study treatment, SAEs and adverse events of special interest will be reported until 90 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first. After this period, investigators should only report SAEs that are attributed to prior study treatment.
- 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 atezolizumab or bevacizumab 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.

The site will submit the completed SAE Submission Form (see Documents/Info tab in the EDC) to Big Ten CRC AHQ within **1 business day** of discovery of the event. The form will be sent electronically to Big Ten CRC AHQ at 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 must be kept within the study file at the study site.

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

11.2.2.2 Big Ten CRC AHQ Requirements for Reporting to Genentech

Big Ten CRC AHQ will report Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints (with or without AEs) to Genentech according to the timeframe specified in the SDEA. Follow-up information will be provided to Genentech as it is received from a site.

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

11.2.2.3 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.

11.2.2.4 Big Ten CRC AHQ Responsibilities for Reporting SAEs to FDA

The FDA has concluded this protocol is exempt from the requirements of an IND. Big Ten CRC AHQ will continue to facilitate compliance of applicable requirements for the sponsor-investigator in relation to this study. This includes but is not limited to 21 CFR 50.20 informed consent, 21 CFR Part 56 IRB, and pertinent sections of the Public Health Service Act and FDAAA.

11.2.2.5 IND Safety Reports Unrelated to this Trial

Genentech will provide Big Ten CRC AHQ with IND safety reports from external studies that involve the study drug(s) per their guidelines. Big Ten CRC AHQ will forward the 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 METHODS

12.1 Study Design

This will be a nonrandomized, single arm feasibility study with the primary goal of evaluating the safety profile of the combination of atezolizumab and bevacizumab in patients with advanced/metastatic HCC with Child-Pugh B7 and B8 liver disease.

The grade 3-5 treatment-related adverse event rate in IMbrave150 was 38%. We hypothesize that a grade 3-5 treatment-related adverse event rate less than 50% in patients with Child-Pugh B7 and B8 liver disease or cirrhosis will be considered acceptable.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

The primary endpoint is safety defined as grade 3-5 treatment-related adverse event rate. Adverse events will be defined according to CTCAE v 5.0.

12.2.2 Definition of Secondary Endpoints

The secondary endpoints are defined as follows:

- Overall response rate (ORR) defined as the proportion of patients who have a partial or complete response to therapy by RECIST 1.1.
- Disease control rate (DCR) defined as the proportion of patients who have a partial/complete response or stable disease by RECIST 1.1.
- Duration of response (DOR) defined as the length of time from the first occurrence of an objective response to disease progression or death from any cause according to RECIST v1.1.
- Progression free survival (PFS) defined as the length of time from start of study therapy to disease progression or death from any cause by RECIST 1.1.
- Overall survival (OS) defined as the length of time from start of study therapy to death from any cause.

12.3 Sample Size and Accrual

The grade 3-5 treatment-related adverse event rate in IMbrave150 was 38%. We hypothesize that a grade 3-5 treatment-related adverse event rate less than 50% in patients with Child-Pugh B7 and B8 liver disease or cirrhosis will be considered acceptable. The upper limit of a 95% one-sided confidence interval (using a Wilson's approach) under each of the assumptions if the true rate were to be 24%, 30% or 38% is listed in the table below.

Table 1. Upper limit of 95% Confidence Interval by True Adverse Event Rate (N = 50)

Adverse Event True Rate (%)	Upper limit of 95% one-sided CI
24	0.351
30	0.415
38	0.496

For example, if the true toxicity rate is 38%, the upper limit of the interval, 0.496, will exclude 50% with 50 patients.

12.4 Assessment of Safety

All subjects who have received at least one cycle of treatment will be evaluable for toxicity. Toxicity will be defined according to CTCAE v 5.0. Please see the Study Calendar for schedule of toxicity assessments.

Patients who are unable to complete at least one cycle of treatment due to non-toxicity reasons (including but not limited to withdrawal of consent or death attributable to disease or disease process) will be replaced.

12.5 Assessment of Efficacy

All subjects with measurable disease who have received at least one cycle of treatment and have their disease re-evaluated or die prior to their first post-baseline disease assessment will be evaluable for assessment of secondary efficacy endpoints.

