A Randomized Phase II Study of Atezolizumab and Bevacizumab with Y-90 TARE in Patients with Unresectable Hepatocellular Carcinoma (HCC)

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PROTOCOL SIGNATURE PAGE

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VERSION DATE: 02DEC2021

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

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Signature of Site Investigator Date

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Site Investigator Name (printed)

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Site Investigator Title

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Name of Facility

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Location of Facility (City and State)

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SYNOPSIS

TITLE	A Randomized Phase II Study of Atezolizumab and Bevacizumab with Y-90 TARE in Patients with Unresectable Hepatocellular Carcinoma (HCC)
SHORT TITLE	Phase II study evaluating atezolizumab and bevacizumab with Y-90 TARE in unresectable HCC
PHASE	II
OBJECTIVES	**Primary Objective** Assess the progression-free survival (PFS) per RECIST 1.1 of patients receiving Y-90 transarterial radioembolization (TARE) combined with atezolizumab and bevacizumab. **Secondary Objectives** • Safety and tolerability of Y-90 TARE combined with atezolizumab and bevacizumab in patients with HCC. • Assess the progression-free survival (PFS) per mRECIST of patients receiving Y-90 transarterial radioembolization (TARE) combined with atezolizumab and bevacizumab. • Time to Progression (TTP) per RECIST 1.1 and mRECIST • Overall response rate (ORR) determined per RECIST 1.1 and mRECIST • Overall survival (OS) • Evaluate PROs of physical functioning, role functioning, social functioning, and global health status/quality of life experienced by patients receiving Y-90 TARE and bevacizumab plus atezolizumab treatment
STUDY DESIGN	This is an open-label, multi-center, randomized phase II study comparing the Y90 TARE followed by bevacizumab and atezolizumab treatment to the Y90 TARE treatment alone in unresectable intermediate stage HCC. Regarding TARE treatment, a comprehensive plan will be made for each patient's liver-targeted therapy. This plan will involve treating the predominant liver lesions with segmental TARE or unilobar TARE using predetermined dosimetry, while keeping FLR $\geq$ 40% (FLR is estimated by excluding the liver volume of Y90 infused distribution area). Any patient who is not a TARE candidate, as defined by a lung dose threshold for Y90 of 30Gy and an estimated FLR of less than 40% at the time of forming the comprehensive treatment plan will be excluded from this study. All candidates who meet the inclusion criteria will be randomized at a 1 to 1 ratio to TARE (Arm A; control arm) or TARE followed

	by the combination of atezolizumab and bevacizumab (Arm B; experimental arm). Patient will have TARE mapping followed by TARE treatment. In Arm B, patient will start the combination of bevacizumab and atezolizumab 4 weeks (± 1 week) after TARE treatment. Patients on study will have abdominal MRI or CT scans every 12 weeks and CT scans of the chest every 24 weeks to evaluate for disease progression. In the case of cancer progression, patients will be taken off study treatment and followed as described in Section 7. All patients will be taken off study treatment at the end of two years from TARE treatment and followed as described in Section 7. Disease progression will be captured by both RECIST 1.1 and mRECIST for the primary and secondary objectives. Infiltrative HCC cannot be evaluated by mRECIST and will only be evaluated by RECIST 1.1. We plan to assess the safety of TARE with bevacizumab and atezolizumab in the first 10 patients randomized to Arm B for two cycles. If there are no Grade ≥ 3 unexpected toxicities possibly, probably or definitely related to TARE in combination with bevacizumab and atezolizumab, the study will continue to accrue an additional 108 patients/to a total of 128 patients. Patients will continue study treatment for a total of 24 months from TARE, or until intolerable toxicity or disease progression occur, whichever is earlier. Archived tumor tissue biopsies or fresh biopsies will be obtained, followed by mapping and Y-90 treatment, as per standard of care. Tissue and blood will be collected for correlative studies.
KEY ELIGIBILITY CRITERIA (See Section 3 for full eligibility criteria)	**Inclusion** 1. Patients must demonstrate adequate hepatic, bone marrow, and renal function as defined in Table below. All screening labs should be performed within 14 days of treatment initiation. 2. ECOG Performance Status of 0-1 at screening. 3. Histological or cytological evidence/confirmation per AJCC, 8th edition, of hepatocellular carcinoma (HCC). 4. Patients must have at least Barcelona Clinic Liver Cancer (BCLC) stage B HCC and must be outside of Milan Criteria;

	and/or HCC with peripheral vascular involvement with any size or number of tumor (segment peripheral, vp1 and vp2 are allowed, but vp3 and vp4 are excluded). **NOTE:** absence of extrahepatic spread, must be confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis. 5. Patient must either (1) not be a candidate for liver transplantation as determined by the liver transplant service or (2) refuse evaluation by the liver transplant service. 6. Patients must have a Child-Pugh score of A, or selected B7. **NOTE:** Definition of the selected B7 patients: Child Pugh B7 patients are allowed if they meet the inclusion criteria 11 and they do not have hepatic encephalopathy or more than a moderate amount of ascites. 7. Archival tissue obtained within 6 months of registration is required. If archival tissue is not available, subjects are not eligible. 8. No prior systemic therapy is permitted. **NOTE:** Patients who received prior local therapy (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound) are eligible provided the target lesion(s) have not been previously treated with local therapy or the target lesion(s) within the field of local therapy have subsequently progressed in accordance with RECIST version 1.1. Prior TACE IS allowed if FLR is ≥ 40%. 9. Patient must be a TARE candidate, as defined by a lung dose threshold for Y-90 of 30 Gy (equal or less than 20% in 99mTc macro-aggregated albumin scan for resin and 30 Gy per treatment for glass) and an estimated (future liver remnants) FLR of ≥ 40% at the time of forming the comprehensive treatment plan. Both the lung dose threshold and FLR values must be obtained and available in source documentation. **Exclusion** 1. Have signs of liver failure, e.g. clinically significant ascites, encephalopathy, or variceal bleeding within six months from enrollment. 2. Have evidence of excessive hepatopulmonary shunting (> 20% in 99mTc macro-aggregated albumin scan for resin and 30 Gy

	per treatment for glass) or angiographically demonstrable and non-occludable gastrointestinal shunting, precluding from Y-90 treatment). 3. Have active autoimmune disease that has required systemic treatment in the past 2 years 4. Have history of idiopathic pulmonary fibrosis (including bronchiolitis obliterans with organizing pneumonia) drug-induced pneumonitis, or idiopathic pneumonitis or evidence of active pneumonitis on screening chest CT scan. **NOTE:** History of radiation pneumonitis in the radiation field (fibrosis) is permitted. 5. Patients with CNS metastatic disease. 6. Have unresolved toxicities from prior anticancer therapy, defined as having not resolved to National Cancer Institute (NCI) CTCAE v5 grade 0 or 1 with the exception of alopecia and laboratory values listed per the inclusion criteria. **NOTE:** Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by any of the investigational products may be included (e.g., hearing loss) after consultation with the sponsor-investigator.
STATISTICAL CONSIDERATIONS	The primary objective of this study is to compare the PFS of patients with HCC receiving a combination of bevacizumab, atezolizumab, and Y90 TARE therapy with that for patients on Y90 TARE therapy alone. The estimated PFS for patients receiving segmental TARE (Arm A) is 9 months. It is hypothesized that the addition of combined bevacizumab and atezolizumab (Arm B) will improve the PFS from 9 months (control arm receiving segmental Y90) to 15 months (bevacizumab plus atezolizumab following Y90 TARE). Assuming a hazard ratio of 0.6 (median PFS of 9 months in Arm A and 15 months in Arm B) and an exponential distribution for PFS in each treatment arm, a total of 97 PFS events (53 in the control group, 44 in experimental arm) are needed to detect a statistically significant difference using a 1-sided alpha of 0.05 with 80% power. With an expected accrual rate of 10 patients per month, and 24 months of follow up after last patient in, a total of evaluable 118 patients will be needed. A total of 128 HCC subjects will be enrolled during the assuming ~8% of dropout/ineligibility and randomized to the two treatment arms at a 1:1 ratio. The study will stratify for AFP

	level (high is defined as ≥ 400; low as < 400), presence or absence of vascular invasion.
TOTAL NUMBER OF SUBJECTS	N = Up to 128 subjects
ESTIMATED ENROLLMENT PERIOD	Estimated 14 months after all participating sites are open to accrual
ESTIMATED STUDY DURATION	Estimated 40 months

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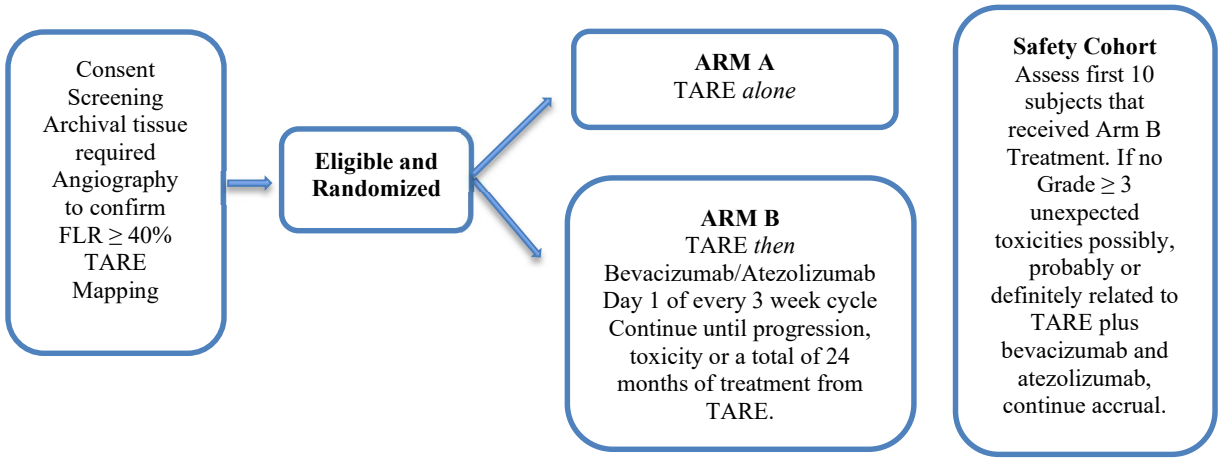
SCHEMA


Consent
Screening
Archival tissue required
Angiography to confirm FLR ≥ 40%
TARE Mapping
Eligible and Randomized
ARM A
TARE *alone*
ARM B
TARE *then*
Bevacizumab/Atezolizumab
Day 1 of every 3 week cycle
Continue until progression, toxicity or a total of 24 months of treatment from TARE.
Safety Cohort
Assess first 10 subjects that received Arm B Treatment. If no Grade ≥ 3 unexpected toxicities possibly, probably or definitely related to TARE plus bevacizumab and atezolizumab, continue accrual.

1. BACKGROUND AND RATIONALE

1.1 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the sixth most common cancer globally and is the second most deadly cancer (International Agency for Research on Cancer 2012). There are over 700,000 new cases diagnosed each year worldwide with large geographic variation in both risk factors and incidence (Ferlay et al. 2010; El-Serag 2011). The majority (about 80%) of cases occur in sub-Saharan Africa and eastern Asia, and China alone accounts for 55% of cases worldwide. Hepatitis B virus infection is the main risk factor for HCC in Asia and Africa, while in Western countries and Japan, the main risk factor is hepatitis C virus (HCV) infection and excessive alcohol intake, along with other causes of cirrhosis.

HCC is a highly lethal disease with the highest mortality-to-incidence rate ratio of 0.98 of any solid tumor (Kamangar et al. 2006). Up to 80% of patients first presenting with HCC have advanced incurable disease because of the late appearance of symptoms. It is a medically complex and difficult to treat disease as the majority of HCC patients have underlying cirrhosis requiring management of both the malignancy and the cirrhosis. In the United States, at 5 years, the overall survival (OS) rate of HCC patients is 17% and falls substantially to only 3% if present with distant metastasis (Siegel et al. 2016). In China, at 5 years, the OS rate of HCC patients is 10.1% (Chen et al. 2016).

1.2 Current Systemic Treatment for Intermediate Stage Hepatocellular Carcinoma

Curative treatment of HCC includes surgical resection and liver transplant. Beyond Milan transplant criteria (as defined as patients with one less < 5cm, 2-3 lesions the largest one < 3cm), patients with one lesion 5-8 cm; 2-3 lesions 3-5 cm, or 4-5 lesions each < 3cm, with total tumor volume <8cm, show comparable outcome when they were down-staged meeting Milan criteria and received a liver transplant to patients have disease within Milan criteria and received a liver transplant, with a 5-year post OLT: 78% vs.81% (p=0.69), respectively. (Yao et al Hepatology 2015).

For patients beyond curative resection or outside transplant or downstage criteria, locoregional therapies (LRT) remain excellent treatment options (EASL, 2012). These include direct lesion ablation and transarterial approaches such as chemoembolization (TACE) and radioembolization (TARE) (NCCN, 2017).

1.2.1 TARE Treatment

Radioembolization (RE) with yttrium-90 (90Y) microspheres is a form of brachytherapy delivered via the hepatic artery, that allows targeted delivery of high-dose radiation to liver tumors. Several retrospective and large cohort studies showed an acceptable safety profile of RE, and good results in terms of local control of the disease and long-term survival in patients with unresectable HCC limited to the liver in the intermediate and advanced stages (Salem, 2010; Sangro, 2011, Mazzaferro, 2013).

