PROTOCOL

PROTOCOL TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) PLUS BEVACIZUMAB VERSUS ACTIVE SURVEILLANCE AS ADJUVANT THERAPY IN PATIENTS WITH HEPATOCELLULAR CARCINOMA AT HIGH RISK OF RECURRENCE AFTER SURGICAL RESECTION OR ABLATION**
PROTOCOL NUMBER:	WO41535
STUDY NAME:	IMbrave050
VERSION NUMBER:	6
TEST COMPOUNDS:	Atezolizumab (RO5541267) Bevacizumab (RO4876646)
STUDY PHASE:	Phase III
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 135913 EudraCT Number: 2019-002 491-14 EU CT Number: 2023-504303-86-00 NCT Number: 04102098
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL	See electronic signature and date stamp on the final page of this document..

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
6	See electronic date stamp on the final page of this document.			
5	25 October 2022	—	—	—
4	30 November 2021	—	—	—
3	3 December 2020	—	—	—
2	17 December 2019	—	—	—
1	17 July 2019	VHP	1	17 October 2019

PROTOCOL AMENDMENT, VERSION 6:
RATIONALE

Protocol WO41535 has been amended to update safety language following the Atezolizumab Investigator's Brochure Version 19, Addendum 2 and to comply with Clinical Trials Regulation (CTR) guidelines. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The following changes have been made to align the protocol with Addendum 2 of the Atezolizumab Investigator's Brochure, Version 19:
  - The medical term "Wegener granulomatosis" has been replaced by the term "granulomatosis with polyangiitis" to align with the updated preferred term in MedDRA (Section 4.1.2 and Appendix 10).
  - The list of identified risks for atezolizumab has been revised to include myelitis and facial paresis (Section 5.1.1).
  - Hemophagocytic lymphohistiocytosis has been updated from a potential risk to an identified risk associated with atezolizumab and language has been revised accordingly (Section 5.1.1).
  - The list of adverse events of special interest has been revised to include myelitis and facial paresis (Section 5.2.3).
  - Appendix 10 has been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a pericardial disorder while receiving another immunostimulatory anti-cancer agent.
  - Appendix 10 has been revised to include autoimmune myelitis.
  - The adverse event management guidelines have been updated to align with the Addendum 2 to the Atezolizumab Investigator's Brochure, Version 19 (Appendix 13).

- The following changes have been made to align the protocol with CTR requirements:
  - The synopsis has been simplified to align with CTR and other guidelines.
  - A section describing the duration of participation has been added to align with CTR requirements (Section 3.3).
  - A comprehensive list of investigational medicinal products and auxiliary medicinal products has been added to align with CTR requirements (Section 4.3 and Appendix 14).
  - Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front matter and Section 5.4.1). Medical Monitor contact information in Section 5.4.1 has been replaced with a sentence indicating that this information will be provided separately to sites.

- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section 8.4).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOLTITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) PLUS BEVACIZUMAB VERSUS ACTIVE SURVEILLANCE AS ADJUVANT THERAPY IN PATIENTS WITH HEPATOCELLULAR CARCINOMA AT HIGH RISK OF RECURRENCE AFTER SURGICAL RESECTION OR ABLATION**
PROTOCOL NUMBER:	WO41535
VERSION NUMBER:	6
TEST COMPOUNDS:	Atezolizumab (RO5541267) Bevacizumab (RO4876646)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) PLUS BEVACIZUMAB VERSUS ACTIVE SURVEILLANCE AS ADJUVANT THERAPY IN PATIENTS WITH HEPATOCELLULAR CARCINOMA AT HIGH RISK OF RECURRENCE AFTER SURGICAL RESECTION OR ABLATION**
REGULATORY AGENCY IDENTIFIER NUMBERS	IND Number: 135913 EudraCT Number: 2019-002 491-14 EU CT NUMBER: 2023-504303-86-00 NCT NUMBER: 04102098

STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of atezolizumab plus bevacizumab, in patients with completely resected or ablated hepatocellular carcinoma (HCC) who are at high risk for disease recurrence. Given the poor prognosis associated with high recurrence rates and absence of treatment options for these patients, this population is considered appropriate for trials of novel therapeutic candidates in the adjuvant setting.