12.6 Data Analysis Plans

12.6.1 Analysis Plans for Primary Objective

A grade 3-5 treatment related adverse event rate will be estimated as a sample proportion along with 95% confidence interval. Test of the rate < 50% will be performed using 95% C.I. (Wilson's approach) as specified in the sample size justification.

We will be using a Bayesian monitoring method on treatment-related grade 3-5 adverse event rate. The early stopping rule is determined by the posterior probability of the treatment-related adverse event rate. The early stopping would be triggered when the posterior probability of the adverse event rate > 50% is greater than 90%. We assume the non-informative prior on the adverse event rate. Then, the posterior distribution of the true rate given that k adverse events are observed out of the first n patients is a beta distribution with shape parameter 1+k and scale parameter 1+n-k. The first monitoring will be initiated after the first 15 patients finish their treatment. The trial will be stopped if 11 or more out of the first 15 patients experience grade 3-5 adverse events as the posterior probability of adverse event rate > 50% is 96.2%. Monitoring will be continued at every 10 patients accrued after initial monitoring. The PI will contact the Biometrics Shared Resources to receive the updated probabilities regarding decision after each scheduled monitoring.

When we have 50% information (25 patients accrued and finish the treatment), we will calculate the predictive probability of the grade 3-5 treatment-related adverse event rate < 50% at the end of study (i.e. treatment being considered acceptable) to gauge. The following table includes predictive probabilities of rate < 50% at the number of patients experienced grade 3-5 treatment-related adverse events when 25 patients are accrued.

# of patients with treatment-related adverse events	Predictive probability of adverse event rate 50% at the end of study
0	1
1	0.9999
2	0.9999
3	0.9999
4	0.9996
5	0.9968
6	0.9836
7	0.9394
8	0.8347
9	0.655

10	0.4311
11	0.2275
12	0.0928
13	0.0283
14	0.0063
15	0.0001

For example, if 6 or less patients experiencing grade 3-5 treatment-related adverse events out of 25, the predictive probability of treatment being acceptable at the end of study is over 95%. If 15 or more patients with grade 3-5 adverse events, the predictive probability of toxicity rate < 50% at the end of study is 0.01%, very unlikely. We will use this information along with the posterior probability calculated above to determine whether the study should stop or warrant a further discussion.

12.6.2 Analysis Plans for Secondary Objectives

For binary endpoints, ORR and DCR, we will summarize them using counts/proportions of patients who have corresponding events. ORR will be testing against the null hypothesis of ORR ≤ 10% using a one-sided z-test at significance level 5%.

For time to event endpoints, DOR, PFS and OS, we will employ Kaplan-Meier product limit methods to estimate them. Median DOR, PFS and OS along with 95% C.I.s will be reported.

12.6.3 Analysis Plans for Exploratory Objectives

Exploratory objectives include:

- Correlation of tumor molecular signature from NGS tissue analysis with clinical outcomes and treatment response.
- Correlation of tumor molecular signature from NGS tissue analysis with ctDNA.
- Correlation of levels of ctDNA with clinical outcomes and treatment response.

Exploratory objectives will be analyzed as follows: (i) logistic regression models will be employed to assess the association of binary response (ORR, DCR) with tumor molecular signature (either continuously measured or categorized) and ctDNA level. Odds ratio (OR) and 95% C.I. will be reported; and (ii) Cox proportional hazard regression models to evaluate the association of time to event (DOR, PFS, and OS) with biomarker data as stated before. Hazard ratio (HR) and 95% C.I. will be reported.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted with guidance from the Rutgers Cancer Institute of New Jersey's DSMP.

Big Ten CRC AHQ oversight activities include:

- Review all adverse events requiring expedited reporting as defined in the protocol
- Notify participating sites of adverse events requiring expedited reporting
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator

- Submit data summary reports to the lead institution Data Safety Monitoring Committee for review as per their DSMP
- Submit data summary reports to the DSMB for review according to the DSMB Charter

13.2 Rutgers Cancer Institute of New Jersey Data Safety Monitoring Committee

The Rutgers CINJ DSMC will review the following:

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

The Rutgers Cancer Institute of New Jersey's DSMC will review study data every quarter. Documentation of DSMC reviews will be provided to sponsor-investigator and Big Ten CRC AHQ. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with Big Ten CRC AHQ to address the DSMC's concerns.

