PROTOCOL

TITLE:	**ATEZOLIZUMAB AND BEVACIZUMAB IN COMBINATION WITH TACE FOR PATIENTS WITH BCLC B HCC**
STUDY NUMBER:	2000026840 NCT05776875
VERSION NUMBER:	4.0
TEST PRODUCTS:	Atezolizumab (RO5541267) Bevacizumab TACE
INDICATION:	Treatment of Barcelona Clinic Liver Cancer B Hepatocellular Carcinoma
INVESTIGATOR:	Stacey Stein MD 333 Cedar St New Haven CT 06520 Telephone: (203) 737-1600 Fax: (203) 785-3788 E-mail: stacey.stein@yale.edu
SUPPORT PROVIDED BY:	Genentech, Inc.
PROTOCOL DATE:	June 30,2023

Confidentiality Statement:

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

I, the undersigned, have read and approve this protocol and agree on its contents. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guideline of Good Clinical Practice, the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements. I agree to conduct the study in compliance with all applicable regulations including International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (International Council for Harmonisation [ICH] 1996), ICH E6 (R2) and concepts that have their origin in the Declaration of Helsinki (World Medical Association 1996, 2008 & 2013).

Protocol Title: Atezolizumab and Bevacizumab in Combination with TACE for Patients with BCLC B HCC

Protocol Version: 4.0 (2023.06.30)

Printed Name of Principal Investigator: _____

Signature of Principal Investigator

Date

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

REVISION HISTORY

Revision #	Version Date
1.0	2022.02.02
2.0	2022.06.09
3.0	2022.12.15
4.0	2023.06.30

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

Table of Contents

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

Protocol Title	Atezolizumab and Bevacizumab in combination with TACE for Patients with BCLC B HCC
Phase	II
Objectives	The primary objective of this study is to examine the safety and tolerability of the combination of atezolizumab and bevacizumab with TACE. The secondary objectives are response rate, time to progression, overall survival, time to TACE progression (TTTP), and time to untaceable progression. Assessment of tumor response will be assessed by both RECIST 1.1 and mRECIST for HCC.
Study Design	This is an open-label, single-arm study which will be performed at 2 sites examining the safety and tolerability of the combination of atezolizumab and bevacizumab with TACE for patients with BCLC B HCC. TACE will be planned for each patient to be completed in up to 4 treatments. Any patient who is not a TACE candidate will be excluded from the study. Patients on study will have abdominal MRI or CT scans and CT chest every 8 weeks for the first year, then every 12 weeks for the second year to evaluate for disease progression. If there is progression, patients will be taken off of study treatment. All patients will be taken off study treatment at the end of two years. Disease progression will be evaluated by both RECIST 1.1 and mRECIST for HCC for the secondary objectives of the study. Patients will continue study treatment for a total of 24 months from start of treatment or until intolerable toxicity or disease progression occur, whichever is earlier.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

Key Eligibility Criteria	1. At least 18 years old 2. ECOG PS of 0 or 1 within 28 days prior to registration ECOG PS of 0 or 1 within 28 days prior to registration 3. No cirrhosis or Child-Pugh A cirrhosis 4. Diagnosis of HCC either by imaging or biopsy 5. Evidence of HCC that meets BCLC B criteria 6. Patients must have adequate hepatic, bone marrow, and renal function. All screening labs should be performed within 14 days of treatment initiation. 7. Patients must not have signs of liver failure or history of liver failure e.g. – encephalopathy or variceal bleeding 8. Patients who are deemed to be candidates for TACE treatment that can be treated in up to 4 sessions 9. Patients can have hepatitis B, as long as they are on antiviral therapy with viral loads less than 500 IU/ml 10. Patients who are positive for HBc, negative for HBsAg, regardless of HBs status, and have an undetectable HBV viral load do not require HBV antiviral prophylaxis 11. Patients who are not on HBV therapy, but positive for HBsAg and have an undetectable viral load are eligible for the study as long as they begin anti-viral prophylaxis prior to the start of study treatment 12. Patients can have untreated hepatitis C 13. At least one unidimensional tumor measurable by RECIST v1.1 criteria 14. Hg ≥ 9 g/dL 15. Creatinine less than 1.5 x ULN 16. Serum bilirubin < 2.5 mg/dl 17. AST < 5X upper limit of normal (ULN) 18. ALT < 5 X ULN 19. Platelet count > 100 x 10^9/L

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

	20. Patients must have an EGD within 6 months with no evidence of esophageal and/or gastric varices with bleeding or high risk of bleeding. Patients with varices must be assessed and treated per local standard-of-care prior to enrollment. 21. Ability to comply with the study protocol, in the investigator's judgment 22. Life expectancy $\geq$ 6 months 23. Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment: 24. ANC $\geq 1.5 \cdot 10^9$/L (1500/$\lceil$L) without granulocyte colony-stimulating factor support 25. Lymphocyte count $\geq 0.5 \cdot 10^9$/L (500/$\lceil$L) 26. Serum albumin $\geq$ 25 g/L (2.5 g/dL) 27. For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \cdot$ ULN 28. For patients receiving therapeutic anticoagulation: stable anticoagulant regimen 29. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below: 30. Women of child-bearing potential must remain abstinent or use contraceptive methods with a failure rate of $<$ 1% per year during the treatment period and for 6 months after the final dose of atezolizumab and bevacizumab. Women must refrain from donating eggs during this same period. a. A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). b. Examples of contraceptive methods with a failure rate of $<$ 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. c. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

	31. For men of childbearing potential: With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period to avoid exposing the embryo. Men must refrain from donating sperm during this same period. 32. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. 33. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

Statistical Considerations	This study will plan to enroll approximately 24 patients. We will examine the rate of grade 3 or higher AEs with the atezolizumab and bevacizumab and TACE combination. Based on collected data from the G030140 study and the IMbrave 150 study, we assume the rate of grade 3 or higher AEs is approximately 55% for the atezolizumab and bevacizumab combination and will likely be higher with the addition of TACE. Safety will be continuously monitored using the Bayesian Predictive Probability approach (Lee, 2008). The predictive probability (PP) of concluding that the toxicity rate is higher than 70% by the end of the trial based on toxicity data in the current stage will be continuously updated. A high PP indicates that the treatment is likely to be overly toxic. We will access safety after 6 patients have completed at least 1 TACE and 2 cycles of systemic therapy and then quarterly thereafter. The PI and Study Statistician will be responsible for review. We recommend halting enrollment on the trial for a safety analysis whenever there is sufficient evidence that the true toxicity rate is significantly greater than .70 (PP >0.80). This study is not powered for hypothesis testing and analysis will be based on descriptive statistics. In general, categorical data will be summarized using frequencies and percentages. Binary endpoints such as response rate will be estimated with corresponding exact 95% confidence intervals. Continuous measures will be summarized using mean, standard deviation, interquartile range, and median. Time to event outcomes will be presented with Kaplan-Meier curves.
Total Number of Subjects	24
Estimated Enrollment Period/Estimated Study Duration	18-month enrollment period/24-month study duration

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

1. BACKGROUND

1.1. BACKGROUND ON HCC

Hepatocellular carcinoma (HCC) is a prevalent cancer worldwide and the incidence in the United States has been increasing over the last several years (Xu, 2018). In addition to Hepatitis B, hepatitis C, and alcohol use, which are well known causes of cirrhosis and HCC, the incidence of nonalcoholic fatty liver disease (NAFLD) is on the rise in the US. The incidence of HCC secondary to NAFLD is expected to increase and become the leading cause of HCC in the US (Younossi, 2019). There is a strong unmet need for patients with HCC given that the 5-year survival is only 18% (Jemal, 2017).

Patients with HCC who are candidates for liver transplant or surgical resection can be offered curative intent therapy. Also, patients with a single small tumor may be candidates for curative therapy with radiofrequency ablation. The Barcelona Clinic Liver Clinic B (BCLC B) patients, who have intermediate-stage tumors, are often candidates for transarterial therapies. A systematic review of transarterial chemoembolization (TACE) examined 101 studies with over 12,000 patients and found an objective response of 52.5% (Llovet, 2003).

Patients with BCLC C HCC have tumors that are more advanced with either portal invasion or extrahepatic spread with a good performance status. These patients are typically offered systemic therapy. Since the approval of sorafenib more than a decade ago, there has been a role for systemic therapy in HCC, although it was limited to one approved treatment with a modest survival benefit (Llovet, 2008). More recently, there have been more systemic therapy options for patients, with the approval of other tyrosine kinase inhibitors lenvatinib (first line non-inferiority study to sorafenib) (Kudo, 2018), regorafenib (second line) (Bruix, 2017), and cabozantinib (second line) (Abou-Alfa, 2018) and the VEGF inhibitor ramucirumab (second line for patients with AFP > 400) (Zhu, 2019).

In addition, there is positive data for immune therapy in HCC with approvals of nivolumab (El-Khoueiry, 2017) and pembrolizumab. Nivolumab was approved as a second line treatment based on the Checkmate 040 study which showed a response rate of approximately 15% (El-Khoueiry, 2017). Based on these positive results, the CheckMate 459 study enrolled 743 patients with advanced HCC who had not received prior systemic therapy. Patients were randomized 1:1 to nivolumab or sorafenib. The primary endpoint of overall survival was not met. The median OS was 16.4 months with nivolumab and 14.7 months with sorafenib (p = 0.0752).

Pembrolizumab was initially approved based on the data from the phase 1 KEYNOTE-224 study (Zhu, 2018), showing a response rate of 17%. This study was followed by the KEYNOTE- 240 study, which enrolled patients who had progressed on or were intolerable to sorafenib. Patients were randomized 2:1 to pembrolizumab and best supportive care or placebo and best supportive care. Co-primary endpoints were OS and PFS. The OS

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

was improved (HR 0.78, one sided p = 0.0238) as was the PFS (HR 0.78, one sided p = 0.0209), but neither met significance per the statistical plan (Finn, 2019).

Given the negative data of these two randomized trials, there is strong interest in ongoing studies with combination studies. There are multiple ongoing studies of combination of PD-1 and PDL-1 inhibitors with TKIs, CTLA-4 antibodies, and bevacizumab.

There was also a recent approval in March 2020 of the combination of nivolumab and ipilimumab for second line treatment based on a small data set from the Checkmate 040 study. There were 49 patients who received the combination with an overall response rate of 33%. Four patients had a complete response, and 12 patients had a partial response (Yau, 2019).

1.2. BACKGROUND ON ATEZOLIZUMAB AND BEVACIZUMAB COMBINATION IN HCC

There is strong rationale for the combination of atezolizumab and bevacizumab in multiple cancers. Bevacizumab seems to restore anti-cancer immunity by inhibiting VEGF-related immunosuppression, promoting T cell tumor infiltration and enabling priming and activation of T cell responses against tumor antigens (Chen, 2018). There have been multiple studies of the combination in different disease groups and there was recent approval for the combination for patients with advanced stage NSCLC (FDA, 2018).