1.2.2.1 TARE in Combination with Systemic Therapy

Until recently two randomized clinical trials (RCTs) comparing the efficacy of TARE with respect to sorafenib had been published. SIRveNIB (selective internal radiation therapy vs.

sorafenib) is a recently published open-label phase III trial that compared 90Y-resin microspheres TARE with sorafenib 800 mg/d in patients with locally advanced HCC, in a two-tailed study designed for superiority/detriment; the primary end point was overall survival (OS). The trial randomized 360 patients (182 to RE, 178 to sorafenib) across 11 countries in the Asia-Pacific region. The study failed to meet the primary endpoint: in fact, median OS in the intention-to-treat population was 8.8 and 10.0 months with TARE and sorafenib, respectively (hazard ratio, 1.1; 95% CI: 0.9–1.4; P=0.36). Similarly, no differences in OS were demonstrated in the treated population (11.3 and 10.4 months in the RE and sorafenib arms, respectively, P=0.27), nor in subgroup analyses. Tumor response rates (TRR) were significantly higher in the RE arm, however disease control rates were similar and no differences in progression-free survival were observed. Fewer patients in the RE group (20.8%) than in the sorafenib group (35.2%) had serious AEs, and mean duration of side effects was shorter in the RE arm. (Chow, 2018). The SARAH trial (SorAfenib versus Radioembolization in Advanced Hepatocellular carcinoma) enrolled 467 patients (237 RE, 222 sorafenib) from 25 centers in France.

Similarly, to SIRveNIB, it was a phase III trial designed for superiority that compared 90Y-resin microspheres TARE with sorafenib 800 mg/d in patients with locally advanced HCC. This Western-based trial failed to meet the primary endpoint since median OS was 8.0 months in the TARE group vs. 9.9 months in the sorafenib group (hazard ratio, 1.15; 95% CI: 0.94–1.41; P=0.18) (Vilgrain, 2017).

In these studies, HCC patients with more than one BCLC stage are included in each study. Patient with BCLC A, B, or C stages of HCC and liver function as determined by Child Pugh class A, B or C, have different clinical outcome after TARE treatment (Salem, 2018), therefore interpretation of the clinical study endpoints of a study with mixed BCLC stage HCC and Child Pugh class liver function is challenging. Studies with more homogenous HCC population in BCLC stage and Child Pugh class are needed to evaluate the efficacy of local regional therapy.

1.3 Atezolizumab

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells. Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved in multiple countries for the treatment of urothelial carcinoma (UC) non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) and triple negative breast cancer. Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.4 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, including locally recurrent or metastatic breast cancer; advanced, metastatic, or recurrent NSCLC; advanced and/or metastatic renal cell cancer (RCC); newly diagnosed glioblastoma multiforme (GBM) and GBM after relapse or disease progression; persistent, recurrent, or metastatic cervical cancer; front-line treatment of epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC); and treatment of platinum-sensitive and platinum-resistant recurrent EOC, PPC, or FTC.

1.5 Clinical Development Program in Hepatocellular Carcinoma

1.5.1 Atezolizumab Monotherapy

A comprehensive overview of atezolizumab efficacy across all indications is provided in the atezolizumab Investigator's Brochure. This section provides an overview of the available efficacy data in patients with HCC treated with atezolizumab as monotherapy. To date, atezolizumab as single agent has shown minimal activity in the treatment of HCC patients with similar characteristics as those that would be included in this study. Safety findings in the HCC cohort are in line with expectations for an HCC population and with the atezolizumab safety profile observed in the overall study population across multiple tumor types. No new safety signals related to atezolizumab monotherapy were observed in the HCC population.

1.5.1.1 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. The largest cohorts enrolled into this trial consisted of patients with NSCLC, RCC, and UC. Expansion cohorts have included patients with CRC, melanoma, NSCLC, pancreatic cancer, UC, breast cancer, esophageal cancer, prostate cancer, small cell lung cancer, malignant lymphoma, multiple myeloma, HCC, and other less common tumor types.

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

patients had discontinued treatment due to disease progression, 1patient 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) at 24 weeks. No patients had SD at 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.

1.5.1.2 Study YO29233

StudyYO29233 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, 21patients 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 2.8months (95% CI: 1.4, 7.8 months) and median OS was 11.1 months (95% CI: 4.7months, NE).

1.5.2 Bevacizumab Monotherapy

A comprehensive overview of bevacizumab efficacy across all indications is provided in the bevacizumab Investigator's Brochure. This section provides an overview of the available efficacy data in patients with HCC treated with bevacizumab as monotherapy. Overall, bevacizumab as a single agent demonstrated minimal activity in HCC, and is unlikely to demonstrate a meaningful clinical benefit over current standard of care (sorafenib) based on the survival data observed. Bevacizumab monotherapy was generally safe and well tolerated in the HCC population, and safety findings were consistent with the HCC population and established safety profile of bevacizumab. No new safety signals related to bevacizumab monotherapy were observed in this patient population.

1.5.2.1 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 (Siegel et al. 2008). 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 10mg/kg every 4 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 5mg/kg and 34patients who received bevacizumab 10mg/kg Q2W.

Clinical activity of bevacizumab was observed in patients with nonmetastatic HCC. Of the 46patients, 6 patients (13%) had objective responses (95% CI: 3%, 23%), and 65% (95% CI: 51%, 79%) of patients were progression free at 6months. Median PFS was 6.9months (95% CI: 6.5, 9.1) and median OS was 12.4months (95% CI: 9.4, 19.9). No significant changes were seen with respect to dose and outcome. The response rates for the 5mg/kg and 10mg/kg groups were 8.3% and 14.7%, respectively (p=0.99 by Fisher's exact test). Median OS times for patients receiving 5mg/kg and 10 mg/kg were 15.1months and 12.2months, respectively (p= 0.64 by the log-rank test) (Siegel et al. 2008). 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 (Boigeet al. 2012). 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 10mg/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 16weeks after study entry, according to RECIST v1.0.

Overall, 48 patients were enrolled, of which 25 patients were planned to receive bevacizumab 5mg/kg and 23 patients were planned to receive bevacizumab 10mg/kg, Q2W. Of the 48 patients enrolled, 43patients 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, 55-362days), 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 5mg/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) (Boige et al. 2012).

1.6 Study Rationale and Benefit-Risk Assessment

1.6.1 Rationale for the Combination of Anti-PD-L1 and Anti-VEGF Therapy in Hepatocellular Carcinoma

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 (Boigeet al. 2012; Frenette2012). 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 (Motz et al. 2014). Furthermore, bevacizumab can restore and/or maintain the antigen presentation capacity of dendritic cells, leading to enhanced T-cell infiltration in tumors (Oelkrug and Ramage 2014; Wallin et al. 2016). In addition to increased trafficking of T cells into tumors (Manning et al. 2007), several publications have illustrated that antiVEGF 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 (Roland et al. 2009; Voronet al. 2015). 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.

1.6.2 Clinical Data of Atezolizumab in Combination with Bevacizumab in Hepatocellular Carcinoma

Preliminary data from Study GO30140 indicates substantial numerical improvement in ORR for the combination of atezolizumab + bevacizumab compared to sorafenib, the current global standard of care, in patients with locally advanced or metastatic HCC, supporting the hypothesis of a synergistic/complementary effect of atezolizumab and bevacizumab.

1.6.2.1 Efficacy: Study GO30140

StudyGO30140 is a Phase Ib, multicenter study of atezolizumab in combination with bevacizumab and/or chemotherapy for first-line metastatic cancer patients. 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 1200mg of atezolizumab plus 15 mg/kg of bevacizumab on Day 1 of every 21-day cycle (Q3W).

Based on a clinical cutoff date of 26 July2018, 103 patients (recruited from United States and South Korea) with HCC had received atezolizumab + bevacizumab combination therapy. All received atezolizumab + bevacizumab as first-line therapy. At the time of the clinical cutoff date, 70 patients remained on treatment, 18 patients had discontinued treatment due to disease progression, 2 patients discontinued treatment due to symptomatic deterioration, 6 patients discontinued treatment due to an adverse event, 4 patients discontinued treatment due to death, and 3 patients discontinued treatment due to patient decision or other reasons.

Efficacy analyses were performed in the efficacy-evaluable population, defined as all patients who received any amount of the combination treatment and have been followed on study for at least 16 weeks. Based on a clinical cutoff date of 26 July2018, 73 patients enrolled into Arm A were efficacy-evaluable with a median duration of survival follow-up of 7.2 months.

Based on IRF assessment per RECIST v1.1, the confirmed ORR was 27.4% (95% CI: 17.6, 39.1). Among the 20 responders, 4 (20%) achieved a CR and the remaining 16 (80%) achieved PR. The ORR based on investigator-assessment per RECIST v1.1 was numerically similar to the ORR based on IRF-assessment per RECIST v1.1. According to investigator-assessment per RECIST v1.1, 23 of the 73 efficacy-evaluable patients (31.5% [95% CI: 21.1, 43.4]) achieved confirmed objective responses, with 1 patient (1.4%) achieving a CR. When tumor scans were assessed by the IRF according to HCC mRECIST criteria, 25 of the 73 efficacy-evaluable patients (34.2% [23.5, 46.3]) achieved a confirmed objective response, 8 of those 25 responders (32%) achieved a best overall response of CR, and 17 of the 25 responders (68%) achieved a best overall response of PR. Importantly, responses were observed in all assessed patient subgroups, including etiology, region, and baseline AFP and tumor burden.

At the time of the clinical cutoff date, 80% (16 of 20) of the IRF-assessed responses per RECIST v1.1 were ongoing, with durations ranging from 1.6 to 22.0 months (denotes censored data). Nine patients had responses of 6 months or longer per IRF assessment by RECIST v1.1.

The median duration of response (DOR) has not been reached by IRF-assessment (per RECIST v.1.1 or HCC mRECIST) or INV-assessment (per RECIST v1.1), nor has the median OS been reached. The median PFS by IRF-assessment per RECIST v1.1 and per HCC mRECIST was 7.5 months (95% CI: 5.4- 14.9) and the median PFS by INV-assessment per RECIST v1.1 was 14.9 months (95% CI: 7.4- NE). The 6-month PFS rate was 56% by IRF-assessment per RECIST v1.1, 65% by INV-assessment per RECIST v1.1 and 58% by IRF-assessment per HCC mRECIST. These estimates of median PFS are considered to be unstable and expected to change with longer follow-up.

1.6.2.2 Safety: Study GO30140

In the analysis of safety data from Study GO30140 (clinical cutoff date of 26 July 2018) in 103 patients with HCC (median treatment duration with atezolizumab was 3.5 months [range: 0-24 months]; median treatment duration with bevacizumab was 3.5 months [range: 0-23 months]), the combination of atezolizumab + bevacizumab was generally safe and well tolerated; no new safety signals related to the combination therapy were identified beyond the established safety profile for each individual agent. Furthermore, no unexpected adverse events were observed.

Overall, 95 patients (92.2%) experienced at least one adverse event. The most common adverse events (≥ 20%) were decreased appetite (28.2%) and fatigue, pyrexia, and rash (20.4% each). Forty-one patients (39.8%) experienced a Grade 3- 4 adverse event, with the most common Grade 3- 4 adverse events (≥ 4%) being hypertension (11.7%) and increased AST (4.9%). Treatment-related Grade3- 4 adverse events were reported in 28 patients (27.2%), the most common being hypertension (9.7%) and neutrophil count decreased (2.9%). A total of 36 patients (35%) experienced serious adverse events. Treatment-related serious adverse events occurred in 19 (18.4%) patients, most of which were single occurrence except colitis, esophageal

varices hemorrhage and pneumonitis (1.9% each). Five patients (4.9%) experienced Grade 5 adverse events, of which 2 patients (1.9%) experienced Grade 5 treatment-related adverse events.

Six patients (5.8%) discontinued both atezolizumab and bevacizumab treatment due to adverse events. Eight patients (7.8%) discontinued atezolizumab and 10 patients (9.7%) discontinued bevacizumab due to adverse events. All adverse events leading to any atezolizumab and/or bevacizumab withdrawal were single occurrence except esophageal varices hemorrhage (n = 2, 1.9%), which led to discontinuation of bevacizumab only.

1.6.2.3 IMbrave 150

The landmark IMbrave150 trial, was a trial that testing the combination of atezolizumab plus bevacizumab and has solidified immunotherapy's role in advanced HCC. Atezolizumab plus bevacizumab is the first therapy to show improved PFS, OS, and improved quality of life when compared to sorafenib. The novel combination of the PD-L1 inhibitor atezolizumab combined with the VEGF inhibitor bevacizumab were thought to both decrease angiogenesis and tumor growth as well as decrease immunosuppression while, at the same time promote T-cell migration into the tumor (Finn). This combination was first testing in a phase Ib GO30140 trial in which untreated unresectable HCC patients (N=119) were randomized to receive atezolizumab 1200 mg IV every 3 weeks alone or with bevacizumab 15 mg/kg IV every 3 weeks until unacceptable toxicity or loss of clinical benefit (Lee). The sixty patients who received the combination showed better results than monotherapy atezolizumab with an ORR of 36%, with a PFS of 5.6 months with acceptable side-effect profile (Lee).