OBJECTIVES AND ENDPOINTS

Primary Efficacy Objective (Primary Objective)	Corresponding Endpoint
• To evaluate the efficacy of atezolizumab plus bevacizumab compared with active surveillance	• RFS after randomization, defined as the time from randomization to the first documented occurrence of intrahepatic or extrahepatic HCC as determined by an IRF, or death from any cause (whichever occurs first)

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of atezolizumab plus bevacizumab compared with active surveillance	• OS after randomization, defined as the time from randomization to death from any cause • RFS after randomization as determined by the investigator • TTR after randomization, defined as the time from randomization to first documented occurrence of intrahepatic or extrahepatic HCC, as determined by the investigator and by an IRF • IRF-assessed RFS and investigator-assessed RFS rate at 24 and 36 months after randomization • OS rate at 24 months and 36 months, defined as the proportion of patients who have not experienced death from any cause at 24 and 36 months after randomization, respectively • Time to EHS or macrovascular invasion after randomization, defined as the time from randomization to the first appearance of EHS or macrovascular invasion, as determined by the investigator • RFS after randomization as determined by the investigator and by an IRF, among patients in the PD-L1–high subgroup
• **Safety Objective**	• **Corresponding Endpoints**
• To evaluate the safety of atezolizumab plus bevacizumab compared with active surveillance	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
• **Pharmacokinetic Objective**	• **Corresponding Endpoint**
• To characterize the PK profile of atezolizumab when given in combination with bevacizumab	• Serum concentration of atezolizumab at specified timepoints
• **Immunogenicity Objective**	• **Corresponding Endpoint**
• To evaluate the immune response to atezolizumab	• Prevalence of ADAs to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study

ADA = anti-drug antibody; EHS = extrahepatic spread; HCC=hepatocellular carcinoma; IRF = Independent Review Facility; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OS = overall survival; PK = pharmacokinetic; RFS = recurrence-free survival; TTR = time to recurrence.

OVERALL DESIGN AND STUDY POPULATION

This is a Phase III, global, multicenter, open-label, two-arm, randomized study designed to evaluate the efficacy and safety of adjuvant therapy with atezolizumab plus bevacizumab compared with active surveillance in patients with completely resected or ablated HCC who are at high risk for disease recurrence. Key aspects of the study design and study population are summarized below.

Phase:	Phase III	**Population Type:**	Adult patients
Control Method:	Standard of care	**Population Diagnosis or Condition:**	HCC with high risk of recurrence after surgical resection or ablation
Interventional Model:	Parallel	**Population Age:**	Age ≥ 18 years
Test Compounds:	Atezolizumab Bevacizumab	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not Applicable	**Study Intervention Assignment Method:**	Randomization and stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 662

STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are atezolizumab and bevacizumab. Atezolizumab will be administered 1200 mg IV every 21 days and bevacizumab will be administered 15mg/kg IV every 21 days. No dose modification for atezolizumab or bevacizumab is allowed.

DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to range from 1 day up to approximately 91 months.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee
Other Committees:	Not Applicable

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
ADA	anti-drug antibody
AFP	α-fetoprotein
ATE	arterial thromboembolic event
BP	blood pressure
CHF	congestive heart failure
COVID-19	coronavirus disease 2019
CR	complete response
CRS	cytokine release syndrome
CT	computed tomography
ctDNA	circulating-tumor DNA
EASL	European Association for the Study of the Liver
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EHS	extrahepatic spread
EORTC	European Organisation for the Research and Treatment of Cancer
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GHS	global health status
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HGRAC	Human Genetic Resources Administration of China
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IFN	interferon