13.3 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. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. For-cause 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.

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

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to 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 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.

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. Carriaga MT, Henson DE. Liver, gallbladder, extrahepatic bile ducts, and pancreas. *Cancer.* 1995;75(1 Suppl):171-190.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA: a cancer journal for clinicians.* 2018;68(1):7-30.
3. Surveillance E, and End Results (SEER) Program Database. Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer. 2018.
4. Kulik L, El-Serag HB. Epidemiology and Management of Hepatocellular Carcinoma. *Gastroenterology.* 2019;156(2):477-491 e471.
5. Mok TS, Leung TW, Lee SD, et al. A multi-centre randomized phase II study of nolatrexed versus doxorubicin in treatment of Chinese patients with advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol.* 1999;44(4):307-311.
6. Zhu AX. Systemic therapy of advanced hepatocellular carcinoma: how hopeful should we be? *The oncologist.* 2006;11(7):790-800.
7. Lind PA, Naucler G, Holm A, Gubanski M, Svensson C. Efficacy of pegylated liposomal doxorubicin in patients with advanced hepatocellular carcinoma. *Acta Oncol.* 2007;46(2):230-233.
8. Yeo W, Mok TS, Zee B, et al. A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. *Journal of the National Cancer Institute.* 2005;97(20):1532-1538.
9. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *The New England journal of medicine.* 2008;359(4):378-390.
10. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 2009;10(1):25-34.
11. Kudo M. Extremely High Objective Response Rate of Lenvatinib: Its Clinical Relevance and Changing the Treatment Paradigm in Hepatocellular Carcinoma. *Liver Cancer.* 2018;7(3):215-224.
12. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet.* 2017;389(10088):2492-2502.
13. Chau I, Park JO, Ryoo BY, et al. Alpha-fetoprotein kinetics in patients with hepatocellular carcinoma receiving ramucirumab or placebo: an analysis of the phase 3 REACH study. *Br J Cancer.* 2018;119(1):19-26.
14. Ohm JE, Carbone DP. VEGF as a mediator of tumor-associated immunodeficiency. *Immunol Res.* 2001;23(2-3):263-272.
15. Cheng AL, Qin S, Ikeda M, et al. IMbrave150: Efficacy and safety results from a ph III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). *Annals of Oncology.* 2019;30(Supplement_9):ix186-ix187.
16. Kitisin K, Packiam V, Steel J, et al. Presentation and outcomes of hepatocellular carcinoma patients at a western centre. *HPB (Oxford).* 2011;13(10):712-722.

17. McNamara MG, Slagter AE, Nuttall C, et al. Sorafenib as first-line therapy in patients with advanced Child-Pugh B hepatocellular carcinoma-a meta-analysis. *European journal of cancer.* 2018;105:1-9.
18. Sundaralingam T, Gill S. Patterns of presentation, referral, and treatment of hepatocellular carcinoma in a pre-sorafenib era: experience of a Canadian provincial cancer agency. *Curr Oncol.* 2011;18(6):e297-303.
19. Ikeda M, Okusaka T, Mitsunaga S, et al. Safety and Pharmacokinetics of Lenvatinib in Patients with Advanced Hepatocellular Carcinoma. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2016;22(6):1385-1394.
20. Kambhampati S, Bauer KE, Bracci PM, et al. Nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh class B cirrhosis: Safety and clinical outcomes in a retrospective case series. *Cancer.* 2019;125(18):3234-3241.
21. Miller AA, Murry DJ, Owzar K, et al. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(11):1800-1805.
22. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet.* 2016;387(10030):1837-1846.
23. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet.* 2016;387(10031):1909-1920.
24. Siegel AB, Cohen EI, Ocean A, et al. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(18):2992-2998.
25. Boige V, Malka D, Bourredjem A, et al. Efficacy, safety, and biomarkers of single-agent bevacizumab therapy in patients with advanced hepatocellular carcinoma. *The oncologist.* 2012;17(8):1063-1072.
26. Frenette CT. Current status of bevacizumab for advanced hepatocellular carcinoma. *Chin Clin Oncol.* 2012;1(1):13.
27. Motz GT, Santoro SP, Wang LP, et al. Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors. *Nature medicine.* 2014;20(6):607-615.
28. Oelkrug C, Ramage JM. Enhancement of T cell recruitment and infiltration into tumours. *Clin Exp Immunol.* 2014;178(1):1-8.
29. Wallin JJ, Bendell JC, Funke R, et al. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. *Nat Commun.* 2016;7:12624.
30. Manning EA, Ullman JG, Leatherman JM, et al. A vascular endothelial growth factor receptor-2 inhibitor enhances antitumor immunity through an immune-based mechanism. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2007;13(13):3951-3959.
31. Roland CL, Lynn KD, Toombs JE, Dineen SP, Udugamasooriya DG, Brekken RA. Cytokine levels correlate with immune cell infiltration after anti-VEGF therapy in preclinical mouse models of breast cancer. *PloS one.* 2009;4(11):e7669.
32. Voron T, Colussi O, Marcheteau E, et al. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. *The Journal of experimental medicine.* 2015;212(2):139-148.