In the phase 1 study (G030140), which enrolled several tumor types, Arm A enrolled 104 patients with advanced HCC. With a median follow-up of 12·4 months, 37 (36%) of 104 patients achieved a confirmed response, including 12 (12%) complete responses. For these 104 patients, the most common grade 3-4 treatment-related adverse events were hypertension (13[13%] and proteinuria 7[7%]). Treatment-related serious events occurred in 25 (24%); treatment-related deaths occurred in 3 (3%) patients (Lee et al, 2020).

Based on the initial positive data from Arm A on the phase I study, a phase III study of atezolizumab and bevacizumab versus sorafenib, the IMbrave 150 study, was initiated (Finn et al, 2020). The study randomized 501 patients with advanced HCC 2:1 to atezolizumab and bevacizumab versus sorafenib. The objective response rate for the combination was 27.3% by RECIST 1.1 vs 11.9% for sorafenib. Progression free survival in the atezolizumab and bevacizumab arm was 6.8 months [95% CI, 5.7 to 8.3] vs 4.3 months [95% CI, 4.0 to 5.6] in the sorafenib arm. Overall survival (OS) was longer in the combination arm, the median OS was not reached in the combination arm and was 13.2 months in the sorafenib arm. The OS at 6 months was 84.8% in the atezolizumab/bevacizumab arm vs 72.2 % in the sorafenib arm. Based on these results, the FDA approved the combination in June 2020 for first line systemic therapy in patients with advanced HCC.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

1.3. BACKGROUND ON TACE IN HCC

Transarterial chemoembolization (TACE) is a local therapy for HCC which induces tumor necrosis. The liver has a dual blood supply and HCC tumors have blood supplied primarily by arterial vascularization compared to the surrounding liver parenchyma. There have been randomized controlled trials which have shown benefit of conventional TACE (cTACE) compared to best supportive care (BSC). A study from 2002 showed a median overall survival of 17.9 months with BSC vs 28.6 months with cTACE (Llovet, 2002). There was also a meta-analysis that examined studies with cTACE vs BSC which showed an improvement in median OS from 16 months with BSC vs 20 months with cTACE (Llovet, 2002).

There is also DEB-TACE, which are drug eluting beads (DEB) released with concomitant embolization. In 2012, two retrospective studies published results from patients with HCC, which showed a median OS 43.8 months and 48 months (Burrel, 2012) (Malagari, 2012). The most common adverse events for either cTACE or DEB-TACE are consistent with a post-embolization syndrome. Patients can develop nausea, vomiting, fever, and pain. Patients can have a transient increase in liver enzymes.

There has not been a clear consensus on many issues regarding local therapy for patients with HCC including how many local therapies a patient with HCC should receive, whether cTACE or DEB-TACE is a better therapy, and which patients with local failure should receive retreatment with TACE (Raoul, 2019). Most centers rely on multidisciplinary discussion at tumor boards to make decisions on a case-by-case basis.

1.4. BACKGROUND ON COMBINATION OF ATEZOLIZUMAB AND BEVACIZUMAB WITH TACE

There has been a longstanding interest in offering patients who are candidates for local therapy a combination of local and systemic therapy. The SPACE study was a global placebo-controlled randomized phase 2 trial of TACE + placebo vs TACE + sorafenib with a primary endpoint of time to progression (Lencioni, 2016). Patients first received sorafenib or placebo for 2-7 days before TACE performed using DEB-TACE. Additional DEB-TACE was given according to a fixed schedule at cycle 3, 7, and 13 and then every six cycles afterwards (4-week cycles). The primary end point of time to progression (TTP) was not statistically different between the two groups (169 days for DEB-TACE with sorafenib vs 166 days for DEB-TACE with placebo).

The TACE-2 study was a randomized placebo-controlled, phase 3 study of DEB-TACE + placebo vs DEB-TACE + sorafenib with a primary endpoint of progression free survival (Meyer, 2017). Patients who received placebo were allowed to cross over at time of progression. Overall survival and time to progression were secondary endpoints. The study was terminated after a planned interim futility analysis. The mPFS was 238 days in the DEB-TACE + placebo group vs 235 days (HR 0.99 [CI 0.77-1.27], p = 0.94).

The ECOG 1208 study was a large cooperative group study in the US which also sought to examine the role of adding sorafenib vs placebo to TACE treatment. Unfortunately, it

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

was not able to accrue to completion and ended early secondary to poor accrual. The results of the study have not yet been published.

A phase II study of the combination of bevacizumab and TACE was performed with 25 patients treated. Patients received TACE and bevacizumab on the same day. The incidence of grade 3-4 events with cycle 1 was 21% and with cycles 2-3 was 10%. There was one patient who died of a perforated duodenal ulcer. The study was considered safe for the combination and there was not an increased incidence of bleeding events with the two events occurring on the same day (Buijs, 2013).

In summary, there remains an unmet need for patients with intermediate stage HCC. It is known that local tumor ablation can increase tumor immunogenicity by releasing tumor associated antigens, potentially increasing the response to immune therapy not just locally, but systemically (Slovak, 2017). In addition, there is now positive data with immune therapy in advanced HCC, there is renewed interest in the combination of local therapy and systemic therapy in BCLC B patients with systemic therapies other than sorafenib. Based on this data, we plan to examine the atezolizumab and bevacizumab combination with TACE in patients with BCLC B HCC.

1.5. STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, RCC, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-related causes consistent with an immunotherapeutic agent, including rash, influenza-like illness endocrinopathies, hepatitis or transaminitis, pneumonitis colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment or interruption of atezolizumab treatment.

The combination of atezolizumab and bevacizumab in HCC has been well studied in both the phase 1 G030140 study and the phase 3 IMBrave150 study with response rates of 36% and 27% respectively (Lee, 2020; Finn 2020). A phase 2 study of bevacizumab and TACE showed that the combination can be safely administered on the same day. Given concern for risk of bleeding with bevacizumab, all patients on these two studies had recent EGDs and no patients with untreated varices were included. The risk of bleeding on both studies were reported as low, and risk of benefit was presented as outweighing risk.

This trial will enroll patients with HCC who have BCLC B disease and are not candidates for curative treatment but are candidates for TACE. Typically, these patients would be

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

treated with local treatment alone, but given the relatively poor prognosis and limited treatment options for these patients, this population is considered appropriate for trials of novel therapeutic candidates. The benefit-risk ratio for atezolizumab and bevacizumab in combination with TACE is expected to be acceptable in this setting. We will continue to watch the incidence of bleeding closely. All patients will have had an EGD in the last 6 months prior to starting treatment.

2. OBJECTIVES AND ENDPOINTS

This is a pilot study designed to evaluate the safety and feasibility of the combination of Atezolizumab and Bevacizumab with TACE in patients with liver limited HCC who are candidates for TACE.

2.1. PRIMARY OBJECTIVE

The primary objective of this study is to examine the safety and tolerability of the combination of atezolizumab and bevacizumab with TACE.

2.2. SECONDARY OBJECTIVES

The secondary objectives are response rate, time to progression, time to TACE progression (TTTP), and time to untaceable progression. Assessment of tumor response will be assessed by both RECIST 1.1 and mRECIST for HCC.
Time to progression will be defined as the time from trial enrollment until objective tumor progression by RECIST criteria, it does not include deaths.
Time to TACE progression is defined as the interval of time from the day of the images after a TACE procedure to the time or progression, new vascular invasion or extrahepatic spread also is counted as progression (Arizumi 2017).
Time to untaceable progression is defined as time to untreatable tumor progression, transient deterioration to Child-Pugh C score, or appearance of vascular invasion/extrahepatic spread.

3. STUDY DESIGN

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

3.1. Trial Schema

Study Population: ~24 patients with BCLC B HCC will be enrolled in this study
Study Duration: 18-month enrollment period; 24-month study duration

	Screening	C1D1 (± 3 days)	C2D1 (± 3 days)	C2D7	C3D1 (± 3 days)	C3D14	C4D1 (± 3 days)	C4D21	C5D1 (± 3 days)	C6D1 (± 3 days)	C6D7	C7D1 (± 3 days)	C8D1 + (± 3 days)
Day	-28-0	1	22	28	43	56	64	84	85	106	112	127	148
Atezolizumab [a]		x[a]	x[a]		x[a]		x[a]		x[a]	x[a]		x[a]	x[a]
Bevacizumab [b]		x[b]											x[b]
TACE [c, d]				x [c, d]		x [c, d]		x [c, d]			x [c, d]		

Footnotes:

[a.] Atezolizumab 1200mg will be administered intravenously on day 1 of every 21-day cycle beginning C1D1 The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[b.] Bevacizumab 15mg/kg will be administered intravenously on C1D1 and resume on Day 1 of the treatment cycle **at least** 4 weeks after the last TACE procedure. Full recovery from the TACE procedure is required prior to re-starting treatment with bevacizumab.

[c.] TACE treatments may occur 1, 2, 3, or 4 times based on the clinical judgement from the investigational radiologist. The first TACE procedure must be **at least** 28 days from the last bevacizumab treatment.

[d.] TACE treatments occur 4-6 weeks apart when clinically indicated. TACE window is +1 week.

Example Treatment Schedule by Number of TACE Procedures:

TACE Procedures = **4**
Earliest possible first TACE Procedure = C2D7 (based on 28 days from last bevacizumab dose)
Earliest possible re-introduction of Bev = C8D1 (based on TACE every 4 weeks ending C6D7)

	Screening	C1D1 (± 3 days)	C2D1 (± 3 days)	C2D7	C3D1 (± 3 days)	C3D14	C4D1 (± 3 days)	C4D21	C5D1 (± 3 days)	C6D1 (± 3 days)	C6D7	C7D1 (± 3 days)	C8D1 + (± 3 days)
Day	-28-0	1	22	28	43	56	64	84	85	106	112	127	148
Atezolizumab		x	x		x		x		x	x		x	x
Bevacizumab		x											x
TACE				x		x		x			x		

TACE Procedures = **3**
Earliest possible first TACE Procedure = C2D7 (based on 28 days from last bevacizumab dose)
Earliest possible re-introduction of Bev = C7D1 (based on TACE every 4 weeks ending C4D21)

	Screening	C1D1 (± 3 days)	C2D1 (± 3 days)	C2D7	C3D1 (± 3 days)	C3D14	C4D1 (± 3 days)	C4D21	C5D1 (± 3 days)	C6D1 (± 3 days)	C6D7	C7D1 (± 3 days)	C8D1 + (± 3 days)
Day	-28-0	1	22	28	43	56	64	84	85	106	112	127	148
Atezolizumab		x	x		x		x		x	x		x	x
Bevacizumab		x										x	x
TACE				x		x		x					

TACE Procedures = **2**
Earliest possible first TACE Procedure = C2D7 (based on 28 days from last bevacizumab dose)
Earliest possible re-introduction of Bev = C5D1 (based on TACE every 4 weeks ending C3D14)

	Screening	C1D1 (± 3 days)	C2D1 (± 3 days)	C2D7	C3D1 (± 3 days)	C3D14	C4D1 (± 3 days)	C4D21	C5D1 (± 3 days)	C6D1 (± 3 days)	C6D7	C7D1 (± 3 days)	C8D1 + (± 3 days)
Day	-28-0	1	22	28	43	56	64	84	85	106	112	127	148
Atezolizumab		x	x		x		x		x	x		x	x
Bevacizumab		x							x	x		x	x
TACE				x		x							

TACE Procedures = **1**
Earliest possible first TACE Procedure = C2D7 (based on 28 days from last bevacizumab dose)
Earliest possible re-introduction of Bev = C4D1 (based on TACE every 4 weeks ending C2D7)

	Screening	C1D1 (± 3 days)	C2D1 (± 3 days)	C2D7	C3D1 (± 3 days)	C3D14	C4D1 (± 3 days)	C4D21	C5D1 (± 3 days)	C6D1 (± 3 days)	C6D7	C7D1 (± 3 days)	C8D1 + (± 3 days)
Day	-28-0	1	22	28	43	56	64	84	85	106	112	127	148
Atezolizumab		x	x		x		x		x	x		x	x
Bevacizumab		x					x		x	x		x	x
TACE				x									

3.2. DESCRIPTION OF THE STUDY

THIS IS A SINGLE ARM PILOT/FEASABILITY STUDY. THE STUDY CONSISTS OF A SCREENING PERIOD (DAY -28 TO DAY -1), A TREATMENT PERIOD, AND A TREATMENT DISCONTINUATION VISIT.