This early phase trial led to the global open-label phase 3 IMbrave150 trial which randomized 501 treatment naive advanced HCC patients with a 2:1 ratio to either combination atezolizumab 1200 mg IV combined with bevacizumab 15 mg/kg IV every 3 weeks or standard of care sorafenib 400mg twice a day (Finn). The results, after 8.6months median duration of follow-up, revealed improved survival in the combined therapy group with a hazard ratio (HR) of 0.58 (95% CI 0.42-0.79, p=<0.001) (Finn). The survival at 6 months and 12 months were 84.8% (95% CI, 80.9-88.7) and 67.2% (95% CI, 61.3-73.1), respectively, in the atezolizumab–bevacizumab group and 72.2% (95% CI, 65.1-79.4) and 54.6% (95% CI, 45.2-64.0) in the sorafenib group (Finn). The median PFS was longer with the atezolizumab-bevacizumab combination than with sorafenib (6.8 months [95% CI, 5.7 to 8.3] vs. 4.3 months [95% CI, 4.0 to 5.6]; stratified HR for progression or death, 0.59; 95% CI, 0.47 to 0.76; P<0.001) (FInn). Secondary outcomes include ORR of 27.3% in the atezolizumab-bevacizumab group versus 11.9% in sorafenib group (95% CI, 7.4-18.0) with sorafenib based on RECIST 1.1 (P<0.001), and 33.2% (95% CI, 28.1-38.6) and 13.3% (95% CI, 8.4-19.6), respectively, hepatocellular carcinoma–specific mRECIST (P<0.001) (Finn). The study also explored quality of life outcomes utilizing the EORTC QLQ-30 questionnaire. Results showed a combination atezolizumab plus bevacizumab delayed time to deterioration compared to sorafenib (11.2 months with combination vs. 3.6months with sorafenib; HR 0.63; 95% CI, 0.46 to 0.85). The most common grade 3 or 4 adverse events with the combination therapy was hypertension (15.2%), elevated AST (7%), and elevated ALT (3.6%) (Finn). Though this landmark trial has changed the landscape of treating advanced HCC, it is not an approved therapy for all patients. The exclusion criteria for the trial included patients with Child-Pugh B and C, ECOG 2 or greater, a history of autoimmune diseases, coinfections

with hepatitis B or C, and untreated esophageal or gastric varices with bleeding or risk of bleeding.

1.7 Summary

Overall, the combination of atezolizumab + bevacizumab may be a promising treatment option for patients with HCC. To address the ongoing high unmet medical need for patients with HCC, Study YO40245 aims to evaluate the efficacy and safety of atezolizumab + bevacizumab against the current standard of care, sorafenib, in patients with locally advanced or metastatic HCC.

1.8 Rationale and Study design

1.8.1 Rationale for LRT using TARE as the control arm and treatment plan

Y-90 TARE treatment of HCC lesions provides good disease control; however, radiation from TARE may result in liver fibrosis (Tomozawa, 2018, Spina, 2019), which may have a negative impact on the survival of patients, especially when systemic treatment options are now available that can extend patient survival to 2 years or beyond. TARE treatment of individual liver segments is preferred to avoid extensive liver fibrosis and liver decompensation post TARE treatment. Data on the maximum number of segments that can receive TARE without causing liver decompensation 2 years or beyond post Y-90 is lacking. The minimum functional liver reserve (FLR) used to guide liver resection in compensated cirrhosis may be extrapolated and used to guide this study design. When liver resection is considered for a patient with compensated cirrhosis, FLR >/= 40% is required to minimize post-surgical liver failure (Vauthey, 2000). When segment TARE treatment is planned, the FLR can be estimated by excluding the Y-90 infused liver volume and infusion distribution area and the untreated HCC area, and if the resulting FLR is equal to or more than 40%, Y-90 TARE is an option. In addition, dosimetry will be defined.

Segmental TARE often results in less long-term liver damage compared to lobar TARE and is the preferred method as long as it can treat the entirety of the predominant lesion and its blood supply. To simplify the treatment plan, if segmental TARE is not sufficient to treat the predominant lesion we will limit the maximal amount of TARE treatment to only one lobe of the liver.

1.8.2 LRT treatment plan

In this study, a comprehensive plan will be made for each patient's liver-targeted therapy; this plan will involve treating the liver lesions with segmental TARE or unilobar TARE using predetermined dosimetry, while keeping FLR equal or greater than 40% (FLR is estimated by excluding the liver volume of Y-90 infused distribution area). Any patient who is not a TARE candidate, as defined by a lung dose threshold for Y-90 of 30Gy and an estimated FLR of less than 40% at the time of forming the comprehensive treatment plan will be excluded from this study. All candidates who meet the inclusion criteria and are registered will be randomized to TARE alone (Arm A; control arm) or TARE followed by the combination of atezolizumab and bevacizumab (Arm B; experimental arm).

1.8.3 Definition of response to LRT

The standard of care for intermediate stage HCC with increased risk of disease progression is TARE, and this is reflected in our control arm (Arm A). In order to demonstrate benefit of combination immune therapy to standard of care, in our experimental arm we plan to add atezolizumab and bevacizumab to TARE (Arm B).

The effect of Y-90 TARE will be evaluated at three months and six months after treatment as the response of Y-90 TARE treatment can be observed in 3-6 months from the TARE treatment. The disease progression on HCC lesions treated with TARE at 12 weeks will be confirmed at 6 months to be counted as having disease progression at 12 weeks as determined by mRECIST for endpoint analysis. If additional treatment is needed after the 12 week assessment that will be considered the date of confirmed progression.

1.8.4 Combination of LRT with the combination of bevacizumab and atezolizumab as the experimental arm

This study rationale is based on compelling preclinical and clinical studies: The anti–PD-L1 antibody atezolizumab prevents PD-L1 from interacting with PD-1 and B7.1, thus reinvigorating anti-tumor T-cell activity. At the same time, anti-VEGF bevacizumab can increase dendritic cell (DC) maturation, enhance T-cell infiltration, and reduce myeloid-derived suppressor cells (MDSCs) and regulatory T-cells (Tregs) in tumors. These additive mechanisms of action provide a strong scientific rationale for the combination of atezolizumab with bevacizumab.

On the other hand, radiotherapy (RT) enhances the diversity of the T cell receptor repertoire (TCR) of intratumoral T cells (Chow et al 2020). Based on this preclinical and clinical data, we hypothesize that the combination of Y-90 TARE, bevacizumab, and atezolizumab induces synergistic tumor killing by the following mechanism: radiation diversifies the TCR repertoire of TILs (Tumor-infiltrating lymphocytes); bevacizumab inhibits the activity of Tregs and increases DC differentiation to promote tumor antigen presentation via the inhibition of VEGF; and atezolizumab reverses T cell exhaustion and inhibits PD-1-PD-L1 signaling.

1.8.5 Rationale for Patient-Reported Outcome Endpoints

Intermediate-stage HCC comprises a heterogenous patient population with respect to liver function, as well as size and number of tumors, and is often minimally symptomatic or asymptomatic, with the majority of patients exhibiting few to no disease-specific, discernable symptoms. Instead, it is largely the impact of treatment and the associated burden, rather than disease burden, that defines the patient experience. Therefore, it is important to document the burden associated with HCC treatment and understand the impact of therapy as reported by patients to inform benefit-risk assessment and treatment decision making.

A fit-for-purpose assessment of function, health related quality of life (HRQoL), and relevant symptoms will be collected in the study. The assessment will include validated physical function, role function, social functioning, global health status (GHS)/HRQoL scales and relevant symptoms (fatigue, pain, lack of appetite, nausea/vomiting) of the European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire (EORTC QLQ-C30), (Aaronson et al. 1993; Fitzsimmons et al. 1999), as well as two relevant symptoms from the EORTC QLQ-HCC18 (fever, abdominal pain) (Blazeby et al 2004, Chie et al 2012).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- Assess progression free survival (PFS) per RECIST 1.1

2.1.2 Secondary Objectives

- Assess safety and tolerability of Y-90 TARE combined with atezolizumab and bevacizumab in patients with HCC.
- Assess the progression free survival (PFS) per mRECIST
- Assess Time to Progression (TTP) per RECIST 1.1 and mRECIST
- Assess Overall response rate (ORR) per RECIST 1.1 and mRECIST
- Assess Overall survival (OS)
- Evaluate PROs of physical functioning, role functioning, social functioning, and global health status/quality of life experienced by patients receiving Y-90 TARE and bevacizumab plus atezolizumab treatment.

2.1.3 Correlative/Exploratory Objectives

- Explore the role of immunoscore and PD-L1 expression in the prediction of improved clinical outcome in patients receiving Y-90 TARE and bevacizumab plus atezolizumab treatment
- Explore the composition of subtypes of tumor infiltrating immune cells in predicting response to a chosen therapy.
- Investigate how Y-90 therapy affects the proportion of antigen presenting cells in the tumor.
- Evaluate PROs of specific symptoms experienced by patients receiving Y-90 TARE and bevacizumab plus atezolizumab treatment.

2.2 Endpoints

2.2.1 Primary Endpoint

PFS is defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) according to RECIST v1.1

2.2.2 Secondary Endpoints

- Safety and tolerability will be assessed according to CTCAE v5.
- PFS is defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) according to mRECIST
- TTP is defined as the time from randomization to the first occurrence of disease progression according to RECIST v1.1 and mRECIST
- ORR is defined as a complete or partial response according to RECIST v1.1 or mRECIST
- OS is defined as the time from randomization to death from any cause.

- Change from baseline in physical functioning, role functioning, social functioning, and global health status/quality of life scores as assessed by a fit for purpose EORTC instrument

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

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

1. Written informed consent and HIPAA authorization for release of personal health information prior to registration. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately. Patients must be willing and able to provide written informed consent for this trial.

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

3. ECOG Performance Status of 0-1 at screening

4. Histological or cytological evidence/confirmation per AJCC, 8th edition, of hepatocellular carcinoma (HCC).

5. Measurable disease by RECIST 1.1.

6. Patients must have a Child-Pugh score of A. or selected B7. **NOTE:** Definition of the selected B7 patients: Child Pugh B7 patients are allowed if they meet the inclusion criteria 11 and they do not have hepatic encephalopathy or more than a moderate amount of ascites.

7. Patients must have at least Barcelona Clinic Liver Cancer (BCLC) stage B HCC and must be outside of Milan Criteria; and/or HCC peripheral vascular involvement of any size or number of tumor (segment peripheral, vp1 and vp2 are allowed, but vp3 and vp4 are excluded). **NOTE:** absence of extrahepatic spread, must be confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis.

8. Patient must either (1) not be a candidate for liver transplantation as determined by the liver transplant service or (2) refuse evaluation for transplantation.

9. Archival tissue obtained within 6 months of registration is required. If archival tissue is not available, subjects are not eligible.

10. No prior systemic therapy is permitted. **NOTE:** Patients who received prior local therapy (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound or TACE) are eligible provided the target lesion(s) have not been previously treated with local therapy or the target lesion(s) within the field

of local therapy have subsequently progressed in accordance with RECIST 1.1. Prior TACE is allowed if FLR is ≥ 40%.

11. Patient must be a TARE candidate, as defined by a lung dose threshold for Y-90 of 30Gy and an estimated (future liver remnants) FLR of ≥ 40% at the time of forming the comprehensive treatment plan. Both the lung dose threshold and FLR values must be obtained and available in source documentation.

12. Patients must demonstrate adequate hepatic, bone marrow, and renal function as defined in Table below. All screening labs should be performed within 14 days of treatment initiation.

System	Laboratory Value
Hematological	
Lymphocyte Count	500/μL
Absolute Neutrophil Count (ANC)	≥ 1,500 /μL
Hemoglobin (Hgb)	≥ 9 g/dL without transfusion or EPO dependency (within 7 days of assessment)
Platelet count (Plt)	≥ 75,000 / μL
Renal	
Serum creatinine OR Measured or calculated CrCl (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) OR ≥ 60 mL/min for subject with creatinine levels > 1.5 x institutional ULN
Hepatic	
Bilirubin	≤ 3.0
Aspartate aminotransferase (AST)	≤ 5 X ULN for subjects with cancer in liver
Alanine aminotransferase (ALT)	≤ 5 X ULN for subjects with cancer in liver
Albumin	> 2.5 mg/dL
Urine Protein	Urine dipstick for proteinuria ≤ 2 g (within 14 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 and must demonstrate < 1 g of protein in 24 hours.
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN
Calcium-Subjects with uncontrolled or symptomatic hypercalcemia are NOT eligible	
Ionized Calcium	< 1.5 mmol/L
Serum Calcium OR Corrected serum calcium	< 12 mg/dL OR < ULN

13. Documented virology status of HIV; **NOTE:** Patients with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count ≥ 200/μL, and have an undetectable viral load.

14. Documented virology status of hepatitis, as confirmed by screening HBV and HCV serology test: For patients with active hepatitis B virus (HBV): HBV DNA <500 IU/mL obtained within 28 days prior to initiation of study treatment, and Anti-HBV treatment (per local standard of care; e.g., entecavir) for a minimum of 14 days prior to study entry and willingness to continue treatment for the length of the study.

15. Subjects with chronic infection by HCV who are untreated or who failed previous therapies for HCV are allowed on study. In addition, subjects with successful HCV treatment (defined as sustained virologic response [SVR] 12 or SVR 24) are allowed as long as patients are not actively receiving anti-HCV treatment at the time of study enrollment. Investigators can stop anti-HCV treatment at their discretion prior to enrolling patients on study.