33. Lee MS, Ryoo BY, Hsu CH, et al. Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study. *Lancet Oncol.* 2020;21(6):808-820.
34. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *The New England journal of medicine.* 2020;382(20):1894-1905.
35. Corcoran RB, Chabner BA. Application of Cell-free DNA Analysis to Cancer Treatment. *The New England journal of medicine.* 2018;379(18):1754-1765.
36. 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.
37. 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.
38. 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.
39. 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 1

Guidelines for Management of Bevacizumab-Specific Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided as outlined below. For cases in which management guidelines are not covered in the bevacizumab Investigator's Brochures or this protocol, patients should be managed as deemed appropriate by the investigator according to best medical judgment.

Event	Grade (CTCAE Version 5.0)	Action to be Taken
Allergic reactions or Infusion-related reactions Or Anaphylaxis	Grade 1	Systemic intervention not indicated – continue bevacizumab
	Grade 2	Oral intervention indicated – slow infusion to 50% or interrupt if clinically indicated (re-start infusion at 50% and increase in 50% increments if well tolerated). Infusion can be re-started at the full rate for subsequent infusions.
	Grade 3	Bronchospasm (allergy-related oedema/angioedema; hypotension); hospitalization for clinical sequelae; intravenous intervention indicated – discontinue bevacizumab
	Grade 4	Life-threatening consequences; urgent intervention indicated - discontinue bevacizumab
Thromboembolic Event (arterial)	Any Grade	Discontinue bevacizumab
Thromboembolic Event (Venous)	Grade 3	Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2weeks, bevacizumab should be held until the full-dose anticoagulation period is over. The use of direct oral anticoagulants is not recommended. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during full-dose anticoagulation *IF* all of the criteria below are met: • The patient must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions) • The patient must not have had hemorrhagic events > grade 2 while on study • The patient must be on stable dose of heparin, low molecular weight heparin, or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4	Discontinue bevacizumab

Event	Grade (CTCAE Version 5.0)	Action to be Taken
Hypertension	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice]	
	Grade 1 (SBP 120-139 mmHg or DBP80-89 mm Hg)	Consider increased BP monitoring; start anti-hypertensive medication if appropriate
	Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg)	Begin (or modify baseline anti-HTN therapy) anti-hypertensive therapy and continue bevacizumab
	Grade 2 symptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg)	Start or adjust anti-hypertensive medication
	Grade 3 (≥ SBP 160 mmHg or ≥ DBP 100 mmHg)	• Modify existing anti-HTN therapy (more than one drug or more intensive therapy than previously indicated. • Hold bevacizumab until symptoms resolve *AND* BP < 160/90mmHg
	Grade 4 (e.g. Hypertensive crisis or malignant hypertension)	Discontinue bevacizumab
Heart Failure or left ventricular dysfunction	Grade 3	Discontinue bevacizumab
	Grade 4	Discontinue bevacizumab
Proteinuria* *Institutional protocols acceptable	1+ proteinuria (≥ ULN - <1.0g/24h)	Continue bevacizumab
	2+ and 3+ proteinuria (1.0 - <3.5g/24h)	• 2+ - administer bevacizumab and obtain 24-hour urine protein before next administration • 3+ - obtain 24-hour urine protein and administer bevacizumab if <2.0 g/24h
	4+ proteinuria (≥ 3.5g/24h)	Obtain 24-hour urine protein and administer bevacizumab only when <2.0 g/24h
Nephrotic syndrome	Grades 3 or 4	Discontinue bevacizumab
Hemorrhage (CNS)	Any grade	Discontinue bevacizumab
Hemorrhage (hemoptysis)	Grade 1	Trace hemoptysis; continue bevacizumab
	Grades 2 - 4	≥ 2.5 mL bright red blood per episode; discontinue bevacizumab
Hemorrhage (other)	Grades 3 - 4	Discontinue bevacizumab
RPLS (Reversible Posterior Leukoencephalopathy syndrome or PRES (Posterior Reversible Encephalopathy Syndrome)		Discontinue bevacizumab
Wound dehiscence requiring medical or surgical intervention		Discontinue bevacizumab
Perforation (GI, or any other organ)		Discontinue bevacizumab
Fistula (GI, pulmonary or any other organ)		Discontinue bevacizumab