The atezolizumab and bevacizumab combination will be given every 21 days, atezolizumab 1200 mg and bevacizumab 15 mg/kg will be administered intravenously on a Q3 week schedule.

Subjects will start the combination of bevacizumab and atezolizumab followed by TACE treatment 4 weeks +1 week or up to 5 weeks after study drugs. Full recovery from the TACE procedure is required prior to further 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 TACE procedure.

The number of TACE procedures performed will be 1-4 based on the evaluation of the interventional radiologist. TACE will be administered every 4-6 weeks, up to 4 TACEs are allowed on study, at the discretion of the treating interventional radiologist. Given the interest in caution of TACE procedure with bevacizumab, there will need to be a 4-week interval between TACE and bevacizumab, 4 weeks before TACE and 4 weeks after TACE. Therefore, around TACE procedures,there will be a longer interval between atezolizumab and bevacizumab cycles. So, during the cycles that have a TACE procedure, there will be at least 8 weeks but no more than 12 weeks between cycles.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

Subjects will have repeat imaging every 8 weeks for the first year and then every 12weeks after the first year. Safety assessments will occur at every treatment visit. Subjects who are tolerating therapy and have not had progression of disease can remainon therapy for up to 2 years.
This study will enroll 24 subjects over an 18-month period, with 1-2 subjects enrolled each month. Efficacy will be assessed by imaging, either MRI or CT.

Atezolizumab will be administered by intravenous (IV) infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle (longer cycle when TACE is administered) until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Bevacizumab will be administered by intravenous (IV) infusion at a dose of 15 mg/kg on day 1 of each 21-day cycle, with holding around each TACE administration so that administration is not within four weeks before or after TACE. Treatment will be given until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, and clinical status.

3.3. END OF STUDY AND LENGTH OF STUDY

The end of study is defined as the date that the last patient, last visit occurs, or the date at which the last data point required for statistical analysis, or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 6 months after the last patient enrolls on the study. In addition, the Investigator may decide to terminate the study at any time.
The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 24 months.

3.4. RATIONALE FOR STUDY DESIGN

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab, as outlined in the prescribing information. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no DLTs were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight-based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

The atezolizumab and bevacizumab combination dosage and schedule is based on both the phase 1 G030140 study and the phase 3 IMbrave studies showing the safety and efficacy of this regimen. The schedule of TACE is based on a standard schedule of this procedure. The schedule of separating bevacizumab infusion from TACE procedure by 4 weeks is out of concern for bleeding risk.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

3.4.1. Rationale for Patient Population

The phase 1 and phase 3 data of the combination of atezolizumab and bevacizumab has shown safety and efficacy in patients with advanced HCC who are no longer candidates for local therapy. The purpose of this study is to examine the role of this regimen in combination with TACE for patients with HCC who would standardly be treated with TACE alone.

3.5. PATIENTS

Approximately 24 patients with BCLC B HCC will be enrolled in this study. Eligibility criteria are to be assessed within 28 days of treatment start unless otherwise noted.

3.5.1. Inclusion Criteria

1. At least 18 years old
2. ECOG PS of 0 or 1 within 28 days prior to registration ECOG PS of 0 or 1 within 28 days prior to registration
3. No cirrhosis or Child-Pugh A cirrhosis
4. Diagnosis of HCC either by imaging or biopsy
5. Evidence of HCC that meets BCLC B criteria
6. Patients must have adequate hepatic, bone marrow, and renal function. All screening labs should be performed within 14 days of treatment initiation.
7. Patients must be candidates for TACE treatment that can be treated in up to 4 sessions
8. Patients who are positive for HBc, regardless of HBs status, and have an undetectable HBV viral load do not require HBV antiviral prophylaxis
9. Patients who are not on HBV therapy, but positive for HBsAg and have an undetectable viral load are eligible for the study as long as they begin anti-viral prophylaxis prior to the start of study treatment
10. Patients can have untreated hepatitis C
11. At least one unidimensional tumor measurable by RECIST v1.1 criteria
12. Hg ≥ 9 g/dL
13. Creatinine less than 1.5 x ULN
14. Serum bilirubin < 2.5 mg/dl
15. AST < 5X upper limit of normal (ULN)

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

16. ALT < 5 X ULN

17. Platelet count > 100 x 10^9/L

18. Patients must have an EGD within 6 months with no evidence of esophageal and/or gastric varices with bleeding or high risk of bleeding. Patients with varices must be assessed and treated per local standard-of-care prior to enrollment.

19. Ability to comply with the study protocol, in the investigator's judgment

20. Life expectancy ≥ 6 months

21. Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:

22. ANC ≥ 1.5 · 10^9/L (1500/㎕) without granulocyte colony-stimulating factor support

23. Lymphocyte count ≥ 0.5 · 10^9/L (500/㎕)

24. Serum albumin ≥ 25 g/L (2.5 g/dL)

25. For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 · ULN

26. For patients receiving therapeutic anticoagulation: stable anticoagulant regimen allowed for both Atezo and Avastin. Please note the most current guidelines for Avastin are: Exclusionary: *Current or recent (< 10 days prior to initiation of study treatment) use of aspirin (> 325 mg/day), or clopidogrel (> 75 mg/day)* Allowed: *Note: The use of full-dose oral or parenteral anticoagulants for therapeutic purpose is permitted as long as the INR and/or aPTT is within therapeutic limits (according to institution standards) within 7 days prior to initiation of study treatment and the patient has been on a stable dose of anticoagulants for ≥ 2 weeks prior to initiation of study treatment. Prophylactic use of anticoagulants is allowed.* However, the use of direct oral anticoagulant therapies such as dabigatran (Pradaxa®) and rivaroxaban (Xarelto®) is not recommended due to bleeding risk.

27. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below. Women of child-bearing potential must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 6 months after the final dose of atezolizumab and bevacizumab. Women must refrain from donating eggs during this same period.

    a. A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
    b. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

c. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.

28. For men of childbearing potential: With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of atezolizumab and bevacizumab to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

29. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure.

Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible

3.5.2. Exclusion Criteria

1. Patients must not have signs of liver failure or history of liver failure e.g. – encephalopathy or variceal bleeding

2. Uncontrolled hepatitis B infection with viral load >500 IU/ml

3. History of hypertensive crisis or hypertensive encephalopathy

4. Patients who are candidates for curative intent therapy (transplant, resection, or thermal ablation) or liver transplant

5. Patients who are on the transplant list

6. Ascites requiring therapeutic paracentesis in the last 12 months

7. Episode of hepatic encephalopathy in the last 12 months

8. Extrahepatic spread: borderline portal lymph nodes deemed to be of indeterminate nature and measuring less than 2 cm are allowed

9. Prior local or systemic therapy for HCC or prior TACE, excluding prior use of RFA

10. Patients cannot have known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC

11. Occlusion of the hepatic artery or main portal vein

12. Pregnant or lactating, or intending to become pregnant during the study

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

13. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or other recombinant human antibodies

14. Known history of HIV infection. No HIV testing is required.

15. Active or history of autoimmune disease or immune deficiency, 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 (see Appendix 8 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
    a. Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
    b. Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
    c. 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:
        i. Rash must cover < 10% of body surface area
        ii. Disease is well controlled at baseline and requires only low-potency topical corticosteroids
        iii. 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

16. History of leptomeningeal disease

17. Active tuberculosis

18. Uncontrolled tumor-related pain
    a. Patients requiring pain medication must be on a stable regimen at study entry.

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

20. Signs or symptoms of significant infection within 2 weeks prior to Day 1

21. Severe infection within 4 weeks prior to initiation of study treatment, including but not limited hospitalization for complications of infection, bacteremia, or severe pneumonia.

22. Received therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to Cycle 1, Day 1

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

23. Significant cardiovascular disease, (such as New York Heart Association cardiac disease Class II or greater, myocardial infarction, or cerebrovascular accident) within 3 months prior to prior to Day 1, unstable arrhythmias, or unstable angina

24. Patients with a known left ventricular ejection fraction (LVEF) $<$ 40% will be excluded. Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF $<$ 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

25. History of stroke, prolonged reversible ischemic neurological deficit or transient ischemic attack within 6 months prior to Day 1

26. Major surgical procedure within 28 days prior to Day 1 or anticipation of need for a major surgical procedure during the course of the study

27. 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.

28. Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study

29. Malignancies within 2 years prior to study start, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS $>$ 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)

30. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

    a. Patients with indwelling catheters (e.g., PleurX®) are allowed.

31. Inadequately controlled arterial hypertension (defined as systolic blood pressure [BP] $\geq$150 mmHg and/or diastolic BP $>$ 100 mmHg), based on an average of $\geq$ 3 BP readings on $\geq$ 2 sessions. Anti-hypertensive therapy to achieve these parameters is allowable

32. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1

33. History of hemoptysis ($\geq$ 2.5 mL of bright red blood per episode) within 1 month prior to Day 1

34. Evidence of bleeding diathesis or significant coagulopathy

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

35. 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

36. Current or recent (< 10 days prior to initiation of study treatment) use of aspirin (> 325 mg/day), or clopidogrel (> 75 mg/day)

    Note: The use of full-dose oral or parenteral anticoagulants for therapeutic purpose is permitted as long as the INR and/or aPTT is within therapeutic limits (according to institution standards) within 7 days prior to initiation of study treatment and the patient has been on a stable dose of anticoagulants for ≥ 2 weeks prior to initiation of study treatment. Prophylactic use of anticoagulants is allowed. However, the use of direct oral anticoagulant therapies such as dabigatran (Pradaxa®) and rivaroxaban (Xarelto®) is not recommended due to bleeding risk.

37. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days of treatment start

38. Proteinuria, as demonstrated by urine dipstick or ≥ 1.0 g of protein in a 24-hour urine collection. All patients with ≥ 2+ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection for protein.

39. Chronic daily treatment with a nonsteroidal anti-inflammatory drug (occasional use for the symptomatic relief of medical conditions such as headache or fever is allowed)

40. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

41. Prior allogeneic stem cell or solid organ transplantation

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

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

44. 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

45. Treatment with investigational therapy within 28 days prior to initiation of study treatment

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

47. Known allergy or hypersensitivity to any component of the bevacizumab or atezolizumab formulation

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

48. History of Grade $\geq$ 4 venous thromboembolism

49. History of abdominal fistula, GI perforation, intra-abdominal abscess, or active GI bleeding within 6 months prior to randomization

50. Serious, non-healing wound, active ulcer, or untreated bone fracture

4. STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are atezolizumab and bevacizumab. TACE is considered a non-investigational medicinal product (NIMP)

4.1. Study Treatment Formulation, Packaging, and Handling

4.1.1. Atezolizumab

The atezolizumab 1200 mg drug product will be supplied in a single-use, 20-mL USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20-mL volume.

For information on the formulation and handling of atezolizumab, see the Atezolizumab Investigator's Brochure.

4.1.2. Bevacizumab

Bevacizumab will be supplied by Genentech, Inc. For information on the formulation and handling of bevacizumab, see the pharmacy manual and the Bevacizumab Investigator's Brochure.

4.1.3. TACE

Doxorubicin is a marketed chemotherapy drug that will be used during TACE for this study. It will be administered as an emulsion with Lipiodol, which is a lipophilic iodinated contrast medium made up of a mixture of ethyl esters of carnation oil fatty acids.

An experienced interventional radiologist will be administering cTACE. Lipiodol 10 mL is usually administered. Only doxorubicin is mixed in pharmacy (50mg in 2mL sterile water). After administered, embolization completed with 250-355 micron polyvinyl alcohol (PVA) particles until near stasis or stasis is achieved.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

4.2. STUDY TREATMENT DOSAGE, ADMINISTRATION, AND COMPLIANCE

Any overdose or incorrect administration of any of the study treatments should be noted in the patient's medical records and reported to the Sponsor Investigator. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded in the patient's medical records.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 10, 11, 12.

4.2.1. Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status Atezolizumab will be administered first, followed by bevacizumab with a minimum of 5 minutes between dosing. The schedule will change on cycles when TACE is being administered, then there will be at least 4 weeks separating infusions from TACE.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 9. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

4.2.1.1. Table 1: Administration of First and Subsequent Atezolizumab Infusions

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

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

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 9.

No dose modification for atezolizumab is allowed.

4.2.2. Bevacizumab

Bevacizumab 15 mg/kg will be delivered as an IV infusion on Day 1 of each 3-week cycle. The infusion will start at least 5 minutes after the atezolizumab infusion finishes. The initial dose will be delivered over 90 minutes (+/- 10 minutes). 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 and 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

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 minutes (+/- 10 minutes). Also, 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).

4.2.3. TACE

TACE will be administered by injection through a transfemorally or transradially placed catheter into the hepatic artery. Hepatic angiography will be performed to determine the vascular anatomy of the liver and feeding arteries to HCCs. As there are frequent arterial anomalies in the blood supply to the liver, the interventionalist must be familiar with those anomalies. Advanced intraprocedural imaging (e.g., cone beam CT) will be used to map the intratumoral vascular supply.

The interventionalist will then insert the catheter selectively into the artery supplying only segment/subsegment that contains the HCCs. The doxorubicin/lipiodol emulsion will then be delivered to the HCCs with sparing as much of the other non-targeted liver as possible. This is an excellent way of delivering high doses of chemotherapy (doxorubicin) to the tumor without any chance of damaging the normal liver.

TACE administration will be performed in an angiography suite with a standard angiographic technique. Administration into the target vessel will occur via a microcatheter. Lipiodol will act as the contrast medium to visualize and monitor the status of flow to the treating tumor and feeding vessel under fluoroscopy.

The end point of the procedure is achieved when either 1) the entire amount of chemotherapeutic: lipiodol emulsion is administered or 2) the emulsion is seen within secondary or tertiary portal venules. If forward flow is visualized after the emulsion is administered, PVA particles are administered to achieve stasis or near stasis. This includes slowing of flow with pruning of the tumor-feeding branches (the “tree-in-winter” appearance) or transit time of contrast in the feeding artery takes 4 heartbeats. Once slow vessel flow is detected, no further injection will be performed. Treat the tumor vascularity until stasis or near stasis is achieved.

Post-Procedure Care

a) Post-arteriography bedrest with monitoring of vital signs and pulses per institutional protocol.

b) Patient can be discharged as soon as they demonstrate adequate oral intake or liquids, and no longer require parenteral narcotics or antiemetics. (Average length of stay is 1 day).

c) Fevers <103.0 are normal in the first week and do not require cultures.

d) Discharge medications:

i. Antibiotics per institutional protocol if felt to be medically necessary by treating physicians.

ii. Tylenol #3 (or narcotic) PRN for pain

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

iii. Nausea medications PRN

e) Patient returns in approximately 4-6 weeks for repeat treatment (up to 4) based on anatomy and tumor burden (remaining lobe of the liver or retreat same territory if incompletely embolized).

4.3. Concomitant Therapy and Additional Restrictions

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

4.3.1. Permitted Therapy

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

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as. influenza, SARS-CoV-2)
    - (Live, attenuated vaccines are not permitted)
- 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
- Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 9.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

4.3.2. Cautionary Therapy for Atezolizumab-Treated Patients

4.3.2.1. Corticosteroids and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids and TNF-á inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-á inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-á 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 Appendix 12).

4.3.2.2. 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 (see Section 4.3.3) may be used during the study at the discretion of the investigator.

4.3.3. Prohibited Therapy

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

- Concomitant therapy, outside of those given a part of this protocol, intended for the treatment of cancer (including, but not limited to, chemotherapy, immunotherapy, radiotherapy), whether health authority–approved or experimental, is prohibited during study treatment, until disease progression is documented, and the patient has discontinued study treatment
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 6 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 drug elimination half-lives (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.

5. STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

for toxicity prior to dose with each study drug; dosing will occur only if the clinical assessment and local laboratory test values are acceptable. Local laboratory tests are done on the day of each treatment, before the cycle atezolizumab, bevacizumab, and TACE. There is a lab window of 48 hours before treatment.

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

5.1. Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-–reported race/ethnicity.

5.2. Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded in the patient’s medical records.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events in the patient’s medical records.

5.3. Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, and temperature.

Vital signs should be measured within 60 minutes prior to each infusion at every cycle. and, if clinically indicated, during or after the infusion. In addition, vital signs should be

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

5.4. Tumor And Response Evaluations

Patients will undergo tumor assessments at baseline, every 8 weeks for the first 12 months following treatment initiation, and every 12 weeks thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 or (loss of clinical benefit as determined by the investigator (see Section 3.2 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening.

Screening assessments must include an MRI of the abdomen, or CT of the abdomen, and a CT of the chest (an MRI of the abdomen is preferred). At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

All measurable and evaluable lesions identified at baseline should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 6 prior to treatment administration at each cycle.

5.5. Laboratory, Biomarker, And Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel): bicarbonate or total carbon dioxide, sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, and AST
- Coagulation: INR, and aPTT

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.

- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

If a patient has a positive HCV antibody test at screening, an HCV RNA test *must also be performed to determine if the patient has an HCV* infection.

- Pregnancy test

All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

5.6. Electrocardiograms

An ECG is required at screening and when clinically indicated. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented in the patient's medical records.

6. TREATMENT, PATIENT, AND STUDY DISCONTINUATION

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

- Intolerable toxicity related to study treatment, including development of an immune–mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

- Investigator determines it is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
    - Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.2 for details)

The primary reason for study treatment discontinuation should be documented in the patient's medical records. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit ≤ 30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments and PRO assessments as outlined in the schedule of activities (see Appendix 1).

Patient Discontinuation from Study

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

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

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented in the patient's medical records. If a patient request to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

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

6.1. Study Discontinuation

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

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

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

7. ASSESSMENT OF SAFETY

7.1. Safety Plan

The safety plan for patients in this study is based on clinical experience with atezolizumab and bevacizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Section 7.1.)

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab and bevacizumab and TACE will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients who experience anticipated adverse events, including treatment interruption or discontinuation, are provided in Appendix 10, 11, 12). Refer to Sections 7.3–7.5 for details on safety reporting (e.g., adverse events, pregnancies) during the study.

7.1.1. Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune–related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis,pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Refer to Appendix 12 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

7.1.2. Risks Associated with Bevacizumab

Bevacizumab has been associated with common risks such as the following: hypertension, proteinuria, epistaxis, dry skin. More serious risks include bleeding, impaired surgical wound healing, arterial thrombotic events, and gastrointestinal perforation. Refer to the Bevacizumab Investigator’s Brochure for a detailed description of anticipated safety risks for bevacizumab.

7.1.3. Risks Associated with TACE

TACE has been associated with infusion-associated symptoms, which can be severe. There is also a risk of post-TACE syndrome where patients can have fever, nausea/vomiting, and pain. There is also a risk of bleeding. This is risk of bleeding comes mostly from groin access, not the TACE administration itself. Refer to the following publications: Bajwa et. al. 2020, Kishore et. al. 2017, and Kishore et. al. 2017, Labeur 2019, Marcacuzco 2018 .

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

TACE Common Side Effects:

- A low-grade temperature (< 102 F) for one week
- Nausea and/or vomiting, lethargy, and decreased appetite for several days
- Bruising at the puncture site
- Some hair loss: this is usually minimal and may be unnoticed by others
- Pain in the upper-right abdomen, under the ribs

Doxorubicin is among the most common chemotherapy drugs used for TACE and will be used for this study. Doxorubicin will be administered as an emulsion with Lipiodol.