16. Females of childbearing potential must have a negative serum pregnancy test within 14 days prior to study treatment. **NOTE:** Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.

17. Female participants of childbearing potential must be willing to abstain from heterosexual intercourse or to use contraception as outlined in Section 5.6. Male participants capable of fathering children must be willing to abstain from heterosexual intercourse or to use contraception as outlined in Section 5.6.

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

3.2 Exclusion Criteria

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

1. Have signs of liver failure, e.g. clinically significant ascites, encephalopathy, or variceal bleeding within six months from enrollment.

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

3. Untreated or incompletely treated esophageal and/or gastric varices with bleeding or high-risk for bleeding.

4. Prior bleeding event due to esophageal and/or gastric varices within 6 months prior to initiation of study treatment. **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 within 6 months of prior to initiation of study treatment do not need to repeat the procedure.

5. Have evidence of excessive hepatopulmonary shunting (> 20% in 99mTc macro-aggregated albumin scan for resin and 30 Gy per treatment for glass) or angiographically demonstrable and non-occludable gastrointestinal shunting, precluding from Y-90 treatment.

6. Inadequately controlled arterial hypertension (defined as systolic blood pressure (BP) ≥ 150 mmHg and/or diastolic blood pressure > 100 mmHg), based on an average of ≥ 3 BP readings on ≥ 2 sessions. **NOTE:** Anti-hypertensive therapy to achieve these parameters is allowable.

7. Prior history of hypertensive crisis or hypertensive encephalopathy.

8. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina.

9. Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC.

10. Major surgery within 4 weeks prior to registration or anticipation of a major surgical procedure during study.

11. Have had prior transplant of any kind (stem cell or solid organ).

12. Have active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis with the following exceptions:
    - Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
    - Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
    - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
    - Rash must cover < 10% of body surface area
    - Disease is well controlled at baseline and requires only low-potency topical corticosteroids

- No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

13. Have history of idiopathic pulmonary fibrosis (including bronchiolitis obliterans with organizing pneumonia) drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. **NOTE:** History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

14. Treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1 and anti-PD-L1 therapeutic antibodies.

15. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment.

16. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
    - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after sponsor-investigator confirmation has been obtained.
    - Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study

17. Uncontrolled tumor-related pain
    - 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.
    - Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.

18. Patients with brain metastases.

19. Have unresolved toxicities from prior anticancer therapy, defined as having not resolved to National Cancer Institute (NCI) CTCAE v5 grade 0 or 1 with the exception of alopecia and laboratory values listed per the inclusion criteria. **NOTE:** Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by any of the investigational products may be included (e.g., hearing loss) after consultation with the sponsor-investigator.

20. Diagnosed or treated for malignancy other than HCC, unless they meet one of the following exceptions:
    - Malignancy treated with curative intent and with no known active disease present for ≥ 2 years before registration and felt to be at low risk for recurrence by the treating physician.
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
    - Adequately treated cervical carcinoma in situ without evidence of disease.

21. Have a known or suspected allergy to bevacizumab or atezolizumab or known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or bevacizumab formulation.

22. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment.

23. History of hemoptysis (≥ 2.5 mL of bright red blood per episode) within 1 month prior to initiation of study treatment.

24. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation).

25. Current or recent (within 10 days of first dose of study treatment) use of aspirin (≥325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and cilostazol.

26. Current or recent (within 10 days prior to study treatment start) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose. **NOTE:** Prophylactic anticoagulation for the patency of venous access devices is allowed provided the activity of the agent results in an INR ≤1.5 x ULN and aPTT is within normal limits within 14 days prior to initiation of study treatment.

27. Have an uncontrolled intercurrent illness including, but not limited to any of the following:
    - Psychiatric illness/social situations that would limit compliance with study requirements
    - Have any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the

interpretation of the results or render the patient at high risk from treatment complications.
- Active alcohol use, drug use, or a psychiatric disease that would, in the opinion of the sponsor-investigator or a sub-investigator (sub-I), prevent the subject from complying with the study protocol and/or endanger the subject during their participation in the study.

28. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia. **NOTE:** Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

29. Active tuberculosis.

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

31. Have received a live attenuated vaccine (e.g., FluMist®) within 30 days of the planned start of study therapy and 180 days after the last dose of the study treatment. **NOTE:** Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

32. Have received or are receiving any investigational therapy within 28 days prior to the first dose of bevacizumab and atezolizumab. **NOTE:** Subjects may be enrolled in an observational (non-interventional) clinical study or in the follow-up period of an interventional study.

4. SUBJECT REGISTRATION

All subjects must be registered through HCRN's electronic data capture (EDC) system. Subjects must be registered and randomized prior to starting protocol therapy. Subjects will sign consent and undergo screening for study. Subjects must be eligible for TARE to participate in this clinical trial with radiology imaging confirming FLR of ≥ 40%. Subjects must have archival tissue (obtained within the previous 6 months) to be eligible for the trial. Treatment should start **within 14 business days** of randomization.

4.1 Randomization

Subjects will be randomized with 1:1 ratio to Arm A (Y-90 TARE) or Arm B (Y-90 TARE + bevacizumab + atezolizumab).

4.2 Stratification

The study will stratify for:
- AFP level
    - High ≥ 400

- Low < 400
- Presence or absence of vascular invasion

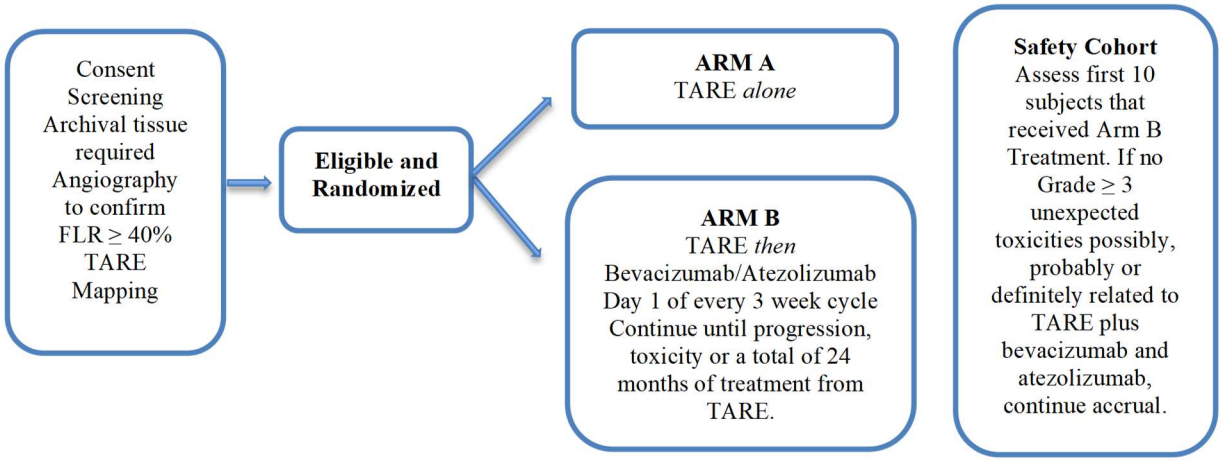
5. TREATMENT PLAN

This is an open-label, multi-center, randomized phase II study of combination therapy with Y-90 TARE, bevacizumab, and atezolizumab versus Y-90 TARE alone in patients with advanced HCC. Subjects will be randomized to Y-90 TARE alone (Arm A) or Y-90 TARE followed by the combination of atezolizumab and bevacizumab (Arm B). Subjects randomized to receive bevacizumab and atezolizumab (Arm B) will start the combination of bevacizumab and atezolizumab 4 weeks (± 1 week) after TARE treatment.

Full recovery from the procedure is required prior to systemic treatment:

- AST and ALT ≤ 5 x upper limit of normal (ULN) and total bilirubin ≤ 3 mg/dL
- Manifestations of post-embolization syndrome (e.g., fever, nausea, vomiting, and abdominal pain) have resolved to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 Grade 1
- No significant medical events (e.g., gastrointestinal [GI] bleeding, cardiac events, hepatorenal syndrome) during or after the TARE procedure.

Arm B subjects will continue the study drugs for a total of 24 months from the TARE treatment, until intolerable toxicity or disease progression occur.



5.1 Safety Cohort

A safety cohort of 10 subjects randomized to Arm B (Y-90 TARE + bevacizumab + atezolizumab) will be assessed for safety after two cycles. Accrual will be halted during this review. Grade ≥ 3 unexpected toxicities; possibly, probably or definitely related to TARE in combination with bevacizumab and atezolizumab will be reviewed (specifically, toxicities beyond those from TARE or the combination of bevacizumab and atezolizumab treatment when used independent to each other). If there are no Grade ≥ 3 unexpected toxicities; possibly, probably or definitely related to TARE in combination with bevacizumab and atezolizumab the combination will be deemed safe and accrual will resume. The decision to resume accrual will be made by the DSMC and sponsor-investigator. Each toxicity meeting the outlined criteria will be reviewed as a separate event.

Toxicities will be graded based on the CTCAE criteria v5. Adverse events will be recorded/reported as outlined in Section 11 regardless of the way in which the information was obtained (email, virtual visit, in person). Adverse event information will be provided to the sponsor-investigator on a weekly basis. If at any time an AE meeting the criteria outlined above occurs during enrollment in the safety cohort, accrual will be halted until the sponsor-investigator or designee reviews the event and determines that accrual can resume.

5.2 Y-90 TARE Administration (Arm A and Arm B)

All subjects will receive Y-90 TARE. Institutional standards will be utilized for Y-90 TARE preparation and administration. A comprehensive plan will be made for each patient's liver-targeted therapy; this plan will involve treating the predominant liver lesions with segment Y-90 TARE using predetermined dosimetry, while keeping FLR equal or greater than 40% (FLR is estimated by excluding the liver volume of Y-90 infused distribution).

The maximal amount of Y-90 TARE treatment will be limited to only one lobe of the liver if segmental Y-90 TARE is not possible to treat the predominant lesion. Since segmental Y-90 TARE may result in less long term liver damage compared to lobal Y-90 TARE, segmental Y-90 TARE treatment is preferred to lobar Y-90 TARE if segmental Y-90 TARE treatment is able to treat all blood supply to the predominant lesion or lesion with vascular invasion to preserve liver function. For segmental treatment, a minimum tumor dose of 190 Gy should be used for glass microspheres and 120 Gy for resin microspheres. For lobar treatment, a minimum dose of 100 Gy should be used for resin microspheres.

5.3 Study Drug(s) Administration (Arm B)

Subjects randomized to Arm B will receive atezolizumab and bevacizumab as intravenous infusions (IV) at least 4 weeks (± 1 week) after completion of Y-90 TARE. **Atezolizumab will be administered first followed by bevacizumab**. The study drug administration will be captured in "cycles" of study treatment. Each cycle lasts 3 weeks. A window of ± 3 days will be applied to all study visits/study drug administration. All dates/times of study treatment will be documented in the EDC system. Institutional standards may be used for study treatment administration (including dosing based on weight changes) and where applicable the investigator's brochure can provide detailed information regarding study drug administration.

5.3.1 Bevacizumab Administration

Bevacizumab 15 mg/kg will be delivered as an IV infusion on Day 1 of each 3 week cycle. The initial dose will be delivered over 90 minutes (±15 minutes) at least 4 weeks (± 1 week) after Y-90 TARE. If the first infusion is tolerated without infusion associated adverse events (fever and/or chills), the second infusion may be delivered over 60 minutes (±10 minutes). If the 60 minute infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes (±10 minutes).

If a subject experiences an infusion–associated adverse event, he or she may be premedicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 minutes (±10 minutes) as long as the subject continues to be premedicated. If a subject experiences an infusion associated adverse event with the 60 minute infusion, all subsequent doses should be given over 90 minutes (±10 minutes). Similarly, if a subject experiences an infusion associated adverse event with the 30 minute infusion, all subsequent doses should be given over 60 minutes (±10 minutes).

5.3.2 Atezolizumab Administration

Atezolizumab 1200 mg will be delivered as an IV infusion on Day 1 of each cycle (every 3 weeks). The initial dose will be delivered over 60 (± 15) minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Atezolizumab infusions instructions outlined in Appendix A.

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

5.4 Standard of Care Medications

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice.

5.5 Concomitant Medications for Atezolizumab

5.5.1 Allowed Concomitant Medications with Atezolizumab

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

- Oral contraceptives
- Hormone-replacement therapy
- Inactivated influenza vaccinations
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency (ie, prednisone 10 mg or equivalent)

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 with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or 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 (e.g., supplemental oxygen and β2-adrenergic agonists; see above for infusion reaction guidelines.

5.5.2 Cautionary Therapy for Atezolizumab-Treated Patients

5.5.2.1 Corticosteroids and Tumor Necrosis Factor-α Inhibitors

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

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

5.5.2.2 Herbal Therapies

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

5.5.3 Prohibited Therapy for Atezolizumab

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent, and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

5.6 Reproductive Information

Participants of childbearing potential who are sexually active and their partners must agree to (1) abstain from heterosexual intercourse or (2) use 2 forms of contraception: two barrier methods, or a barrier method plus a hormonal method.

5.6.1 Subjects randomized to the experimental arm

Female participants of child-bearing potential that are sexually active with a male capable of fathering children must agree to use contraception from the time of informed consent, during the study and for 180 days after the last dose of study drug(s). Male participants capable of fathering children that sexually active with a female of child-bearing potential must agree to use contraception from the time of informed consent, during the study and for 180 days after the last dose of study drug(s). This timeframe is also applicable to breast feeding and sperm donation.