Abbreviation	Definition
IL	interleukin
IL42	item list 42
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRF	Independent Review Facility
IRR	infusion-related reaction
ITT	intent-to-treat (population)
IxRS	interactive voice or web-based response system
LMWH	low-molecular-weight heparin
MAS	macrophage activation syndrome
MDD	minimum detectable difference
MRI	magnetic resonance imaging
MWA	microwave ablation
NAFLD	non-alcoholic fatty liver disease
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NED	no evidence of disease
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
Q3W	every 3 weeks
QoL	quality of life
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	radiofrequency ablation
RFS	recurrence-free survival
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TACE	transarterial chemoembolization
TNF-α	tumor necrosis factor-α
TTR	time to recurrence

Abbreviation	Definition
ULN	upper limit of normal
VAS	Visual Analog Scale
VEGF	vascular endothelial growth factor
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON HEPATOCELLULAR CARCINOMA

1.1.1 Epidemiology and Disease Burden

Liver cancer is the fifth most common cancer, accounting for 7% of all cancers, and the second most frequent cause of cancer-related death globally, with 854,000 new cases and 810,000 deaths per year. Hepatocellular carcinoma (HCC) represents approximately 90% of primary liver cancers and thus represents a significant global public health issue. On the basis of annual projections, the World Health Organization estimates that in excess of 1 million people will die from liver cancer in 2030 (Villanueva 2019).

The majority of HCCs occur in patients with underlying liver disease, mostly as a result of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or alcohol abuse. HBV infection accounts for the majority of HCC cases worldwide; however, in Western countries and Japan, HCV is the main cause of HCC (Villanueva 2019). Universal HBV vaccination and wide implementation of direct-acting antiviral agents against HCV are likely to change the etiologic landscape of HCC. However, the incidence of non-alcoholic fatty liver disease (NAFLD), which is a risk factor for HCC, is increasing worldwide and NAFLD will soon become a leading cause of liver cancer in Western countries (Villanueva 2019).

1.1.2 Unmet Need in Patients following Resection or Ablation

There are several potentially curative approaches to the treatment of HCC, including surgical resection and ablation.

Liver resection provides an opportunity for long-term, cancer-free survival and represents the primary curative treatment option for patients with HCC deemed to be surgical candidates. Eligibility for curative resection is typically based on disease stage as well as assessment of functional liver reserve; however, the concept of "resectability" varies significantly depending on local clinical practice and guidelines. Notably, eligibility criteria for curative resection are more aggressive in many Asian guidelines, including patients with minor vascular invasion of the portal vein, compared to Western treatment guidelines.

Local ablative strategies such as radiofrequency ablation (RFA) and microwave ablation (MWA) are potentially curative options typically offered to patients with very early or early stage HCC who are not candidates for resection (Villanueva 2019). As compared with resection, ablation has fewer complications but provides worse local control for larger tumors (Villanueva 2019).

Tumor recurrence is a major post-procedural complication associated with both resection and ablation, with 50% to 70% of patients experiencing recurrence by 5 years (Villanueva 2019). The risk of HCC recurrence after curative intervention is primarily

related to tumor burden (the number and size of tumors) and pathologic characteristics or the tumor such as degree of differentiation and the presence of vascular invasion (either microvascular or macrovascular).

For patients harboring one or more of these high risk features (tumor size, tumor number, vascular invasion, and poorly differentiated tumor), the prognosis following curative intervention is poor. In one study, 5-year disease-free survival rates following resection were 26% in patients with large/multinodular HCC and 18% in patients with macrovascular invasion (Zhong et al. 2015). Five-year survival rates were 42% in patients with large/multinodular HCC and 18% in patients with macrovascular invasion. In a retrospective analysis, 5-year recurrence-free survival (RFS) rates following resection were 13% versus 34% in patients with and without microvascular invasion, respectively (Shen et al. 2018). In addition, histologic tumor grade has been shown to influence survival after resection, with patients harboring poorly differentiated tumors having a worse prognosis compared with patients with moderately or well-differentiated tumors (Pawlik et al. 2005; Martins-Filho et al. 2017). For patients with high risk disease, effective and well-tolerated adjuvant therapies are needed in order to prevent disease recurrence and to increase cure rates.