Event	Grade (CTCAE Version 5.0)	Action to be Taken
Obstruction of GI tract	Grade 2 requiring medical intervention	Hold bevacizumab until complete resolution
	Grades 3-4	Hold bevacizumab until complete resolution If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion
Febrile neutropenia	Grade 3	Continue bevacizumab
	Grade 4	Hold bevacizumab until resolution or return to baseline
Platelet count decreased	Grades 1 - 3	Continue bevacizumab
	Grade 4	Hold bevacizumab until resolution or return to baseline
Other Unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	Hold bevacizumab until symptoms resolve to ≤ grade 1 or baseline
	Grade 4	• Discontinue bevacizumab • Upon consultation with the sponsor investigator, resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the Grade 4 toxicity is transient, has recovered to ≤ grade 1 (or baseline) and unlikely to recur with retreatment.

18. APPENDIX 2

Guidelines for 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. All events attributed to atezolizumab should be thoroughly evaluated for other commonly reported etiologies.

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 for a given patient 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-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator.

Pneumonitis/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.

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.

Event	Management
Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab.
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. [c] • For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Bronchoscopy or BAL is recommended.

	• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids.

BAL = bronchoscopic alveolar lavage.

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

[b] If corticosteroids have been initiated, they must be tapered 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-mediated event. Patients can be re-challenged with atezolizumab only after the investigator has performed a benefit-risk assessment and approval has been documented by the investigator (or an appropriate delegate).

Hepatic Events

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

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, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Event	**Management**
If AST/ALT is within normal limits at baseline and increases to >3×ULN to ≤10×ULN or If AST/ALT is >ULN to ≤3×ULN at baseline and increases to >5×ULN to ≤10×ULN or If AST/ALT is >3×ULN to 5×ULN at baseline and increases to >8×ULN to ≤10×ULN	• Monitor LFTs more frequently until return to baseline values. • Withhold atezolizumab for up to 12 weeks after event onset. [a] Events of > 5 days' duration: • Consider initiating treatment with 1–2 mg/kg/day prednisone or equivalent. • If event resolves to baseline or to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to baseline or to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.[c]

If AST/ALT increases to > 10x ULN or total bilirubin increases to > 3x ULN	• 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 prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to baseline, taper corticosteroids.

LFT = liver function tests; ULN = upper limit of normal.

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

[b] If corticosteroids have been initiated, they must be tapered 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-mediated event. Patients can be re-challenged with atezolizumab only after the investigator has performed a benefit-risk assessment and approval has been documented by the investigator (or an appropriate delegate).

Gastrointestinal Events (Diarrhea or Colitis)

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.

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. • If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b]

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

GI = gastrointestinal.

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

[b] If corticosteroids have been initiated, they must be tapered 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-mediated event. Patients can be re-challenged with atezolizumab only after the investigator has performed a benefit-risk assessment and 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.

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.