Doxorubicin Side Effects:

CATEGORY	ADVERSE REACTIONS
Cardiac	• Cardiogenic shock
Cutaneous	• Skin and nail hyperpigmentation • Oncolysis • Rash • Itching • Photosensitivity • Urticaria • Acral erythema • Palmar plantar erythrodysesthesia
Gastrointestinal	• Nausea • Mucositis • Stomatitis • Necrotizing colitis • Typhlitis • Gastric erosions • Gastrointestinal tract bleeding • Hematochezia • Esophagitis • Anorexia • Abdominal pain • Dehydration • Diarrhea • Hyperpigmentation of the oral mucosa
Hypersensitivity	• Anaphylaxis
Laboratory Abnormalities	• Increased ALT, increased AST
Neurological	• Peripheral sensory and motor neuropathy • Seizures • Coma

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

Ocular	• Conjunctivitis • Keratitis • Lacrimation
Vascular	• Phlebosclerosis • Phlebitis/thrombophlebitis • Hot flashes • Thromboembolism
Other	• Malaise/asthenia • Fever • Chills • Weight gain

Lipiodol Side Effects:

System Organ Class	Adverse Reaction
Endocrine disorders	• hypothyroidism • hyperthyroidism • thyroiditis
Eye disorders	• retinal vein thrombosis
Gastrointestinal disorders	• nausea • vomiting • diarrhea
General disorders and administration site conditions	• fever • pain • granuloma
Hepatobiliary disorders	• hepatic vein thrombosis
Immune system disorders	• hypersensitivity • anaphylactic reaction • anaphylactoid reaction
Nervous system disorders	• cerebral embolism
Respiratory, thoracic, and mediastinal disorders	• pulmonary embolism* • dyspnea • cough • acute respiratory distress syndrome
Urinary system disorders	• renal insufficiency

* Lipiodol technically can embolize to the lungs, albeit rarely. Occurs when larger doses (e.g., 20 mL lipiodol administered during a single session).

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

7.2. Safety Parameters and Definitions

Safety assessments will consist of monitoring and reporting adverse events and serious adverse events per protocol. This includes all events of death and any study-specific issue of concern.

7.2.1. Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

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

7.2.2. Serious Adverse Events

An AE should be classified as an SAE if any of the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It 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).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

7.2.3. Adverse Events of Special Interest

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

to the Sponsor-Investigator is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor-Investigator to other parties (e.g., Regulatory Authorities) may also be warranted.

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

- 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 $> 3 \cdot$ ULN (or $> 3 \cdot$ baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin $> 2 \cdot$ ULN (of which $\geq 35\%$ is direct bilirubin)

  Treatment-emergent ALT or AST $> 3 \cdot$ ULN (or $> 3 \cdot$ baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice

- Data related to a suspected transmission of an infectious agent by the study treatment, as defined below

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

Atezolizumab Events of Special Interest to be reported to the PI as SAEs:

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, macrophage activating syndrome, 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)
- Myelitis
- Facial paresis

There are no Bevacizumab-specific AESIs.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

7.2.4. Selected Adverse Events

Additional data collection or analysis will be performed for selected adverse events.

Selected Adverse Events for this study are:
• *Hemorrhage*
– *Any grade CNS bleeding*
– *Grade ≥ 2 hemoptysis*
– *Other Grade ≥ 3 hemorrhagic event*

Note: Selected adverse events should not be confused with adverse events of special interest (see Section 7.2.3)

7.2.5. Other Special Situation Reports

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

- 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

Product Complaints

- A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

7.3. Methods and Timing for Assessing and Recording Study Variables

7.3.1. Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record.

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

After initiation of study treatment, all adverse events will be reported until ***30 days*** after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

will continue to be reported until ***90 days*** after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

7.3.2. Assessment of Adverse Events

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 bevacizumab and atezolizumab (see following guidance), and actions taken.

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

Yes (definitive, probable, possible, unlikely)

There is a plausible temporal relationship between the onset of the AE and administration of 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 and bevacizumab or with similar treatments; and/or the AE abates or resolves upon discontinuation of atezolizumab and bevacizumab 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 and bevacizumab administration (e.g., cancer diagnosed 2 days after first dose of atezolizumab and bevacizumab).

Expected adverse events are those adverse events that are listed or characterized in the current Investigator Brochure (I.B) for both atezolizumab and bevacizumab.

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

In addition, adverse events thought to be TACE procedure will be reported as an adverse event of the study. These will include any bleeding related events.

For patients receiving combination therapy (atezolizumab, bevacizumab and/or TACE procedure), causality will be assessed individually for each protocol-mandated therapy.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

7.4. Procedures for Eliciting, Recording, and Reporting Adverse Events

7.4.1. Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

7.4.2. Specific Instructions for Recording Adverse Events

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

7.4.2.1. Diagnosis versus Signs and Symptoms

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

7.4.2.2. Deaths

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”.

7.4.2.3. 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”).

7.4.2.4. Hospitalizations for Medical or Surgical Procedures

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

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

- 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

7.4.2.5. Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE 5 will be used for assessing adverse event severity. Table 2 should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

7.4.2.5.1. Table 2: 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]

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

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

7.4.2.6. Pregnancies

If a female subject or female partner of male study subject becomes pregnant while receiving atezolizumab and bevacizumab or within 6 months after the last dose of atezolizumab and bevacizumab, a report should be completed and expeditiously submitted to Sponsor Investigator. 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 to the Sponsor Investigator as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the atezolizumab should be reported to the Sponsor Investigator as an SAE.

7.4.2.7. 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 or TACE 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.

7.5. Adverse Event Reporting

7.5.1. Adverse Event Reporting to Sponsor Investigator

Please refer to the Manual of Procedures (MOPs) for SAE reporting procedures.

The investigators will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports), Selected Adverse Events and Product Complaints (with or without an AE) originating from the Study for the Product.
Investigators must report all the above-mentioned single case reports adequately to the Sponsor Investigator within the timelines described below. The completed MedWatch

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

reporting form should be emailed immediately upon completion to the Sponsor Investigator, and designee at the contact information listed in the Manual of Procedures.

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

These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

7.5.2. Sponsor-Investigator Adverse Event Reporting to Genentech

This study has SDEA.

The Sponsor Investigator will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product. The completed MedWatch form should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be submitted electronically or by fax b the Project Manager as outlined in the Manual of Operations (MOP). Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints without an AE should be called into the phone number below:

Phone: 800-334-0290 (M-F: 5 am to 5 pm PST)

These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Type of Report	Timelines
Serious Adverse Events (related and not related to the Product)	30 calendar days from awareness date
Special Situation Reports (With or without AE and pregnancy)	
Product Complaints (With or without AE)	
AESI	

7.5.3. MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C and D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at https://www.fda.gov/media/69876/download

Please reference the Manual of Operations (MOP) for additional information.

7.5.4. Reporting to Regulatory Authorities, Ethics Committees and Investigators

The Sponsor Investigator, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

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

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

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

Please reference the Manual of Operations (MOP) for additional information.

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

8. AGGREGATE REPORTS

Final Study Report

The study Sponsor Investigator will forward a copy of the Final Study Report to Genentech upon completion of the Study Close-Out.

9. STATISTICAL CONSIDERATIONS

We will examine the rate of grade 3 or higher AEs with the TACE combination. Based on collected data from the GO and the IMbrave 150 study, we assume the rate of grade 3 or higher AEs for the atezolizumab and bevacizumab combination is approximately 55%. Therefore, with the addition of TACE, the rate of grade 3 or higher AEs will likely be higher. Safety will be continuously monitored using the Bayesian Predictive Probability approach (Lee, 2008). We will access safety after 6 patients have completed at least 1 TACE and 2 cycles of systemic therapy and then quarterly thereafter. Safety will be reviewed based on AEs, SAEs and lab values. The PI and Study Statistician will be responsible for review. We recommend halting enrollment on the trial for a safety analysis whenever there is sufficient evidence that the true toxicity rate is significantly greater than .70 (PP >0.80). The predictive probability (PP) of concluding that the toxicity rate is higher than 70% by the end of the trial based on toxicity data in the current stage will be continuously updated. A high PP indicates that the treatment is likely to be overly toxic. If the probability of true toxicity rate is higher than .70 (PP >0.80) we will halt accrual and conduct a comprehensive safety review.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

This study is not powered for hypothesis testing and analysis will be based on descriptive statistics. In general, categorical data will be summarized using frequencies and percentages. Binary endpoints such as response rate will be estimated with corresponding exact 95% confidence intervals. Continuous measures will be summarized using mean, standard deviation, interquartile range, and median. Time to event outcomes will be presented with kaplan-meier curves.

8.1. Determination of Sample Size

This pilot study will plan to enroll approximately 24 patients. This is a sufficient number of patients to allow us to assess the safety and tolerability of the combination. This allows us to treat patients in a reasonable amount of time (1 year) to know if this is a feasible combination to move ahead with in a larger patient population.

8.2. Primary Efficacy Variables

The primary objective of this study is to examine the safety and tolerability of the combination of atezolizumab and bevacizumab with TACE.

8.3. Secondary Efficacy Variables

The secondary objectives are response rate, time to progression, overall survival, time to TACE progression (TTTP), and time to untaceable progression. Assessment of tumor response will be assessed by both RECIST 1.1 and mRECIST for HCC.
Time to progression will be defined as the time from trial enrollment until objective tumor progression by RECIST criteria, it does not include deaths.
Overall survival will be defined as time from trial enrollment until death from any cause in the intent-to-treat population.
Time to TACE progression is defined as the interval of time from the day of the images after a TACE procedure to the time or progression, new vascular invasion or extrahepatic spread also is counted as progression (Arizumi 2017).
Time to untaceable progression is defined as time to untreatable tumor progression, transient deterioration to Child-Pugh C score, or appearance of vascular invasion/extrahepatic spread.

10. INVESTIGATOR REQUIREMENTS

9.1. Retention of Records

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

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

9.2. Study Medical Monitoring Requirements

10.2.1. Data and Safety Monitoring Committee (DSMC)

The Yale Cancer Center (YCC) Data and Safety Monitoring Committee (DSMC) will provide the primary oversight of data and safety monitoring. The Yale DSMC will review and monitor compliance, toxicity and deviations from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator.

The DSMC will review this protocol bi-annually, at a minimum. Information to be provided to the committee includes: a study narrative by the PI, a summary DSMC report produced by OnCore (which includes participant accrual, response, trial status history, SAEs, adverse events, deviations and survival); audit results, and monitoring reports, as applicable. Other information (e.g., scans, laboratory values, etc.) will be provided upon request. Upon completing the review, the DSMC will approve whether the study should continue as planned, require modification/ amendment, or be placed on administrative hold with accrual temporarily suspended.

Trials being monitored by the YCC DSMC will remain under the YCC DSMC purview until a DSMC review has occurred that includes the research activity of the last subject who completed the intervention, or until the DSMC feels there are no patient safety concerns that require further monitoring. The DSMC will determine the length of continued DSMC review.

The DSMC has authority to intervene in the conduct of these studies as necessary to ensure the safety of the participants and to maintain the highest quality in the clinical research performed at YCC. The DSMC has the authority to require additional monitoring and/ or more frequent reporting on study progress and serious adverse events.

10.2.2. Study Site Monitoring

Study site monitoring is necessary to assure adequate protection of the rights of human subjects and the safety of all subjects involved in clinical investigations and the quality and integrity of the resulting data submitted.