1.2 ADJUVANT TREATMENT FOR HEPATOCELLULAR CARCINOMA

Most treatment guidelines do not recommend adjuvant treatment after resection or ablation for HCC because to date no adjuvant treatment has been proven effective in randomized studies (EASL 2018; Heimbach et al. 2018). Strategies tested in the adjuvant setting have included interferon (IFN), vitamin K2, retinoids, systemic chemotherapy, heparanase inhibitors, multikinase inhibitors, and adoptive immunotherapy.

In a randomized, double-blind, placebo-controlled, Phase III trial of sorafenib versus placebo as adjuvant therapy after curative resection or ablation of HCC, there was no statistically significant difference between the groups in median RFS (33.3 months in the sorafenib group vs. 33.7 months in the placebo group; hazard ratio [HR] = 0.94; 95% CI: 0.78 to 1.13; p = 0.26; Bruix et al. 2015).

Chinese HCC treatment guidelines recommend the use of adjuvant transarterial chemoembolization (TACE) for high risk cases following resection (Zhou et al. 2017). This recommendation is based on multiple retrospective studies, randomized trials, and meta-analyses that have reported that administration of adjuvant TACE following curative resection can improve time to recurrence and survival (Wang et al. 2018; Wei et al. 2018). However, most of these studies have been single-center trials conducted in China in patients with predominantly HBV etiology.

A multicenter Phase IV study conducted in China found significant prolongation of RFS in patients receiving Huaier granule, a traditional Chinese medicine, as adjuvant therapy

after surgical resection of HCC (Chen et al. 2018). Although not formally recommended in Chinese guidelines (Zhou et al. 2018), use of such medicines following HCC resection is not uncommon in China.

1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved in approximately 90 countries for one or more of the following indications: urothelial carcinoma, non–small cell lung cancer (NSCLC), extensive-stage small-cell lung cancer, melanoma and triple-negative breast cancer. In May 2020, atezolizumab in combination with bevacizumab was approved by the U.S. Food and Drug Administration (FDA) for the treatment of unresectable or metastatic HCC in patients who have not received prior systemic therapy.

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

1.4 BACKGROUND ON BEVACIZUMAB

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in in vitro and in vivo assay systems.

Bevacizumab was first granted marketing approval in the United States on 26 February 2004 in combination with IV 5-fluorouracil–based chemotherapy for the first-line treatment of patients with metastatic carcinoma of the colon or rectum. Bevacizumab is approved in over 100 countries for one or more of the following indications: breast cancer, NSCLC, renal cell cancer, glioblastoma multiforme, cervical cancer, epithelial ovarian cancer, primary peritoneal cancer, and fallopian tube cancer. In May 2020, bevacizumab in combination with atezolizumab was approved by the US FDA for the treatment of unresectable or metastatic HCC in patients who have not received prior systemic therapy.

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

1.5 CLINICAL STUDIES OF ATEZOLIZUMAB PLUS BEVACIZUMAB IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

The efficacy and safety of atezolizumab plus bevacizumab combination therapy as first-line treatment of non-resectable or metastatic HCC is currently being assessed in two studies: GO30140 and YO40245 (IMbrave150).

1.5.1 Study GO30140

Study GO30140 is a Phase Ib, multicenter, open-label study of atezolizumab in combination with bevacizumab and/or chemotherapy as first-line therapy in patients with various metastatic cancers (Lee et al. 2020). Arms A and F of Study GO30140 were specific to unresectable or advanced HCC. Arm A was designed to evaluate the combination of atezolizumab plus bevacizumab in 104 patients with locally advanced or metastatic HCC who have not received prior systemic therapy. Arm F was later added to the study to compare combination treatment with atezolizumab plus bevacizumab to atezolizumab alone, in which 119 patients with locally advanced or metastatic HCC were randomized 1:1 to atezolizumab plus bevacizumab or atezolizumab monotherapy. Results for Arm A and Arm F have been recently presented (Lee et al. 2019).