5.6.2 Subjects randomized to the control arm

Female participants of child-bearing potential must agree to use contraception from the time of informed consent and for 60 days after TARE procedure. Male participants must agree to use contraception from the time of informed consent, during the study and for 60 days after the TARE procedure. This timeframe is also applicable to breast feeding and sperm donation.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

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

6.1 Dose Delays/Dose Modifications

Unless otherwise noted in the dose modification tables in the Appendix A and B, treatment (bevacizumab and atezolizumab) may be delayed ≤ 12 weeks from the expected day of the next treatment for any reason. Patient will continue to receive scans on schedule. If bevacizumab and atezolizumab treatment has to be put on hold, as long as the treatment hold is ≤ 12 weeks from the expected day of the next treatment, patient may resume therapy without making up any doses.

6.2 Dose Levels for Dose Reductions

There is no dose reduction for either bevacizumab or atezolizumab.

6.3 Protocol Therapy Discontinuation

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

- Documented disease progression per RECIST 1.1; **NOTE:** patient can continue treatment beyond image progression if there is no intolerable toxicity, no clinical decline, until confirmation of disease progression at the next scheduled scan or scan sooner than scheduled scan but at least 4 weeks from the previous scan.
- Site investigator determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - In a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- Female subject becomes pregnant
- Protocol therapy is interrupted for > 12weeks

6.4 Protocol Discontinuation

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

7. STUDY CALENDAR & EVALUATIONS

7.1 Arm A Calendar (Control)

Study Evaluation	Screening	Pre-TARE	TARE	Safety follow up visit[9]	Long-term Follow up[10]
	-28 days	- 14 days		30 days post TARE ± 7 days	Every 3 months (±14 days)
REQUIRED ASSESSMENTS					
Informed Consent	X				
Medical History[1]	X				
Physical Exam	X			X	
Vital signs and ECOG Performance Status[2]	X			X	
Angiography[3]		X	X		
TARE Mapping[3]		X			
AEs & concomitant medications	X			X	
PRO instrument[11]		X[11]	X[11]	X[11]	X[11]
LABORATORY ASSESSMENTS					
Complete Blood Cell Count with diff (CBC)	X			X	X[4]
Comprehensive Metabolic Profile (CMP)	X			X	X[4]
PT/INR and aPTT[4]	X				
Thyroid Function Testing[4]	X				
HIV, Hepatitis B and C testing[4]	X				
Pregnancy test (serum or urine) (WOCBP)[4]	X				
Urine protein[4]	X				
DISEASE ASSESSMENT					
CT of chest[5]	X				X[5]
MRI or CT of abdomen and pelvis[5]	X				X[5]
Brain or Bone Scan[5]	Done ONLY if clinically indicated				
RECIST 1.1 and mRECIST evaluations[5]	X				X[5]
TREATMENT EXPOSURE					
TARE[6]			X		
CORRELATIVE STUDIES SPECIMEN COLLECTION					
Archival Tumor Tissue[7]	X				
Blood Samples[8]		X[8]		X	X[8]
BANKING SAMPLES					
Tissue[12]		X			

Study Evaluation	Screening	Pre-TARE	TARE	Safety follow up visit[9]	Long-term Follow up[10]
	-28 days	- 14 days		30 days post TARE ± 7 days	Every 3 months (±14 days)
Blood[12]		X		X	
FOLLOW-UP					
Survival Status, Subsequent Therapy					X

CBC with differential and platelet to include: WBC, ANC, Hgb, Hct, PLT. CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

Key to Footnotes

1: Medical History; other data to be obtained during this assessment includes a smoking history questionnaire and trial awareness question. In addition, prior anti-cancer treatment should be documented including medications (chemotherapy, checkpoint inhibitors, etc) radiation or surgery. If prior genomic results are available those are required for EDC entry. Diagnosis and staging to include pathology report and TNM staging documentation (date of first biopsy and date of first radiology imaging to be included). AJCC staging manual v8 will be utilized.

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

3: Angiography will be used to confirm FLR ≥ 40%. If FLR is < 40% the subject is not eligible for the study. Angiography will also be done prior to the TARE treatment. A window of -14 days for TARE mapping may be applied. Both the lung dose threshold and FLR values must be obtained and available in source documentation.

4: PT/aPTT/INR will be performed at screening. After screening, monitoring of PT/aPTT/INR is at the investigator's discretion. Thyroid Function testing should be performed at screening then as clinically indicated. TSH will be obtained. T4 and T3 including free versus total testing is at the discretion of the site investigator. HIV and Hepatitis testing required at screening. Women of childbearing potential (WOCBP) will have a urine or serum βhCG performed if clinically appropriate. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Testing is required within 14 days prior to initiation of study treatment. Urine protein will be obtained within 14 days prior to treatment initiation. During long term follow up, the type and frequency of laboratory monitoring should be done per standard of care.

5: Tumor response assessment will consist of evaluation by MRI (preferred) or CT (triple phase CT scan with a liver protocol) of abdomen and pelvis at screening then every 3 months and CT scan of the chest every 6 months (imaging selected for each subject should remain the same throughout the study). If tumor assessments are available for subjects who have not yet experienced progressive disease (PD) after TARE treatment, the follow-up tumor evaluations will be documented in the eCRF. Brain or Bone scans should be performed ONLY if clinically indicated at investigator's discretion. CT/MRI image scans may be submitted for central analysis once funding is available. Images will be de-identified prior to sending to a central location. Window of ± 7 days for radiology imaging is allowed. Disease assessment per RECIST 1.1 and mRECIST will be done based on radiology imaging performed (abdomen/pelvis ± chest CT/MRI) at the disease assessment timepoints previously described. These results will be captured in the EDC system.

6: Details regarding treatment administration can be found in Section 5.

7: Archival tissue from a biopsy obtained in the last 6 months is required. Archival tissue will be identified at screening and shipped by the day of TARE treatment. If archival tissue is not available, the subject is not eligible for the trial. Any leftover samples after protocol specified testing complete will be banked for future unspecified cancer related research after subject consent obtained.

8: Whole blood, plasma, serum and buffy coat samples will be collected (1) after consent, during screening or day of TARE treatment prior to procedure, (2) 4 weeks after TARE during safety follow up visit, (3) 12 weeks after TARE treatment during long term follow up, and (4) at progression. All blood samples are required. Any leftover samples after protocol specified testing complete will be banked for future unspecified cancer related research after subject consent obtained.

9: Safety Follow Up: The safety follow-up visit should be performed 30 days (± 7 days) after TARE. Subjects who have an ongoing Grade ≥ 2 or serious AE (SAE) at this visit will continue to be monitored by a member of the study team until the event is resolved, stabilized, determined to be irreversible by the site investigator or a new anti-cancer treatment starts, whichever occurs earlier.

10: Long Term Follow Up: Subjects will have tumor response assessment consisting of evaluation by MRI (preferred) or CT (triple phase CT scan with a liver protocol) of abdomen and pelvis every 3 months and CT scan of the chest every 6 months (imaging selected for each subject should remain the same throughout the study) for up to 3 years until progression, initiating a new cancer treatment, withdrawing consent or becoming lost to follow-up. The scan interval may be reset if scans were done sooner for clinical reasons. This imaging may be done locally. Once disease progression is documented, subjects will be followed for survival every 6 months for 5 years from the time of documented progression. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate. Information regarding scans and lab results should be obtained if available. Information regarding scans and lab results should be obtained if available. A window of ± 14 days will be applied to follow up.

11: The EORTC fit-for-purpose instrument will be completed after consent, during screening or day of TARE treatment prior to procedure then at the D30 safety visit (4 weeks after TARE) then every 3 months for 1 year to coincide with radiology imaging if possible. The instrument should be completed prior to any other assessment(s) at the clinical site. Study personnel should review the instrument for completeness before the patient leaves the investigational site. The PRO instrument may be completed at the investigational site or be administered via telephone calls.

12: All banking samples are optional. Whole blood for banking is to be collected at Pre-Treatment Cycle 1 Day 1. 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. Submission of unstained slides for banking from an archived FFPE tumor block (if available). See CLM for collection, labeling, and shipping instructions. Subjects will also be consented for optional storage of any remaining tissue/blood samples after protocol-specified studies are complete. These samples will be stored for future unspecified cancer-related research and are considered “banking samples”.

7.2 Arm B Calendar

Study Evaluation Cycle = 21 days	Screening	Pre-TARE	TARE	On Treatment Cycle 1-n	Safety follow up visit[9]	Long-term Follow up[10]
	-28 days	- 14 Days		Day 1 ± 3 days	30 days post last dose ± 7 days	Every 3 months (±14 days)
REQUIRED ASSESSMENTS						
Informed Consent	X					
Medical History[1]	X					
Physical Exam	X			X	X	
Vital signs and ECOG Performance Status[2]	X			X	X	
Angiography[3]	X[3]		X			
TARE Mapping[3]	X[3]					
AEs & concomitant medications	X			X	X	
PRO instrument[11]		X		X[11]	X[11]	
LABORATORY ASSESSMENTS						
Complete Blood Cell Count with diff (CBC)	X			X	X	X[4]
Comprehensive Metabolic Profile (CMP)	X			X	X	X[4]
PT/INR and aPTT[4]	X					
Thyroid Function Testing[4]	X			X[4]		
HIV, Hepatitis B and C testing[4]	X					
Pregnancy test (serum or urine) (WOCBP)[4]	X					
Urine protein[4]	X			X[4]		
DISEASE ASSESSMENT						
CT of chest[5]	X			X[5]		X[5]
MRI or CT of abdomen and pelvis[5]	X			X[5]		X[5]
Brain or Bone Scan[5]	Done ONLY if clinically indicated					
RECIST 1.1 and mRECIST Evaluations[5]	X			X[5]		X[5]
TREATMENT EXPOSURE						
TARE[6]			X			
Bevacizumab and Atezolizumab[6]				X		
CORRELATIVE STUDIES SPECIMEN COLLECTION						
Archival Tumor Tissue[7]	X					
Fresh Tissue[7]					X[7]	
Blood Samples[8]	X[8]			X[8]	X[8]	
BANKING SAMPLES						
Tissue[12]		X				

Study Evaluation Cycle = 21 days	Screening	Pre-TARE	TARE	On Treatment Cycle 1-n	Safety follow up visit[9]	Long-term Follow up[10]
	-28 days	- 14 Days		Day 1 ± 3 days	30 days post last dose ± 7 days	Every 3 months (±14 days)
Blood[12]		X			X	
FOLLOW-UP						
Survival Status, Subsequent Therapy						X

CBC with differential and platelet to include: WBC, ANC, Hgb, Hct, PLT. CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

Key to Footnotes

1: Medical History; other data to be obtained during this assessment includes a smoking history questionnaire and trial awareness question. In addition, prior anti-cancer treatment should be documented including medications (chemotherapy, checkpoint inhibitors, etc) radiation or surgery. If prior genomic results are available those are required for EDC entry. Diagnosis and staging to include pathology report and TNM staging documentation (date of first biopsy and date of first radiology imaging to be included). AJCC staging manual v8 will be utilized.

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

3: Angiography will be used to confirm FLR ≥ 40%. If FLR is < 40% the subject is not eligible for the study. Angiography will also be done prior to the TARE treatment. A window of 7-14 days for TARE mapping may be applied. Both the lung dose threshold and FLR values must be obtained and available in source documentation.

4: PT/aPTT/INR will be performed at screening. After screening, monitoring of PT/aPTT/INR is at the investigator's discretion. Thyroid Function testing should be performed at screening then every 3 cycles. TSH will be obtained. T4 and T3 including free versus total testing is at the discretion of the site investigator. HIV and Hepatitis testing is required at screening. Women of childbearing potential (WOCBP) will have a urine or serum βhCG performed if clinically appropriate. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Testing is required within 14 days prior to the initiation of study treatment. Urine protein will be obtained within 14 days prior to treatment initiation then Day 1 of each Cycle. During long term follow up, the type and frequency of laboratory monitoring should be done per standard of care.

5: Tumor response assessment will consist of evaluation by MRI (preferred) or CT (triple phase CT scan with a liver protocol) of abdomen and pelvis at screening then every 3 months and CT scan of the chest every 6 months (imaging selected for each subject should remain the same throughout the study) while subjects are on treatment. If tumor assessments are available for subjects who have not yet experienced progressive disease (PD) at the time treatment is discontinued, the follow-up tumor evaluations will be documented in the eCRF. Brain or Bone scans should be performed ONLY if clinically indicated at investigator's discretion. CT/MRI image scans may be submitted for central analysis once funding is available. Images will be de-identified prior to sending to a central location. Window of ± 7 days for radiology imaging is allowed. Disease assessment per RECIST 1.1 and mRECIST will be done based on radiology imaging performed (abdomen/pelvis ± chest CT/MRI) at the disease assessment timepoints previously described. These results will be captured in the EDC system.

6: Details regarding treatment administration can be found in Section 5.

7: Archival tissue from a biopsy obtained in the last 6 months is required. Archival tissue will be identified at screening and shipped by the day of TARE treatment. If archival tissue is not available, the subject is not eligible. A biopsy will be obtained at progression. If a patient discontinues study due to progression, the progression sample may be collected at the D30 safety visit. This biopsy is required. Any leftover samples after protocol specified testing complete will be banked for future unspecified cancer related research after subject consent obtained.