The Sponsor Investigator designated monitoring conducts monitoring visits to ensure that clinical investigators and study team members are compliant with the protocol, ICH good clinical practice, federal, state and local regulations and institutional policies and procedures, that data are of high quality and integrity, and that the facilities and staffing are adequate for continued study participation. This will be performed by conducting

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

monitoring visits including a site initiation visit, regularly scheduled interim monitoring visits and/or remote interim monitoring visits while subjects are on study, and a site close-out visit at all participating sites. Following each site visit, a visit report will be generated containing information on site activities and a summary of pertinent points and action items. The report will be provided with a follow-up letter. Site-specific data status reports will be distributed to the site regularly to outline planned, missing or incomplete case report forms and any outstanding data queries.

During monitoring visits, the following may be reviewed:

- Protection of the rights, safety and welfare of subjects through review of documentation, adverse events (AEs) and serious adverse events (SAEs) and safety procedures
- Subject eligibility
- Source verification
- Protocol compliance
- Deviations and Non-compliance
- Investigator Site File
- GCP compliance
- If applicable, include: Investigational Drug/ Device Storage and Accountability (including quantity and disposal procedures)
- If applicable, include: Laboratory Facilities
- If applicable, include: Equipment maintenance and calibration
- Additional study supplies inventory and assessment
- Study progress and/or follow-up on issues with Site Principal Investigator (PI) and relevant members of the study team

The Sponsor Investigator. and YCCI will define the required study monitoring activities in a Study Monitoring Plan.

9.3. Study Medication Accountability

The Sponsor Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62 and Genentech requirements.

All unused remaining product at the end of the study should be disposed of at the study site according to institutional standard operating procedure. If there is no SOP at the site for drug destruction, return study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

9.4. Data Collection

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or PI. All source documents will be available for routine monitoring, and inspection by the FDA and the Yale IRB.

11. ETHICAL CONSIDERATIONS

11.1. Informed Consent

The informed consent document must be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

11.2. Institutional Review Board or Ethics Committee

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs per local policy.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator's Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report provided by the sponsor investigator per their local policy.

11.3. Confidentiality

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

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

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

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

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

12. REFERENCES

Lee J and Liu D. A Predictive Probability Design for Phase II Cancer Clinical Trials. Clinical Trials. 2008; 5(2): 93-106.

Xu J. Trends in Liver Cancer Mortality Among Adults Aged 25 and Over in the United States 200-2016. NCHS Data Brief, 2018. Jul; (314): 1-8.

Younossi Z, Stepanova M, Ong JP, et al. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol 2019;17(4):748-755.e3.

Jemal A, Ward EM, Johnson CJ, et al. Annual report to the nation on the status of cancer, 1975-2014, featuring survival. J Natl Cancer Inst 2017;109(9).

Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatoceullar carcinoma: Chemoembolization improves survival. Hepatology 2003; 37-429-42.

Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib in Advanced Hepatocellular Carcinoma. New England Journal of Medicine 2008; 359: 378-390.

Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-1173.

Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389:56-66.

Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018;379:54-63.

Zhu et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): a randomized, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology 2019.

El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492-2502.

Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol 2018;19:940-952.

Finn R, Ryoo BY, Merle P, et al. Results of KEYNOTE-240: phase 3 study of pembrolizumab vs BSC for second line therapy in advanced HCC. JCO 2019.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

Chen DS and Hurwitz H. Combinations of Bevacizumab with Cancer Immunotherapy. Cancer Journal 2018.

FDA. FDA approves atezolizumab with chemotherapy and bevacizumab for first-line treatment of metastatic non-squamous NSCLC. FDA website (fda.gov), 2018

Lee, M. S., Ryoo, B. Y., Hsu, C. H., Numata, K., Stein, S., Verret, W., ... & Tebbutt, N. (2020). Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study. The Lancet Oncology, 21(6), 808-820.
Finn R, Qin S, Ikeda Met al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020; 382: 1894-905.

Yau T, Kang YK, Kim TY, et al. Nivolumab + Ipilimumab Combination Therapy in Patients with Advanced Hepatocellular Carcinoma: Results From CheckMate 040. Presentation at American Society of Clinical Oncology congress, May 31-June 4, 2019.

Llovet JM, Real MI, Montana X, et al. Arterial embolization or chemoembolization versus symptomatic treatment in patients with unresectable hepatoceullar carcinoma: a randomized controlled trial. Lancet 2002; 359: 1734-9.

Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatoceullar carcinoma: Chemoembolization improves survival. Hepatology 2003; 37-429-42.

Burrel M, Reig M, Forner A, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolization (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. J Hepatol 2012, 56: 1330-5.

Malgari K, Pomoni M, Moschouris H, et al. Chemoembolization with doxorubicin-eluting beads for unresectable hepatoceullar carcinoma: five-year survival anlaysis. Cardiovasc Interv Radiol 2012; 35: 1119-28.

Raoul J-L, Forner A, Bolondi L, et al. Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence. Cancer Treatment Reviewes 72(2019) 28-36.

Lencioni et al, Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial; 2016

Meyer et al, Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomized placebo-controlled, double-blind, phase 3 trial. Lancet Gastroenterology Hepatology 2017 Aug 2 565-575.

Buijs et al, Phase II trial of concurrent bevacizumab and transhepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. Cancer 2013 March 1; 119(5): 1042-1049.

Slovak R, Ludwig JM, Gettinger SN, et al. Immuno-thermal ablations – boosting the anticancer immune response. Journal of Immunotherapy Cancer. 2017 Oct 17; 5(1): 78.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

Lee, Michael S., et al. "Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study." The Lancet Oncology 21.6 (2020): 808-820.

Lee, Michael S., et al. "Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study." The Lancet Oncology 21.6 (2020): 808-820.

Finn, Richard S., et al. "Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma." New England Journal of Medicine 382.20 (2020): 1894-1905.

Finn, Richard S., et al. "Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma." New England Journal of Medicine 382.20 (2020): 1894-1905.

Arizumi T, Ueshima K, Iwanishi M, et al. The Overall Survival of Patinets with Hepatocellular Carinoma Correlates with the Newly Defined Time to Progression after Transarterial Chemoembolization. Liver Cancer 2017; June; 6(3): 227-235.

Deng, Rong, et al. "Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor." MAbs. Vol. 8. No. 3. Taylor & Francis, 2016

Labeur T, Takkenberg R, Klumpen HJ, et al. Reason of Discontinuation after Transarterial Chemoembolization Influences Survival in Patients with Hepatocellular Carcinoma. CardioVascular and Interventional Radiology 2019, Volume 42, Issue 2 230-238.

Marcacuzco Q, Nutu OA, San Roman Manso R, et al. Complications of transarterial chemoembolization (TACE) in the treatment of liver tumors. Cir Esp 2018. Nov; 96(9) 56067.

Bajwa, Raazi, David C. Madoff, and Sirish A. Kishore. "Embolotherapy for Hepatic Oncology: Current Perspectives and Future Directions." Digestive disease interventions 4.2 (2020): 134.

Kishore, Sirish A., Raazi Bajwa, and David C. Madoff. "Embolotherapeutic strategies for hepatocellular carcinoma: 2020 update." *Cancers* 12.4 (2020): 791.

Kishore, Sirish, Tamir Friedman, and David C. Madoff. "Update on embolization therapies for hepatocellular carcinoma." *Current oncology reports* 19.6 (2017): 40.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

13. LIST OF APPENDICES

13.1. Appendix 1: Study Flowchart

	Screening [a]	C1D1 (± 3 days)	C2D1 (± 3 days)	TACE Procedure #1	C3D1 (± 3 days)	TACE Procedure #2	C4D1 (± 3 days)	TACE Procedure #3	C5D1 (± 3 days)	C6D1 (± 3 days)	TACE Procedure #4	C7D1 (± 3 days)	C8D1 + (± 3 days)	Treatment Discontinuation	Long Term Follow Up – Every 3 Months
Day	-28-0	1	22	28	43	56	64	84	85	106	112	127	148	≤ 30 post last dose [b]	Every 90 day ± 7 days
Informed consent	x [c]														
Demographic data	x														
Medical history and baseline conditions	x														
Vital signs [d]	x	x	x	x	x	x	x	x	x	x	x	x	x		
Weight	x	x	x		x		x		x	x		x	x		
Height	x														
Complete physical examination [e]	x														
Limited physical examination [f]		x	x	x	x		x		x	x		x	x	x	
ECOG Performance Status	x	x	x	x	x		x		x	x		x	x		
Child Pugh	X		X		X		X		X	X		X	X	X	
ECG (12-lead) [g]	x														
Hematology [h]	x [n]	x [o]	x [o]	x	x [o]	x	x [o]	x	x [o]	x [o]	x	x [o]	x [o]		
Pregnancy test [i]	x [j]	x	x		x		x		x	x		x	x	x	
Coagulation (INR, aPTT)	x [j]		X		X		X		X	X		X	X	x	
TSH, free T3 (or total T3), free T4 [m]	x [j]	x [m]	x [m]		x [m]		x [m]		x [m]	x [m]		x [m]	x [m]	x	
Viral serology [n]	x [j]														
Urinalysis [o]	x [j]	x [p]	x [p]		x [p]		x [p]		x [p]	x [p]		x [p]	x [p]		
Chemistry [l]	x [k]	x	x		x		x		x	x		x	x	x	
Tumor response assessments [q]		x [q]	x [q]		x [q]		x [q]		x [q]	x [q]		x [q]	x [q]		x [q]
Concomitant medications	x [r]	x	x		x		x		x	x		x	x	x	
Atezolizumab		x [s]	x [s]		x [s]		x [s]		x [s]	x [s]		x [s]	x [s]		
Bevacizumab		x [t]					x [t]		x [t]	x [t]		x [t]	x [t]		
TACE				x [u]		x [u]		x [u]			x [u]				
Adverse events	x	x	x		x		x		x	x		x	x	x	x [v]

HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; NA = not applicable; PK = pharmacokinetic; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WES = whole exome sequencing.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded in the patient's medical records (except in the case of an adverse event).

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 7 days prior to Day 1 may be used; such tests do not need to be repeated for screening. Screening laboratory assessments that were performed within 3 days prior to Day 1 of Cycle 1, do not have to be repeated.

[b] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[c] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[d] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline in the patient's medical records. At subsequent visits, record new or worsened clinically significant abnormalities in the patient's medical records. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (± 5) minutes during and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (± 10) minutes after the infusion.

[e] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline in the patient's medical records. At subsequent visits, record new or worsened clinically significant abnormalities in the patient's medical records.

[f] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities in the patient's medical records.

[g] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[h] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[i] All women of childbearing potential will have a serum pregnancy test at screening, within 14 days prior to initiation of study treatment. (Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.)

[j] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[k] If screening laboratory assessments were performed within 3 days prior to Day 1 of Cycle 1, they do not have to be repeated.

[l] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH. There is a lab window of 48 hours before treatment.

[m] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter. NOTE-frequency of thyroid testing should be every fourth cycle for 21-day cycle.

[n] At screening, patients will be tested for HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[o] Includes pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted.

[p] Urinalysis should be performed prior to each treatment with bevacizumab during study treatment.

[q] Imaging will be every 8 weeks for the first year on treatment and then imaging will be every 12 weeks for the second year. There is a 1-week window allowed for imaging.