Arm A

As of the clinical cutoff date of 14 June 2019, the efficacy data for Arm A showed clinically meaningful and durable objective responses. The confirmed objective response rate (ORR) based on Independent Review Facility (IRF) assessment per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 was 35.6% (37 of 104 patients; Table 1). Among the 37 responders, 12 patients (11.5%) achieved a complete response (CR) and the remaining 25 patients (24.0%) achieved a partial response (PR). Median duration of response was not reached at the time of this analysis.

Arm F

At the same clinical cutoff date of 14 June 2019, Arm F met its primary efficacy endpoint by demonstrating a statistically significant and clinically meaningful improvement in progression-free survival (PFS) with the combination compared to atezolizumab monotherapy. Median PFS for the combination was 5.6 months compared to 3.4 months for the monotherapy resulting in a HR of 0.55 and a stratified p-value of 0.0108 (Table 1). These results demonstrate the need for combination therapy rather than checkpoint inhibition alone to effectively increase progression free survival in patients with HCC.

Table 1 Study GO30140: Overall Efficacy Summary

Arm	Median Duration of Follow-Up	Key Efficacy Endpoint
Arm A	12.4 m	ORR (95% CI): 35.6% (26.4–45.6%) Median DOR: Not reached with 76% ongoing responders
Arm F	6.6 m	Median PFS: 5.6 m (Atezo + Bev) vs. 3.4 m (Atezo) Stratified HR (80% CI): 0.55 (0.40–0.74) Stratified p-value: 0.0108

Atezo = atezolizumab; Bev = bevacizumab; DOR = duration of response; HR = hazard ratio; m = month; ORR = objective response rate; PFS = progression-free survival.

The combination of atezolizumab plus bevacizumab was generally well tolerated; no new safety signals related to the combination therapy were identified beyond the established safety profile for each individual agent. Furthermore, no unexpected adverse events were observed. The most common adverse events were proteinuria, decreased appetite, fatigue, pyrexia, and rash.

1.5.2 Study YO40245

Study YO40245 (IMbrave150) is a Phase III, multicenter, randomized, open-label study designed to evaluate the efficacy and safety of atezolizumab plus bevacizumab versus sorafenib in patients with advanced or metastatic HCC who have received no prior systemic treatment (Cheng et al. 2019; Finn et al. 2020). The study enrolled 501 patients randomized in a 2:1 ratio to one of the following treatment arms:

- Arm A (experimental arm): atezolizumab 1200 mg IV every 3 weeks (Q3W) + bevacizumab 15 mg/kg IV Q3W (336 patients)
- Arm B (control arm): sorafenib 400 mg by mouth, twice per day, continuously (165 patients)

The co-primary efficacy endpoints were overall survival (OS) and IRF-assessed PFS by RECIST v1.1.

The last patient was enrolled in April 2019. Based on a clinical cutoff date of 29 August 2019, the primary analysis of Study YO40245 demonstrated statistically significant and clinically meaningful improvements with atezolizumab plus bevacizumab compared with sorafenib in the co-primary endpoints of OS and IRF-assessed PFS per RECIST v1.1 in the intent-to-treat (ITT) population (Table 2).

- The co-primary endpoint of OS demonstrated a statistically significant and clinically meaningful improvement for atezolizumab plus bevacizumab over sorafenib. The observed OS translated into a reduction in the risk of death by 42% in the atezolizumab plus bevacizumab arm compared with sorafenib (HR = 0.58 [95% CI: 0.42 to 0.79], p = 0.0006, median OS: NE vs. 13.24 months).

  OS benefits were generally consistent across predefined subgroups.