8: Whole blood, plasma, serum and buffy coat samples will be collected (1) after consent, during screening or day of TARE treatment prior to procedure, (2) prior to treatment C1D1, (3) prior to treatment C5D1, (4) and at progression (may be performed at the D30 safety visit for those subjects discontinuing study treatment due to progression). All blood samples are required. Any leftover samples after protocol specified testing complete will be banked for future unspecified cancer related research after subject consent obtained.

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

10: Long Term Follow Up: Subjects who discontinue for reasons other than progressive disease, will have tumor response assessment consisting of evaluation by MRI (preferred) or CT (triple phase CT scan with a liver protocol) of abdomen and pelvis every 3 months and CT scan of the chest every 6 months (imaging selected for each subject should remain the same throughout the study) for up to 3 years until progression, initiating a new cancer treatment, withdrawing consent or becoming lost to follow-up. The scan interval may be reset if scans were done sooner for clinical reasons. This imaging may be done locally. Once disease progression is documented, subjects will be followed for survival every 6 months for 5 years from the time of documented progression. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate. Information regarding scans and lab results should be obtained if available. A window of ± 14 days will be applied to follow up.

11: The EORTC fit-for-purpose instrument will be completed after consent, during screening or day of TARE treatment prior to procedure, C1D1, every 4 cycles thereafter starting with Cycle 4 and at the D30 safety visit. The instrument should be completed prior to administration of study drug and prior to any other study assessment(s) at the clinical site. Study personnel should review the instrument for completeness before the patient leaves the investigational site. The PRO instrument may be completed at the investigational site or be administered via telephone calls.

12: All banking samples are optional. Whole blood for banking is to be collected at Pre-Treatment Cycle 1 Day 1. 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. Submission of unstained slides for banking from an archived FFPE tumor block (if available). See CLM for collection, labeling, and shipping instructions. Subjects will also be consented for optional storage of any remaining tissue/blood samples after protocol-specified studies are complete. These samples will be stored for future unspecified cancer-related research and are considered “banking samples”.

8. BIOSPECIMEN STUDIES AND PROCEDURES

Please see the Correlative Laboratory Manual (CLM) for additional details regarding correlatives for this study.

8.1 Tissue

We propose examination of the role of immunoscore and PD-L1 expression in the prediction of improved clinical outcome in patients receiving Y-90 TARE and bevacizumab plus atezolizumab treatment. Immunoscore and PD-L1 expression in addition to other protein biomarkers will be measured in HCC biopsies. In addition, immune-inhibitory proteins including B7H3, B7H4, indoleamine 2,3-dioxygenase (IDO), and arginase will be evaluated as predictors of effectiveness of Y-90 TARE and bevacizumab plus atezolizumab combination therapy and mechanisms of resistance to the study treatment.

8.1.1 Archival Tissue

Archival tissue obtained in the last 6 months is required. Archival tissue will be identified at screening and shipped by the day of TARE treatment. If archival tissue is unavailable, the subject is not eligible.

8.1.2 Fresh Tissue

A biopsy will be obtained at progression for subjects on Arm B (experimental Arm). This sample is required.

8.2 Peripheral Blood Samples

Peripheral blood samples will be collected to study methylation patterns, germline testing, buffy coat and circulating tumor DNA. Whole blood, serum, plasma and buffy coat will be collected. All blood samples are required.

8.2.1 Whole Blood

Whole blood samples will be collected (1) after consent, during screening or day of TARE treatment prior to procedure, (2) 4 weeks post TARE during safety follow up visit (Arm A) or prior to Cycle 1 Day 1 (Arm B), (3) 12 weeks post TARE (Arm A) or prior to Cycle 5 Day 1 (Arm B) and (4) at progression (may be performed at the D30 safety visit for those subjects discontinuing study treatment due to progression). Whole blood samples will support germline and methylation pattern testing.

8.2.2 Plasma

Plasma samples will be collected (1)) after consent, during screening or day of TARE treatment prior to procedure, (2) 4 weeks post TARE during safety follow up visit (Arm A) or prior to Cycle 1 Day 1 (Arm B), (3) 12 weeks post TARE (Arm A) or prior to Cycle 5 Day 1 (Arm B) and (4) at progression (may be performed at the D30 safety visit for those subjects discontinuing study treatment due to progression). Plasma samples will support circulating tumor DNA analysis.

8.3 Genetic Testing

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

8.4 Banking of Leftover Biospecimens

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

8.5 Banking Samples for Future Unspecified Research

Subject consent will be obtained to collect additional samples for future unspecified cancer related research. HCRN will manage the banked samples. Samples will be coded and 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.

8.6 Confidentiality of Biospecimens

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

9. CRITERIA FOR DISEASE EVALUATION

9.1 Measurability of Tumor Lesions at baseline

9.1.1 RECIST 1.1 measurable lesions at baseline

A tumor lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter for non-nodal lesions or ≥15 mm in short axis diameter for lymph node lesions with IV contrast enhanced CT or MRI and that is suitable for accurate repeated measurements. Please see additional mRECIST guidance below on measurability of intrahepatic HCC lesions and portal hepatis lymph nodes.

The short axis is defined as the longest in-plane axis perpendicular to long axis

9.1.2 mRECIST measurable lesions at baseline

Typical and atypical intrahepatic, and extrahepatic measurable HCC lesions are defined as follows:

- Typical measurable intrahepatic lesions by mRECIST are liver lesions that show typical features of HCC on IV contrast-enhanced CT or MRI scans, ie, hypervascularity in the arterial phase with wash-out in the portal or the late venous phase, and the viable, non-necrotic portion (arterial phase IV contrast-enhancing) can be accurately measured at baseline as ≥10 mm in the longest diameter.
- Atypical measurable intrahepatic lesions are liver lesions that do not show typical features of HCC on contrast-enhanced CT or MRI studies (ie, lack hypervascularity in the arterial phase with wash-out in the portal or late venous phase), and are well delineated, can be considered measurable lesions if the entire tumor measured in the portal venous phase is ≥10 mm in the longest diameter. Well-delineated atypical intrahepatic lesions are measured as RECIST 1.1 non-nodal lesions, with the entire tumor dimension (whether necrotic or viable) included in the measurement (similar to a RECIST 1.1 measure of a non-nodal lesion).
- Extrahepatic measurable lesions include all other lesions thought to be part of the HCC burden, and are considered to be measurable lesions if ≥10 mm in the long axis diameter for non-nodal lesions or ≥15 mm in the short axis diameter for lymph node lesions as per standard RECIST 1.1 criteria where the entire tumor dimension is measured in the delayed phase of IV contrast-enhancement. One exception exists for mRECIST: lymph nodes detected at the porta hepatis can be considered malignant and measurable if the lymph node short axis diameter is at least 20 mm.

9.1.3 Non-measurable lesions at baseline

- Truly non-measurable lesions include the following:
    - Bone lesions (see exception below for soft tissue component)
    - Leptomeningeal disease
    - Ascites, pleural, or pericardial effusion
    - Inflammatory breast disease
    - Lymphangitic involvement of skin or lung
- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis diameter at baseline[3]).

- Previously irradiated lesions
- Brain metastasis

Lymph nodes with <10 mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

Localized post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

9.1.4 Special considerations regarding lesion measurability at baseline

- Bone lesions
    - Bone scan, PET scan or plain X-ray are not considered adequate imaging techniques to measure 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, can be considered measurable if the soft tissue component meets the definition of measurability.
    - Blastic bone lesions are considered non-measurable.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected over cystic lesions as TLs.

9.1.5 Special considerations for mRECIST in HCC regarding lesion measurability at baseline

- Infiltrative type and diffuse type liver HCC where the lesions are ill-defined (poorly demarcated) and not suitable for repeat measurements will be considered non-measurable.
- Portal vein thrombosis. Malignant portal vein thrombosis should be considered a nonmeasurable lesion due to the difficulty in performing consistent measurements of the malignant thrombus during the course of the treatment. Measurements of the extent of the malignant thrombus may be impaired by the possible presence of a bland component of the thrombosis.
- Porta hepatis lymph node. Lymph nodes detected at the porta hepatis can be considered as malignant if the lymph node short axis diameter is at least 20 mm. Evidence of reactive lymph nodes at the porta hepatis, in fact, is a common finding in patients with cirrhosis regardless of the presence of an HCC. The short axis diameter of the node is used to judge if a node is involved by solid tumor.

9.1.6 RECIST 1.1 Target Lesion selection at baseline

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TLs at baseline. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter for nodal lesions), 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.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph node locations as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

9.1.7 mRECIST Target Lesion selection at baseline

As in RECIST 1.1, mRECIST allows a maximum of 5 measurable lesions, with a maximum of 2 lesions per organ, identified as TLs at baseline. In HCC, liver lesions should be prioritized as TLs over measurable lesions in other organs. Up to 2 HCC liver lesions may be chosen as mRECIST TLs at baseline, and these lesions can include typical or atypical, well-delineated, measurable intrahepatic lesions (described above). Preference as choice of liver TL should be given to typical as opposed to atypical intrahepatic target lesions if both are present. An infiltrative-type HCC liver lesion should be considered as a NTL when the mass shows ill-defined borders and therefore does not appear to be suitable for accurate and repeat measurements.

HCC lesions previously treated with locoregional or systemic treatments may or may not be considered as suitable to be selected as target lesions for mRECIST. If the lesion shows a well-delineated area of viable tumor (IV contrast enhancement in the arterial phase with later washout) that is at least 10mm in longest diameter, then it can be selected as a target lesion. In contrast, if the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a TL for mRECIST.

9.1.8 Special cases for Target Lesion assessment at baseline

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.
- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non- nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.

9.1.9 RECIST 1.1 Non-Target Lesion selection at baseline

All other lesions, including non-measurable lesions and surplus measurable lesions not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

9.1.10 mRECIST Non-Target Lesion selection at baseline

NTL selection at baseline is fundamentally identical between RECIST 1.1 and mRECIST with a few exceptions on intrahepatic HCC lesions: Infiltrative-type HCC should be considered as an NTL when the mass shows ill-defined borders and therefore does not appear to be suitable for accurate and repeat measurements. HCC lesions previously treated with locoregional or systemic treatments may or may not be considered as suitable to be selected as target lesions for mRECIST: If the lesion shows a well-delineated area of viable tumor (contrast enhancement in the arterial phase) that is at least 10 mm in longest diameter, then it can be selected as a target lesion. In contrast, if the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a TL for mRECIST and should be considered as an NTL.

9.2 Evaluation of tumor response and progression

9.2.1 RECIST 1.1 Target Lesion assessment at follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimeters. The sum of the diameters for all TL at each follow-up visit will be compared to the baseline sum of diameters (for response or stable disease) or to the smallest prior (nadir) sum of diameters (for progression).

9.2.2 Special cases for Target Lesion assessment at follow-up

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter.
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion. The choice of ‘Too large to measure’ in the case report form will trigger an overall visit response of PD.

- When a TL has had an intervention, the following apply:
    - Target Lesion Intervention may include radiotherapy, embolization, excisional biopsy, surgery, etc. that is not a part of study treatment and might adversely affect the size of that Target lesion
    - If an Intervention on a Target Lesion is ticked in the case report form, the diameter of the lesion is still recorded (0mm if no longer present) and is included in the sum of diameters.
    - If a Target Lesion Intervention is ticked, the Intervention must be reported for all subsequent assessments of that Target lesion.
    - If a Target Lesion has an Intervention, the only Overall Visit Responses allowed to be recorded by the Investigator are NE or PD, with PD if the sum of diameters exceeds a 20% increase and at least a 5mm absolute increase in the visit sum of diameters compared to the previous minimum (nadir) sum of diameters.
    - No visit with a recorded Target Lesion Intervention can be used as the minimum (nadir) sum of diameters

9.2.3 mRECIST evaluation of Target Lesions for HCC

Complete response (CR)	Disappearance of any intratumoral arterial enhancement in all typical intrahepatic target lesions, and complete disappearance of all atypical intrahepatic lesions, and complete disappearance of all extrahepatic lesions, and absence of any new unequivocal lesions, and any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm (including porta hepatis nodes).
Partial response (PR)	A combined decrease of at least 30% in the sum of diameters of viable tissue (contrast-enhancement in the arterial phase) for typical intrahepatic target lesions, the long axis diameters for atypical intrahepatic and all extrahepatic non-nodal target lesions, and short axis diameters for extrahepatic nodal lesions, taking as reference the baseline sum of diameters of target lesions.
Stable disease (SD)	Neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD
Progression of disease (PD)	A combined increase of ≥20% in the sum of diameters based on the longest diameters of viable (enhancing) tissue in typical intrahepatic target lesions, the longest diameter of atypical intrahepatic target lesions potentially containing necrotic and non-necrotic areas, the longest diameter of all extrahepatic non-nodal target lesions, and short axis diameters for extrahepatic nodal lesions, taking into reference the smallest previous sum of diameters (nadir) including the baseline sum if that is the smallest. The sum of diameters must also demonstrate an absolute increase of at least 5 mm from nadir.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg, missing anatomy, poor image quality) or had a lesion intervention at this visit. Note: If the sum of diameters without unevaluable TLs meets the PD criteria, PD overrides Not Evaluable as a TL response

The measurement of the longest axis diameter of the viable (arterial enhancing) intrahepatic HCC tumor may be challenging in lesions showing partial internal necrosis. The following points should be taken into account in such cases:

- The measurement of the viable tumor should be performed on CT or MRI obtained in the arterial phase, when the contrast between viable vascularized tumor tissue and nonenhancing necrotic tissue is the highest.
- The longest axis diameter of the viable tumor is not necessarily located in the same scan plane or vector in which the baseline diameter was measured – a thorough careful evaluation of the phased CT or MRI scans is required.
- The measurement of the viable tumor long axis diameter should not include any major intervening areas of necrosis.