All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with oral or IV contrast) or MRI scans of the chest, abdomen, pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, should be performed. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

[r] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[s] Atezolizumab 1200mg will be administered intravenously on day 1 of every 21-day cycle beginning C1D1

[t] Bevacizumab 15mg/kg will be administered intravenously on C1D1 and resume on Day 1 the treatment cycle at least 4 weeks after the last TACE procedure. Full recovery from the TACE procedure is required prior to re-starting treatment with Bev.

Bevacizumab will **ONLY** resume when it has been at least 4 weeks after the last TACE procedure and all TACE related effects are resolved.

[u] TACE treatments may occur 1, 2, 3, or 4 times based on the clinical judgement from the investigational radiologist. The first TACE procedure must be at least 28 days from the last Bevacizumab treatment. TACE treatments occur 4-6 weeks apart. Bevacizumab should be resumed at the first Atezolizumab administration that occurs at least 28 days from the last TACE procedure.

[v] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (unless the patient withdraws consent, or the Investigator terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

13.2. Appendix 2: Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

$$\text{Creatinine Clearance (men)} = \frac{(140\text{-Age}) \cdot \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \cdot 72}$$

$$\text{Creatinine Clearance (women)} = \frac{0.85 \cdot (140\text{-Age}) \cdot \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \cdot 72}$$

Source: Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine (editorial). Nephron 1992;62:249.

13.3. Appendix 3: Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

GENENTECH SUPPORTED RESEARCH

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

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

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

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

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

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

13.4. Appendix 4: FDA Medwatch 3500 Form

This form is included in the study start-up zip file to be sent to sites via email.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

13.5. Appendix 5: Current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

Please use the following link to the NCI CTCAE website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

13.6. Appendix 6: Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST V1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval ≤ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

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

Cystic Lesions:

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

Lesions with Prior Local Treatment:

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

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should 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 that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\cdot$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but $<$ 15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$ 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non□lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

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

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

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

document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45: 228–47.

APPROVED BY THE YALE UNIVERSITY IRB 2/15/2024

TARGET LESIONS

The target lesions selected at baseline should continue to be measured at all tumor assessment timepoints after disease progression per RECIST v1.1, according to RECIST v1.1 conventions.

NON-TARGET LESIONS

Non-target lesions selected at baseline should continue to be followed at all tumor assessment timepoints after disease progression per RECIST v1.1. At each timepoint, non-target lesions should continue to be categorized as "absent" (complete response [CR]), "unequivocal progression" relative to baseline (progressive disease [PD]), or "present without unequivocal progression" (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous timepoint should be evaluated to determine whether there has been any further increase in size.

NEW LESIONS

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST v1.1 (e.g., non–lymph node lesions must be ≥ 10 mm on the longest diameter; new lymph nodes must be ≥ 15 mm on the short axis [see note below]). All new lesions (measurable or non–measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint should be measured from that point on, if the maximum number of measurable new lesions has not been reached.

All non-measurable new lesions and additional measurable new lesions (in excess of five total or two per organ) should be categorized as "absent" or "present." All non–measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is ≥ 15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is ≥ 10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is < 10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is ≥ 15 mm. Measurable new lymph node lesions should continue to be measured at all subsequent timepoints, even if the short axis decreases to < 15 mm (or even < 10 mm).

13.7. Appendix 7: Hepatocellular Carcinoma-Specific Modified RECIST (HCC mRECIST)

IMAGE ACQUISITION FOR HCC-SPECIFIC MODIFIED RECIST

Optimization of image acquisition protocols and consistency in the use of the same protocol throughout follow-up examinations are key for proper application of HCC-specific modified RECIST (HCC mRECIST; Lencioni et al. 2010).

Patients can be followed with either contrast-enhanced spiral computed tomography (CT) preferably with use of multislice scanners or contrast-enhanced dynamic magnetic resonance imaging (MRI). The administration of intravenous contrast is recommended for all CT or MRI studies if not medically contraindicated. In contrast-enhanced studies, it is mandatory to obtain a dual-phase imaging of the liver. Every effort should be made to time the contrast administration so that high-quality arterial-phase imaging is obtainedthroughout the liver on the first run and that high-quality portal venous-phase imaging is obtained throughout the liver on the second run. Delayed imaging obtained in the equilibrium phase may be useful, but it is not mandatory and should be done only if it is part of clinical practice.

For multidetector CT scanners that are capable of acquiring very thin slices, it is mandatory to use contiguous slices for image read and interpretation, to avoid missingsmall lesions. For example, the analysis of contiguous slices with traditional 5-mm thickness and 5-mm reconstruction interval is acceptable; however, the analysis of 2.5-mm thickness slices at 5 mm intervals is not acceptable.

ASSESSMENT OF TUMOR LESIONS

TARGET LESIONS

The measurement of the longest viable tumor diameter for the assessment of responseaccording to HCC mRECIST can be applied only on typical lesions. Conversely, for non-enhancing atypical lesions, as well as for any extrahepatic neoplastic niches, the
measurements of the longest overall tumor diameter as per conventional RECIST shouldprevail. To be selected as a target lesion using HCC mRECIST, an HCC lesion should meet all the following criteria:

- The lesion is classified as a measurable lesion (i.e., the lesion can be accuratelymeasured in at least one dimension as 1 cm or more).
- The lesion is suitable for repeat measurement.
- The lesion shows intratumoral arterial enhancement on contrast-enhanced CT or MRI. It is important to point out that only well-delineated, arterially enhancing lesionscan be selected as target lesions for HCC mRECIST. This may not be the case of infiltrative-type HCC. Infiltrative-type HCC should be considered as a non-target

lesion when the mass shows ill-defined borders and therefore does not appear to besuitable for accurate and repeat measurements.

- HCC lesions previously treated with locoregional or systemic treatments may or maynot be considered as suitable to be selected as target lesions for HCC mRECIST: If the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is at least 1 cm in longest diameter, then it can be selectedas 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 atarget lesion for HCC mRECIST.

Table 1 Target Lesion Selection Criteria

RECIST v1.1		HCC-Specific mRECIST
Measurable disease	Lesion able to be accurately measured in at least one dimension > 1 cm and suitable for repeat measurement	Lesion able to be accurately measured in at least one dimension > 1 cm and suitable for repeat measurement and lesion shows intratumoral arterial Enhancement
Non-measurable disease	All other lesions (< 1 cm lesions and truly non measurable lesions)	All other lesions (< 1 cm lesions and truly non measurable lesions) and lesions exhibiting atypical Enhancement
Number of lesions	Up to 5 (2 per organ)	Up to 5 (2 per organ)
Measurement	Sum of longest diameters of individual lesions	Sum of longest diameters of individual lesions showing arterial enhancement

HCC= hepatocellular carcinoma; mRECIST = modified Response Evaluation Criteria in Solid Tumors; RECIST *vl.1* =Response Evaluation Criteria in Solid Tumors, *Version 1.1.*

Defining Treatment Response and Tumor Progression:

- Complete response: the disappearance of any intratumoral arterial enhancement inall target lesions

- Partial response: at least a 30% decrease in the sum of the longest diameters ofviable (contrast enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
- Progressive disease: an increase of at least 20% in the sum of the longest diameters of viable (enhancing) target lesions, taking as reference the smallest sumof the diameters of viable (enhancing) target lesions recorded since the treatment started
- Stable disease: any cases that do not qualify for either partial response or progressive disease

Table 2 Target Lesion Response Definition

RECIST v1.1		HCC-Specific mRECIST
Complete response	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target Lesions
Partial response	30% decrease in sum of the longest diameters of target lesions compared with baseline	30% decrease in sum of the longest diameters of viable (arterially enhancing) target lesions compared with baseline
Progressive disease	20% increase in sum of the longest diameters of target lesions compared with the smallest sum of longest diameters recorded (nadir)	20% increase in sum of the longest diameters of viable (arterially enhancing) target lesions compared with the smallest sum of longest diameters recorded (nadir)
Stable disease	Neither PR or PD	Neither PR or PD

HCC = hepatocellular carcinoma; mRECIST = modified Response Evaluation Criteria in Solid Tumors; PD= progressive disease; PR= partial response; RECIST *v*1.1 = Response Evaluation Criteria in Solid Tumors, *Version* 1.1.

NON-TARGET LESIONS

According to HCC mRECIST, tumor necrosis should be taken into account when assessing the response of non-target lesions. The disappearance of intratumoral arterial enhancement in non-target lesions should be considered equivalent to the disappearance of non-target lesions, and therefore, should declare complete response of non-target lesions. The persistence of intratumoral arterial enhancement in one or more non-target lesions should be considered equivalent to persistence of one or more non-target lesions, and therefore, should declare incomplete response or stable disease.Special recommendations for the

assessment of tumor response in non-target lesions in patients with HCC and cirrhosis can be made regarding the following points:

- Portal vein thrombosis. Malignant portal vein thrombosis should be considered a non-measurable lesion due to the difficulty in performing consistent measurements of the malignant thrombus during the course of the treatment. Measurements of theextent of the malignant thrombus may be impaired by the possible presence of a bland component of the thrombosis.
- Porta hepatic lymph node. Lymph nodes detected at the portal hepatitis can be considered as malignant if the lymph node short axis is at least 20 mm. Evidence ofreactive lymph nodes at the porta hepatic, in fact, is a common finding in patients with cirrhosis regardless of the presence of an HCC. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor.
- Pleural effusion and ascites. The original RECIST publication specifies that cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed).
- The emergence or the increase in ascites is a common event during the course of treatment in a cirrhotic patient, which may be due to worsening of the underlying chronic liver disease and be unrelated to cancer progression. Other effusions, such as pleural effusion, may also be unrelated to cancer progression and be caused by the liver insufficiency. Thus, the HCC mRECIST emphasizes that cytopathologic confirmation of the neoplastic nature of any effusion (particularly ascites) that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. It has to be underlined that peritoneal carcinomatosis is a very rare event in HCC.

Table 3 Non-Target Lesion Response Definition

RECIST v1.1		HCC-Specific mRECIST
Complete response	Disappearance of all non-target lesions	Disappearance of any intratumoral arterial enhancement in all non-target lesions
Progressive disease	Unequivocal increase in size of non-target lesions, or new lesions	Unequivocal increase in size of non-target lesions, or new lesions meeting specific criteria (see text)
Incomplete response of Stable disease	Persistence of one or more non-target lesions	Persistence of arterial enhancement in one or more non-target lesions

HCC= hepatocellular carcinoma; mRECIST = modified Response Evaluation Criteria in SolidTumors; RECIST *v1.1* = Response Evaluation Criteria in Solid Tumors, *Verison 1.1.*

NEW LESIONS

Newly detected hepatic lesions must be 1cm in diameter and show a vascular pattern typical of HCC. The appearance of one or more new lesions should declare progressivedisease.

OVERALL VISIT RESPONSE

Overall visit response is obtained in a similar fashion as for RECIST1.1 by combining theresponse assessment for target lesions, non-target lesions and new lesions.