Event	Management
Grade 1 hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• Consider withholding atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving.
Grade 3 or 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer to an endocrinologist. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Otherwise, permanently discontinue atezolizumab. [c]
Grade 1 hyperthyroidism	TSH ≥ 0.1 mU/L and < 0.5 mU/L: • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. TSH < 0.1 mU/L: • Follow guidelines for Grade 2 hyperthyroidism. • Consider patient referral to endocrinologist.
Grade 2 hyperthyroidism	• Consider withholding 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.
Grade 3 or 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Refer to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Otherwise, permanently discontinue atezolizumab. [c]
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging.

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

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

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

[b] If corticosteroids have been initiated, they must be tapered 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-mediated event. Patients can be re-challenged with atezolizumab only after the investigator has performed a benefit-risk assessment and approval has been documented by the investigator (or an appropriate delegate).

Ocular Events

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

Event	Management
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.
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]
Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on a benefit–risk assessment by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.
[b] If corticosteroids have been initiated, they must be tapered 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-mediated event. Patients can be re-challenged with atezolizumab only after the investigator has performed a benefit-risk assessment and approval has been documented by the investigator (or an appropriate delegate).

Immune-Mediated Cardiac Events

Immune-mediated Myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from

infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated as below.

Immune-Mediated pericardial disorders

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

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

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

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

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

Management Guidelines for Immune-Mediated Cardiac Events

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

Infusion-Related Reactions and Cytokine-Release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive medication 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[36]. 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[37, 38], including atezolizumab.

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

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

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]	• Immediately interrupt atezolizumab infusion.

Fever[b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen[d] by nasal cannula or blow-by	• Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab.[e] • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the sponsor-investigator.
Grade 3[a] Fever[b] with hypotension requiring a vasopressor (with 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.[e] • Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator.
Grade 4[a] Fever[b] with hypotension requiring multiple vasopressors	• Permanently discontinue atezolizumab.[e] • Administer symptomatic treatment.[c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice.

(excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments[f] may be considered at the discretion of the investigator. • 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 5) 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. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab according to institutional guidelines and the above table. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after considering the benefit-risk ratio.
f. Refer to Riegler et al. (2019)[39].

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.

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.

Event	Management
	• 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 corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, permanently discontinue atezolizumab. [c]
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [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-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

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

[b] If corticosteroids have been initiated, they must be tapered 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-mediated event. Patients can be re-challenged with atezolizumab only after the investigator has performed a benefit-risk assessment and approval has been documented by the investigator (or an appropriate delegate).

Rash/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. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A biopsy should be considered unless contraindicated.

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

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

[b] If corticosteroids have been initiated, they must be tapered 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-mediated event. Patients can be re- challenged with atezolizumab only after the investigator has performed a benefit-risk assessment and 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 the table below, with specific guidelines for myelitis provided in the separate table.

Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, Grade 2, including facial paresis	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy: o If event resolves to Grade 1 or better, resume atezolizumab. [b] o If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For facial paresis: o If event resolves fully, resume atezolizumab [b] o If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Immune-mediated neuropathy, Grade 3 or 4, including facial paresis	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

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

[b] If corticosteroids have been initiated, they must be tapered 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-mediated event. Patients can be re- challenged with atezolizumab only after the investigator has performed a benefit-risk assessment and approval has been documented by the investigator (or an appropriate delegate).

Management Guidelines for Immune-Mediated Myelitis

Event	Management
Immune-mediated myelitis, Grade 1	• Continue atezolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

Immune-Mediated Meningoencephalitis

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

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

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

Renal Events

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and

treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

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

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

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

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

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

Immune-Mediated Myositis

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

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

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Immune-mediated 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 prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, treat as a Grade 4 event. Permanently discontinue atezolizumab. [c]
Immune-mediated 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 limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids,

	consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

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

Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

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

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Hemophagocytic Lymphohistiocytosis (HLH)

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

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

Macrophage Activation Syndrome (MAS)

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

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

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

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

References

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.

La Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology Am Soc Hematol Educ Protram 2015;1:190−6.

La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465−77.

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;25:625-38.

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355−62.

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–9.

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.

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.

Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908–14.

19. APPENDIX 3

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. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
5. Administer antihistamines, epinephrine, or other medications as required by participant status and as directed by the physician in charge.
6. Continue to observe the participant and document observations.

20. APPENDIX 4

Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study.

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

Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life–threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anti-cancer agent.

Contact Study PI, Howard Hochster, MD, regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

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