9.2.4 RECIST 1.1 Non-Target Lesion assessment at follow-up

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or partial response in TLs, the overall tumor burden has increased sufficiently to merit unequivocal progression by NTLs. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of stable disease (SD) or progressive disease (PR) of target disease will therefore be extremely rare.

9.2.5 mRECIST Non-Target Lesion assessment at follow-up

Assessment of NTLs by mRECIST is virtually identical to RECIST 1.1 with the following additional guidance for intrahepatic HCC lesions. This section provides mRECIST definitions of the criteria used to determine and record overall response for NTL at the investigational site at each follow-up visit

9.2.6 mRECIST evaluation of Non-Target Lesions

Complete response (CR)	Disappearance of all extrahepatic non-nodal NTLs, disappearance of intratumoral arterial enhancement in typical intrahepatic NTLs, complete disappearance of infiltrative intrahepatic NTLs with ill-defined borders, and complete disappearance of atypical intrahepatic NTLs. All lymph node NTLs must become non-pathological in size (<10 mm short axis diameter or <20 mm short axis diameter for porta hepatis nodes) to allow CR of NTLs.
Non CR/non PD	Persistence of one or more NTL without progression, including persistence of intratumoral arterial enhancement in one or more typical intrahepatic NTLs.
Progression (PD)	Unequivocal progression may be due to an important progression in one lesion only or in several or all NTLs, including an unequivocal increase in the size of the viable (arterial phase enhancing) portion of typical intrahepatic NTLs.

Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if *any* of the NTLs were not evaluable at this visit and the progression criteria have not been met.

9.2.7 RECIST 1.1 New Lesion identification at follow-up

Details including the imaging modality, the date of scan, and the location of any NLs will be recorded in the case report form. The presence of 1 or more NLs is assessed as progression. The finding of an NL should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. If an NL is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously (pre-existing) new lesion has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a NL and will indicate disease progression.

9.2.8 mRECIST New Lesion identification at follow-up

The following are considerations using mRECIST in the assessment of tumor progression:

- A newly detected hepatic nodule will be classified as HCC—and therefore will be declared as evidence of progression—when its longest diameter is at least 10mm and the nodule shows the typical vascular pattern of HCC on dynamic imaging, that is, hypervascularization in the arterial phase with washout in the portal venous or late venous phase.
- Liver lesions larger than 10 mm that do not show a typical vascular pattern (atypical) may be diagnosed as HCC by evidence of at least 10-mm-interval growth in subsequent scans.
- For any equivocal new lesion that is later determined to be unequivocal the timepoint of progression will be the timepoint the lesion was first noted as equivocal.
- Any newly-detected focal liver lesion that does not meet the criteria for a new lesion should be considered equivocal and not conclusive for disease progression.
- A lymph node is considered as a "new lesion" and, therefore, indicative of PD if for the first time in the study, the short axis diameter increases in size to ≥10 mm for nodes other than porta hepatis nodes or ≥20 mm for porta hepatis nodes and the absolute short axis diameter increase is at least 5 mm relative to nadir for that node.
- As fluid accumulations (eg, ascites) are common in HCC, an effusion that appears or significantly worsens (from trace to large) radiologically by CT/MRI anatomical scans should not be considered alone as disease progression by NL, unless a soft tissue mass (eg, peritoneal mass) is associated with the fluid accumulation.

9.3 RECIST 1.1 and mRECIST evaluation of overall visit response at follow-up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs is identical between RECIST 1.1 and mRECIST using the algorithm shown below.

9.3.1 RECIST 1.1 and mRECIST overall visit response

Target Lesions	Non-Target Lesions	New Lesions	Overall Visit Response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non-CR/Non-PD	No	SD (Non-CR/Non-PD[a])
NE	Non PD or NE	No	NE
NA	NE	No	NE
NA	NA	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[a] Non-CR/Non-PD for Overall Response if only non-target lesions (no TLs) are present at baseline.
Note: An overall assessment of Complete Response (all other disease disappears/reverts to normal) would be changed to Partial Response if ascites remains present radiologically.

The following overall visit responses are possible depending on the extent of tumor disease at baseline:

- For subjects with TLs (at baseline): CR, PR, SD, PD, or NE
- For subjects with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE
- For subjects with no disease at baseline: NED (no evidence of disease; available as an option in the electronic case repot form), PD, or NE

9.3.2 Radiological criteria for scans subsequent to mRECIST-defined progression

A follow-up scan requested at least 4 weeks after an mRECIST-defined radiological progression and no later than the next regularly scheduled imaging visit. The follow-up scans provide additional information to the Investigator for patient management and further treatment decisions, and since the published RECIST 1.1 and mRECIST criteria (Eisenhauer 2009; Lencioni and Llovet 2010) do not provide guidance on how to assess scans acquired after (m)RECIST-defined PD, supplemental instructions for Investigators on how to evaluate these follow-up scans are provided below. The supplemental criteria are used to distinguish patients who are on a trajectory of radiological worsening from those who are stable or improved. In order for a scan visit following a prior mRECIST-defined radiologic PD to be classified as progressive disease, *any* of the following criteria must be met:

- ≥20% increase and at least a 5-mm increase in the sum of diameters of viable (enhancing) tissue in typical intrahepatic target lesions, the longest diameter of atypical intrahepatic target lesions potentially containing necrotic and non-necrotic areas, the longest diameter of all extrahepatic non-nodal target lesions, and short-axis diameters for extrahepatic nodal lesions compared with the previous minimum (nadir) sum of diameters at 2 consecutive visits, and a further increase of ≥5 mm in the sum of diameters at the follow-up scan timepoint compared with the immediate prior timepoint,
- significant progression (worsening) of NTLs at the follow-up scan timepoint compared with the immediate prior timepoint,
- significant progression (worsening) of previously new lesions (pre-existing new lesions) at the follow-up scan timepoint compared with the immediate prior timepoint,
- additional brand-new unequivocal lesions at the follow-up scan timepoint

If none of these criteria are met, then the follow-up visit assessment should be one of the following: SD, PR, CR, or NE.

10. DRUG INFORMATION

10.1 Atezolizumab (Tecentriq)

Atezolizumab is a humanized immunoglobulin (IgG1) monoclonal antibody that is produced in Chinese hamster ovary (CHO) cells. Atezolizumab targets programmed death-ligand 1 (PD-L1) on tumor-infiltrating immune cells (ICs) or tumor cells (TCs) and prevents interaction with the programmed death-1 (PD-1) receptor and B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells and other immune cells.

10.1.1 Supplier/How Supplied

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

Injection: 840 mg/14 mL (60 mg/mL) and 1200 mg/20 mL (60 mg/mL) sterile, preservative-free, colorless to slightly yellow solution in a single-dose vial.

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

10.1.2 Preparation

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

- Select the appropriate vial(s) based on the prescribed dose.
- Withdraw the required volume of atezolizumab from the vial(s).
- Dilute into a 250 mL polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% Sodium Chloride Injection, USP. Infusion lines equipped with 0.2 or 0.22 μm in-line filters will be used.
- Dilute with only 0.9% Sodium Chloride Injection, USP.
- Mix diluted solution by gentle inversion. Do not shake.

This product does not contain a preservative. Administer immediately once prepared. If diluted atezolizumab infusion solution is not used immediately, store solution either:

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

10.1.3 Storage and Stability

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.

10.1.4 Dispensing

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

10.1.5 Adverse Events

Refer to the current IB for additional information regarding adverse events. The most common adverse events of atezolizumab are fatigue, nausea, cough, dyspnea, decreased appetite, hair loss, and diarrhea. Atezolizumab can cause immune mediated side effects such as IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab).

Refer to Appendix A and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

10.2 Bevacizumab (Avastin)

Bevacizumab is a recombinant humanized anti-vascular endothelial growth factor (anti-VEGF) monoclonal immunoglobulin G1 (IgG1) antibody. VEGF, a diffusible glycoprotein produced by normal and neoplastic cells, is an important regulator of physiologic and pathologic angiogenesis. Increased levels of VEGF expression have been found in most human malignancies examined to date.

10.2.1 Supplier/How Supplied

Genentech will supply bevacizumab at no charge to subjects participating in this clinical trial.

Avastin (bevacizumab) injection is a clear to slightly opalescent, colorless to pale brown, sterile solution for intravenous infusion supplied as single-dose vials in the following strengths:

- 100 mg/4 mL: carton of one vial (NDC 50242-060-01); carton of 10 vials (NDC 50242-060-10).
- 400 mg/16 mL: carton of one vial (NDC 50242-061-01); carton of 10 vials (NDC 50242-061-10).

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

10.2.2 Preparation

- Use appropriate aseptic technique.
- Visually inspect vial for particulate matter and discoloration prior to preparation for administration. Discard vial if solution is cloudy, discolored or contains particulate matter.
- Withdraw necessary amount of bevacizumab and dilute in a total volume of 100 mL of 0.9% Sodium Chloride
- Injection, USP. DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.
- Discard any unused portion left in a vial, as the product contains no preservatives.
- Store diluted Avastin solution at 2°C to 8°C (36°F to 46°F) for up to 24 hours.
- No incompatibilities between bevacizumab and polyvinylchloride or polyolefin bags have been observed.

10.2.3 Storage and Stability

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton until time of use to protect from light. Do not freeze or shake the vial or carton.

10.2.4 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.

10.2.5 Adverse Events

Refer to the current IB for additional information regarding adverse events. The most common adverse events related to bevacizumab include epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. Infusion reactions may occur. Other side effects to note include gastrointestinal perforations and fistula, wound healing complications, and thromboembolic events.

10.3 TARE

TARE treatment will be administered either using Glass or Resin Yttrium-90 containing microspheres. The choice on the most appropriate TARE treatment will be made after the mapping and will be per the discretion of the local interventional radiologist. All TARE treatments are preferred to be delivered in a segmental or subsegmental fashion, if feasible, but lobar treatments will be allowed as long as the estimated FLR $\geq$ 40%. All treatment vessels

should undergo contrast enhanced cone beam CT demonstrating complete tumor coverage and no non-target enhancement. It is preferred that segmental/subsegmental treatments with Glass should target for doses >190 Gy or >1 Gbq. BSA or partition dosing methods are acceptable for Resin. Pressure assistance devices, such as antireflux catheters or balloon microcatheters, is permitted. Total lung dose should not exceed 30 Gy per session or 50 Gy total.

For glass users, the minimum threshold of 190 Gy MIRD will be used for segmental treatment. For resin user, a minimum threshold of 100 – 120 Gy calculated with the partition method will be used for segmental treatment. For lobar treatment, the BSA method will be used to determine the dosage, or a minimum threshold of 100 Gy will be used for treatment.

11 ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v5 will be utilized for AE assessment. A copy of the CTCAE v5 can be downloaded from the CTEP website at http://ctep.cancer.gov. All forms for AE/SAE recording and reporting can be found in the EDC system (Documents and Information Tab).

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to atezolizumab and bevacizumab (see following guidance), and actions taken.

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.
- Preexisting medical conditions: A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)

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

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

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

11.1.2 Serious Adverse Event (SAE)

A SAE is an adverse event that meets any of the following criteria:

- Results in death. All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death". **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.
- If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE. Hospitalizations for the following reasons do not require reporting:
    - Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
    - Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
    - Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study
- 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 IMP.

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

11.1.3 Adverse Events of Special Interest (AESI)

The following AEs are considered of special interest:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
  - Treatment-emergent ALT or AST > 3 × ULN (or > 3 × baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin > 2 × ULN (of which ≥ 35% is direct bilirubin)
  - Treatment-emergent ALT or AST > 3 × ULN (or > 3 × baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, macrophage activating syndrome and hemophagocytic lymphohistiocytosis
- Nephritis
- Ocular toxicities (e.g. uveitis, retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Hemorrhage
  - Any grade CNS bleeding
  - Grade ≥ 2 hemoptysis
  - Other Grade ≥ 3 hemorrhagic event

11.1.4 Expected/Unexpected Adverse Event

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

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the 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.

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

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

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

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

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

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

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

11.1.6 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (V5 .0 Update current versions) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (V5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

11.2 Reporting

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

11.2.1 Adverse Events

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

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to HCRN

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

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

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

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

11.2.3 Post-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 who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up period

11.3 Special Situation Reports

11.3.1 Pregnancy reports

If a female subject or female partner of a male study subject becomes pregnant while receiving the study drug or within 6 months after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE to HCRN **within thirty (30) calendar days of the awareness date**. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

11.3.2 Other Special Situation Reports

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

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

11.3.3 Product Complaints

All Product Complaints (with or without an AE) shall be forwarded to HCRN **within thirty (30) calendar days** of the awareness date. A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

11.4 HCRN Requirements for Reporting SAEs to Genentech

HCRN will report all protocol-defined Adverse Events (AEs)/SAEs, AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product to Genentech **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to Genentech as it is received from site.