Table 4 Summary Table

Target Lesions		
Response Category	RECIST v1.1	HCC-Specific mRECIST
Complete response	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target Lesions
Partial response	:2: 30% decrease in sum of the longest diameters of target lesions compared with baseline	:2: 30% decrease in sum of the longest diameters of viable (arterially enhancing) target lesions compared with baseline
Progressive disease	:2: 20% increase in sum of the longest diameters of target lesions compared with the smallest sum of longest diameters recorded (nadir)	:2: 20% increase in sum of the longest diameters of viable (arterially enhancing) target lesions compared with the smallest sum of longest diameters recorded (nadir)
Stable disease	Neither PR or PD	Neither PR or PD
Non-target Lesions		
Response Category	RECIST v1.1	HCC-Specific mRECIST
Complete response	Disappearance of all non-target lesions	Disappearance of any intratumoral arterial enhancement in all non-target Lesions
Progressive disease	Unequivocal increase in size of non-target lesions, or new lesions	Unequivocal increase in size of non-target lesions, or new lesions meeting specific criteria (see text)
Incomplete response of stable disease	Persistence of one or more non-target lesions	Persistence of arterial enhancement in one or more non-target lesions
mRECIST Recommendations		
Pleural effusion and ascites	Cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD.	
Portal hepatis lymph node	Lymph nodes detected at the porta hepatis can be considered malignant if the lymph node short axis is :2: 2 cm.	
Portal vein thrombosis	Malignant portal vein thrombosis should be considered as a non-measureable lesion and thus included in the non-target lesion group	
New lesion	A new lesion can be classified as HCC if its longest diameter is :2: 1 cm and the enhancement pattern is typical for HCC. A lesion with atypical radiological pattern can be diagnosed as HCC by evidence of :2: 1 cm interval growth.	

HCC= hepatocellular carcinoma; mRECIST = modified Response Evaluation Criteria in Solid Tumors; PD= progressive disease; PR= partial response; RECIST *vl.1* =Response Evaluation Criteria in Solid Tumors, *Version* 1.1.

APPROVED BY THE YALE UNIVERSITY IRB 2/26/2023

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412–20.

Seymour L, Bogaerts J, Perrone A, et al., on behalf of the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143–52.

13.8. Appendix 8: Preexisting Autoimmune Diseases and Immune Deficiencies

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

Autoimmune Diseases and Immune Deficiencies

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

APPROVED BY THE YALE UNIVERSITY IRB 2/16/2024

13.9. Appendix 9: Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

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

13.10. Appendix 10: Guidelines for Management of Adverse Events Associated with Bevacizumab

This appendix provides guidelines for the management of patients who experience adverse events associated with bevacizumab. Appendix 12 describes risks associated with atezolizumab and provides guidelines for management of patients who experience atezolizumab-associated IRRs and immune-related adverse events (e.g., pulmonary, hepatic, gastrointestinal, endocrine, ocular, myocarditis, pancreatic, dermatologic, neurologic, meningoencephalitis, renal, myositis, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome events).

DOSE MODIFICATIONS

There are no dose modifications for bevacizumab.

MANAGEMENT GUIDELINES

Guidelines for management of patients who experience adverse events associated with bevacizumab are provided in Table 1a- Bev.

For cases in which management guidelines are not covered in the protocol patients should be managed as deemed appropriate by the investigator according to best medical judgment.

Table 1a- Bev Guidelines for Management of Patients Who Experience Adverse Events Associated with Bevacizumab

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

Appendix 10:Guidelines for Management of Adverse Events Associated with Bevacizumab

	Grade 4	Life-threatening consequences; urgent intervention indicated - discontinue bevacizumab
Thromboembolic Event (arterial)	Any Grade	Discontinue bevacizumab
Thromboembolic Event (Venous)	Grade 3	Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2weeks, bevacizumab should be held until the full-dose anticoagulation period is over. The use of direct oral anticoagulants is not recommended. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during full-dose anticoagulation IF all of the criteria below are met: - The patient must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions) - The patient must not have had hemorrhagic events > grade 2 while on study - The patient must be on stable dose of heparin, low molecular weight heparin, or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4	Discontinue bevacizumab
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

Appendix 10:Guidelines for Management of Adverse Events Associated with 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
Haemorrhage (CNS)	Any grade	Discontinue bevacizumab
Haemorrhage (haemoptysis)	Grade 1	Trace haemoptysis; continue bevacizumab
	Grade 2 - 4	≥ 2.5 mL bright red blood per episode; discontinue bevacizumab
Haemorrhage (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

Appendix 10:Guidelines for Management of Adverse Events Associated with Bevacizumab

	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.

13.11. Appendix 11: Overall Guidelines for Management of Patients who Experience Adverse Events

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the treating physician agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The investigator will determine the acceptable length of treatment interruption.

Bevacizumab treatment may be temporarily suspended in patients experiencing a grade 3 or 4 toxicity considered to be related to this drug. Bevacizumab can be restarted when the toxicity decreases to a grade 2 or below toxicity.

MANAGEMENT GUIDELINES

Guidelines for management of patients who experience specific adverse events are provided in Table 1a- Bev and Table 1b-Atezo.

13.12. Appendix 12: 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).

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

MANAGEMENT GUIDELINES

PULMONARY EVENTS

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Table 1b- Atezo 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 Grade 1 pneumonitis, consider withholding atezolizumab.
Pulmonary event, Grade 2	● Withhold atezolizumab for up to 12 weeks after event onset. [a] ● Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. ● Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] ● For recurrent events, or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	● Permanently discontinue atezolizumab. [c] ● Bronchoscopy or BAL is recommended. ● Initiate treatment with corticosteroids equivalent to 1□2 mg/kg/day IV methylprednisolone. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

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

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

HEPATIC EVENTS

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

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

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

Table 2 Management Guidelines for Hepatic Events

Event	Management
AST/ALT is within normal limits at baseline and increases to $>3\times$ ULN to $\leq 10\times$ ULN **or** AST/ALT is $>$ ULN to $\leq 3\times$ ULN at baseline and increases to $>5\times$ ULN to $\leq 10\times$ ULN **or** AST/ALT is $>3\times$ ULN to $\leq 5\times$ ULN at baseline and increases to $>8\times$ ULN to $\leq 10\times$ ULN	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Monitor LFTs more frequently until return to baseline values. • For events of >5 days' duration, consider initiating treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to baseline or to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to baseline or to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
AST or ALT increases to $>10\times$ ULN or total bilirubin increases to $>3\times$ ULN	• Permanently discontinue atezolizumab. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to baseline, taper corticosteroids over ≥ 1 month.

LFT = liver function test.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

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

GASTROINTESTINAL EVENTS

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

GI = gastrointestinal.

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

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

GI = gastrointestinal.

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

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

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

ENDOCRINE EVENTS

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism ,Grade 1	● Continue atezolizumab. ● Initiate treatment with thyroid replacement hormone. ● Monitor TSH closely.
Symptomatic hypothyroidism , Grade 2	● Consider withhold atezolizumab. ● Initiate treatment with thyroid replacement hormone. ● Monitor TSH closely. ● Consider patient referral to endocrinologist. ● Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Hypothyroidism, Grade 3 or 4	● Withhold atezolizumab. ● Initiate treatment with thyroid replacement hormone. ● Monitor TSH closely. ● Refer patient to endocrinologist. ● Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). ● Resume atezolizumab when symptoms are controlled, and thyroid function is improving. ● Permanently discontinue atezolizumab. [c]
Hyperthyroidis m, Grade 1	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** ● Continue atezolizumab. ● Monitor TSH every 4 weeks. ● Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** ● Follow guidelines for symptomatic hyperthyroidism. ● Consider patient referral to endocrinologist.
Hyperthyroidis m, Grade 2	● Consider 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. ●

Hyperthyroidism, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer patient to endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab. [c]

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

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

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Table 4 Management Guidelines for Endocrine Events (cont.)

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

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

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

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Table 4 Management Guidelines for Endocrine Events (cont.)

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

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

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

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

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

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

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

IMMUNE-MEDIATED MYOCARDITIS

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

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

IMMUNE-MEDIATED PERICARDIAL DISORDERS

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

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

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

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

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6. *Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.*

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Table 6 Management Guidelines for Immune-Related Myocarditis

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

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

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (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 medication with antihistamines, antipyretics and/or analgesics (e.g., acetaminophen). Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

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

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]	● Immediately interrupt atezolizumab infusion.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Fever[b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen[d] by nasal cannula or blow-by	● Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. ● If symptoms recur, discontinue infusion of this dose. ● Administer symptomatic treatment.[c] ● For hypotension, administer IV fluid bolus as needed. ● Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. ● Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy.[e] ● Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. ● If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. ● If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the sponsor-investigator.
Grade 3[a] Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	● Permanently discontinue atezolizumab.[f] ● Administer symptomatic treatment.[c] ● For hypotension, administer IV fluid bolus and vasopressor as needed. ● Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. ● Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy.[e] ● Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator.
Grade 4[a] Fever[b] with hypotension requiring multiple vasopressors	● 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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

(excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. ● Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy.[e] For patients who are refractory to anti-cytokine therapy, experimental treatments[g] may be considered at the discretion of the investigator. ● Hospitalize patient until complete resolution of symptoms.

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

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

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

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

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

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

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and 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 assessing the benefit–risk ratio.

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

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

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

GI = gastrointestinal.

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

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

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

GI = gastrointestinal.

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

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

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

DERMATOLOGIC EVENTS

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

NEUROLOGIC DISORDERS

Myasthenia gravis, Guillain-Barré syndrome,immune-mediated myelitis and immunemediated facial paresis, have been observed with single□agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Table 10 Management Guidelines for Neurologic Disorders

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

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

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

IMMUNE-MEDIATED MENINGOENCEPHALITIS

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

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

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

Table 11 Management Guidelines for Immune-Mediated Meningoencephalitis

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

RENAL EVENTS

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

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

Table 12 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.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

---

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

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

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

IMMUNE-MEDIATED MYOSITIS

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

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

Table 13 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

---

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

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

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

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

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

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 < $100 \cdot 10^9$/L (100,000/⌈L)
  - ANC < $1.0 \cdot 10^9$/L (1000/⌈L)
- 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

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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 $\leq 181 \cdot 10^9$/L (181,000/$\lceil$L)
  - AST $\geq$ 48 U/L
  - Triglycerides $>$ 1.761 mmol/L (156 mg/dL)
  - Fibrinogen $\leq$ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

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

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

REFERENCES

Adashek ML, Feldman M. Cytokine release syndrome resulting from anti–programmed death-1 antibody: raising awareness among community oncologist. J Oncol Practice 2019;15:502–4.

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

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

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–38.

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

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

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

Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323–35.

Rotz SJ, Leino D, Szabo S, et al. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. Pediatr Blood Cancer 2017;64:e26642.

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

Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellularcarcinoma. Semin Liver Dis 2010;30:52- 60.