Genentech Drug Safety at:
Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should be called at:
PCHotlineNumber:(800)334-0290

11.5 Sponsor-Investigator Responsibilities

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

11.6 HCRN Responsibilities to FDA

This protocol is IND exempt per FDA communication 5/7/2020. HCRN will continue to facilitate compliance of applicable requirements for the sponsor-investigator in relation to this study. This includes but is not limited to 21 CFR 50.20 informed consent, 21 CFR Part 56 IRB, and pertinent sections of the Public Health Service Act and FDAAA.

11.7 IND Safety Reports Unrelated to this Trial

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

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

12 STATISTICAL METHODS

12.1 Study Design

This is an open-label, multi-center, randomized phase II study of combination therapy with Y-90 TARE, bevacizumab, and atezolizumab in patients with advanced HCC. Patients will be randomized 1:1 to receive TARE with or without atezolizumab + bevacizumab. Stratification factors include AFP level (high is defined as ≥ 400; low as < 400) and presence or absence of vascular invasion.

12.3 Endpoints

12.2.1 Definition of Primary Endpoint

PFS is defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) according to mRECIST. Patients without disease progression (and did not die) at the time of analysis will be censored at the last disease assessment date. Patients with no post-baseline disease assessment will be censored at the randomization date.

12.2.2 Definition of Secondary Endpoints

- Safety and tolerability will be measured on the basis of toxicities experienced graded by CTCAE v5.
- PFS is defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) according to RECIST v1.1.
- TTP is defined as the time from randomization to the first occurrence of disease progression according to RECIST v1.1 and mRECIST. Patients without disease progression (including death) will be censored at the last disease assessment date. Patients who have no post-baseline disease assessment will be censored at randomization date.
- ORR is defined as a complete or partial response according to RECIST v1.1 and mRECIST.
- OS is defined as the time from randomization to death from any cause. Patients alive at the time of analysis will be censored at the time of last contact. Patients without post-baseline assessment will be censored at randomization date

- Change in physical functioning, role functioning, social functioning, and global health status/quality of life from the EORTC fit-for-purpose instrument is defined as change from baseline (first treatment cycle) at each follow up timepoint, i.e. each subsequent treatment cycle, safety follow up visit, and long-term follow up.

12.3 Sample Size and Accrual

The first 10 subjects randomized to Arm B and receives Y-90 radioembolization followed by two cycles of the combination of bevacizumab and atezolizumab will make up the safety lead in. If there are no Grade ≥ 3 unexpected toxicities possibly, probably or definitely related to the TARE plus bevacizumab and atezolizumab combination, the study will continue enrollment to meet the primary study endpoint. The estimated median PFS for patients receiving segment TARE (Arm A) is 9 months. It is hypothesized that the addition of combined bevacizumab and atezolizumab (Arm B) will improve the median PFS from 9 months (control arm receiving segment Y-90) to 15 months (bevacizumab plus atezolizumab following Y-90 TARE). Assuming a hazard ratio of 0.6 (median PFS of 9 months in Arm A and 15 months in Arm B) and an exponential distribution for PFS in each treatment arm, a total of 97 events (53 in the control group, 44 in experimental arm) are needed to detect a statistically significant difference using a 1-sided alpha of 0.05 with 80% power. With an expected accrual rate of 10 patients per month and 24 months of follow up after last patient in, a total of 118 patients will be needed for evaluation, consider about 8% drop out rate which will lead to 128 patients to be enrolled during the randomized phase of the study.

12.4 Assessment of Safety

All randomized patients who receive TARE and any amount of bevacizumab and atezolizumab will be included in the safety analysis for Arm B. All randomized patients who receive TARE will be included in the safety analysis for Arm A. Patients will be grouped according to the actual treatment received and patients who received any amount of atezolizumab and bevacizumab will be assigned to Arm B (experimental arm) for safety analysis even if it's given in error.

12.5 Assessment of Efficacy

Analysis of efficacy will be based on treatment assigned at randomization regardless of actual treatment received. All randomized patients will be included in the analysis for PFS, TTP and OS. Arm A subjects that received TARE and Arm B subjects that received TARE and any amount of bevacizumab and atezolizumab with measurable disease and have their disease re-evaluated will be evaluable for assessment of objective response.

12.6 Data Analysis Plans

12.6.1 Analysis Plans for Primary Objective

The primary objective of this study is to evaluate the PFS per RECIST v1.1 for patients with HCC receiving Y-90 TARE therapy with the combination of bevacizumab and atezolizumab compared with those receiving Y-90 TARE therapy alone.

The stratified log-rank will be used as the primary analysis to compare PFS between the two treatment arms. Kaplan-Meier methodology will be used to estimate the PFS for both treatment

groups. Stratified Cox proportional hazard model will be fit to estimate the hazard ratio and 95% confidence intervals (CI). Unstratified analysis will also be conducted.

12.6.2 Analysis Plans for Secondary Objectives

Patients' toxicity data will be tabulated according to their grades and attribution by groups. TTP and OS will be analyzed using similar methods as for PFS (primary endpoint). ORR will be estimated and presented with its 95% confidence interval.

The PRO instrument is a reduced version of the EORTC QLQ-C30. The instrument includes only questions related to the physical, emotional, and social function domains, as well as overall health-related quality of life. The purpose of using a limited instrument is two-fold: 1) given the nature of the study design and patient population, treatment-related, rather than disease-related symptoms will be most likely to impact patient QoL, and we are most interested in measuring the impact of treatment on function and QoL, rather than the symptoms themselves; and 2) generally we want instruments to be as short as possible to limit patient burden. Completion rates, compliance rates, and reasons for missing data will be summarized for each of the EORTC fit-for-purpose instrument measures by treatment arm. Summary statistics (mean, standard deviation, median, range, and CIs) of absolute scores and mean changes from baseline scores will be conducted for all measures at each assessment timepoint. Previously published minimally important differences will be used to identify meaningful change from baseline within each treatment group on the functional and disease/treatment related symptoms scales (Osoba et al. 1998). In the event of incomplete data for any questionnaire subscales, if more than 50% of the constituent items are completed, a prorated score will be computed, consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing (Fayers et al. 2001; Chie et al. 2012).

12.6.3 Analysis Plans for Correlative/Exploratory Objectives

The correlative studies will be exploratory in nature. Fisher's exact tests, Wilcoxon rank-sum tests, log-rank tests, and descriptive statistics will be used as appropriate to explore associations between biomarkers and clinical outcomes.

12.6.4 Subgroup Analyses

In order to assess the consistency of treatment effect with respect to the primary endpoint across prognostic subsets, subgroup analysis will be conducted, including, but not limited to the following variables:

- Presence or absence of vascular invasion
- AFP level (high is defined as ≥ 400; low as < 400)
- Prior TACE treatment (Yes vs No)
- lobar Y-90 TARE vs. segmental TARE

Unstratified analysis results will be presented for subgroup analyses due to the potentially limited number of patients in each subgroup.

12.7 Interim Analysis

The safety cohort of 10 subjects randomized to Arm B (TARE plus bevacizumab plus atezolizumab) will be assessed for safety after two cycles. Accrual will be halted during this review. Grade ≥ 3 unexpected toxicities; possibly, probably or definitely related to the TARE

plus bevacizumab plus atezolizumab will be reviewed (specifically, toxicities beyond those from TARE or the combination of bevacizumab and atezolizumab treatment when used independent to each other). If there are no Grade ≥ 3 unexpected toxicities; possibly, probably or definitely related to TARE in combination with bevacizumab and atezolizumab the combination will be deemed safe and accrual will resume. The decision to resume accrual will be made by the DSMC and sponsor-investigator. Each toxicity meeting the outlined criteria will be reviewed as a separate event.

Toxicities will be graded based on the CTCAE criteria v5. Adverse events will be recorded/reported as outlined in Section 11 regardless of the way in which the information was obtained (email, virtual visit, in person). Adverse event information will be provided to the sponsor-investigator on a weekly basis. Adverse event information will be provided to the sponsor-investigator on a weekly basis. If at any time an AE meeting the criteria outlined above occurs, accrual will be halted until the sponsor-investigator or designee reviews the event and determines that accrual can resume.

13 TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted with guidance from the Georgetown Lombardi Comprehensive Cancer Center's DSMP.

HCRN oversight activities include:

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

13.2 Georgetown Lombardi Comprehensive Cancer Center Data Safety Monitoring Committee

HCRN will provide the following for the Georgetown Lombardi Comprehensive Cancer Center DSMC to review:

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

The Georgetown Lombardi Comprehensive Cancer Center DSMC will review study data every quarter for the first six months, if no significant safety concerns are noted, the review will then be performed semiannually. Documentation of DSMC reviews will be provided to sponsor-investigator and HCRN. 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 HCRN to address the DSMC's concerns.

13.3 Data Quality Oversight Activities by HCRN

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

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

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

13.4 Compliance with Trial Registration and Results Posting Requirements

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

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

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

14.2 Case Report Forms and Submission

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

document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

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

14.3 Record Retention

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

14.4 Confidentiality

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

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

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

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

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

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require. Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

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

15.3 Informed Consent Process

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

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

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APPENDIX A:
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

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

PULMONARY EVENTS

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

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

Management Guidelines for Pulmonary Events, Including Pneumonitis

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

BAL = bronchoscopic alveolar lavage.

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

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

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

HEPATIC EVENTS

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

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

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

Management Guidelines for Hepatic Events

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

LFT = liver function tests.

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

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

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

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

Table 43 Management Guidelines for Hepatic Events (cont.)

CTCAE = Common Terminology Criteria for Adverse Events; GI=gastrointestinal; LFT = liver function test; NCI = National Cancer Institute; ULN=upper limit of normal.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

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

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

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

GASTROINTESTINAL EVENTS

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

Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

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

GI = gastrointestinal.

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

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

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

ENDOCRINE EVENTS

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

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

Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab. c
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable

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

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

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

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

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

OCULAR EVENTS

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

Management Guidelines for Ocular Events

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

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

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

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

IMMUNE-RELATED MYOCARDITIS

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of GI illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy. All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated. Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines below.

Management Guidelines for Immune-Related Myocarditis

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

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

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

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

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

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

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

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

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction [29]. CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 [30, 31], including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 7.

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

Event	Management
Grade 1[a] Fever[b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment,[c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2[a] Fever[b] with hypotension not requiring vasopressors **and/or**	• Immediately interrupt atezolizumab infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if

Hypoxia requiring low-flow oxygen[d] by nasal cannula or blow-by	appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.
<u>Grade 3</u>[a] Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	• Permanently discontinue atezolizumab.[f] • Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator.
<u>Grade 4</u>[a] Fever b with hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and	• Permanently discontinue atezolizumab.[f] • Administer symptomatic treatment.[c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] For patients who are refractory to anti-cytokine therapy, experimental treatments[g] may be considered at the discretion of the investigator.

mechanical ventilation)	• Hospitalize patient until complete resolution of symptoms.

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

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

a. Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
b. Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
c. Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
d. Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.
e. There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
f. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate). For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after considering the benefit-risk ratio.
g. Refer to Riegler et al. [32] for information on experimental treatments for CRS.

PANCREATIC EVENTS

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

Management Guidelines for Pancreatic Events, Including Pancreatitis

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

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

Event	Management

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

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

DERMATOLOGIC EVENTS

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

Management Guidelines for Dermatologic Events

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

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

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

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

NEUROLOGIC DISORDERS

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

Management Guidelines for Neurologic Disorders

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

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

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

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

IMMUNE-RELATED MENINGOENCEPHALITIS

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

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

Management Guidelines for Immune-Related Meningoencephalitis

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

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

IMMUNE-RELATED NEPHRITIS

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as nonsteroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment. If no alternative cause of acute kidney injury is identified, patients with signs and symptoms of acute kidney injury, in the absence of an identified alternate etiology, should be treated according to the management guidelines for immune-related renal events in the table below.

Management Guidelines for Renal Events

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.

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

atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the sponsor-investigator.

IMMUNE-RELATED 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.

Management Guidelines for Immune-Related Myositis

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

Immune-related myositis, Grade 4	• Permanently discontinue atezolizumab and contact site investigator.[c] • Refer subject to rheumatologist or neurologist • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases • Initiate treatment with corticosteroid equivalent to 1-2 mg/kg/day IV methylprednisolone or higher dose bolus if subject is severely compromised (eg, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

IV, intravenous

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

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

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

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

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

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

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

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

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

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 1.

Table 1 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

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

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

References

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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.

APPENDIX B: BEVACIZUMAB SPECIFIC AE MANAGEMENT GUIDELINES

Event	CTCAE Version 5.0 Grade	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: o The patient must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions) o The patient must not have had hemorrhagic events > grade 2 while on study o 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
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*	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	Grade 3 or 4	Discontinue bevacizumab
Hemorrhage (CNS)	Any grade	Discontinue bevacizumab
Hemorrhage (haemoptysis)	Grade 1	Trace hemoptysis; continue bevacizumab
	Grade 2 - 4	≥ 2.5 mL bright red blood per episode; discontinue bevacizumab
Hemorrhage (other)	Grade 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
Obstruction of GI tract	G2 requiring medical intervention	Hold bevacizumab until complete resolution
	G3-4	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 study chair/medical monitor, resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the G4 toxicity is transient, has recovered to ≤ grade 1 (or baseline) and unlikely to recur with retreatment.

*Institutional protocols acceptable