- The co-primary endpoint of IRF-assessed PFS per RECIST v1.1 demonstrated a statistically significant and clinically meaningful improvement for atezolizumab plus bevacizumab over sorafenib (HR = 0.59 [95% CI: 0.47 to 0.76]; p < 0.0001; median PFS: 6.83 vs. 4.27 months).

  These PFS benefits were generally consistent across predefined subgroups.

Similar to Study GO30140, the safety of the combination was consistent with the known safety profile of each agent and no new safety signals were identified.

Table 2 Study YO40245: Overall Efficacy Summary

Co-Primary Efficacy Endpoints	Median Duration of Follow-Up		Sorafenib (n = 165)	Atezo+Bev (n = 336)
OS	8.6 months	Median (months) (95% CI)	13.2 (10.4, NE)	NE
		Stratified HR (95% CI)	0.58 (0.42, 0.79)	
		Stratified log rank p-value	0.0006	
IRF-PFS	8.6 months	Median (months) (95% CI)	4.3 (4.0, 5.6)	6.8 (5.7, 8.3)
		Stratified HR (95% CI)	0.59 (0.47, 076)	
		Stratified log rank p-value	<0.0001	

Atezo = atezolizumab; Bev = bevacizumab; HR = hazard ratio; IRF = Independent Review Facility; NE = not estimable; OS = overall survival; PFS = progression-free survival.

1.6 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Multiple lines of evidence suggest that immune-based therapies may be beneficial in patients with resected or ablated HCC. The PD-L1/PD-1 inhibitors have demonstrated clinical benefit across a wide range of cancer types, including HCC. Although the majority of studies with these agents have been conducted in patients with advanced unresectable disease, data from studies in resected Stage III melanoma and Stage III NSCLC following definitive chemoradiation have shown that PD-1/PD-L1 blockade may be effective in the adjuvant setting (Antonia et al. 2017; Weber et al. 2017; Eggermont et al. 2018).

Despite the clinical benefit associated with PD-1/PD-L1 blockade, patients who experience durable response and/or survival remain only a subset of those treated. One likely reason for this finding is that human cancer can utilize multiple immune inhibitory mechanisms, leading to primary or secondary immune escape. One such mechanism relates to VEGF. In addition to its role in angiogenesis, the VEGF pathway is thought to play a crucial role in exerting and maintaining an immunosuppressive tumor microenvironment through several mechanisms, including downregulating T-cell activation via inhibition of dendritic cell maturation, reducing T-cell tumor infiltration; and increasing inhibitory cells in the tumor microenvironment (e.g., regulatory T cells and myeloid-derived suppressor cells). The cellular underpinnings of these immune suppressive mechanisms have been recently reviewed in depth (Chen and Hurwitz 2018).

The majority of HCC tumors are non-inflamed tumors with immune cells present solely in the periphery or with limited or no infiltration of immune cells (Sia et al. 2017; Okrah et al. 2018; Gabrielson et al. 2016; unpublished data from the Sponsor). Non-inflamed tumors are not as responsive to single-agent immune checkpoint inhibition compared with inflamed tumors (Chen and Mellman 2017). Therefore, combination approaches may be needed to address these inherent immune deficits. Treatment with combined PD-L1 and VEGF antagonism may overcome deficits in immune infiltration and myeloid-induced immune suppression and therefore represent a more effective treatment approach versus single-agent PD-L1 inhibition (Chen and Hurwitz 2018).

Atezolizumab has been combined with bevacizumab in patients with a range of different tumor types in Phase I-III studies. Overall, the adverse events observed with atezolizumab in combination with bevacizumab are consistent with the known risks of each individual study treatment across tumor types including HCC (Socinski et al. 2018; Rini et al. 2019).

This trial will enroll patients with high risk HCC who have been definitively treated with resection or local ablation. Given the poor prognosis and limited treatment options for these patients, this population is considered appropriate for trials of novel therapeutic candidates in the adjuvant setting. The benefit–risk profile for atezolizumab in combination with bevacizumab in this patient population is expected to be favorable.

Covid-19 Benefit–Risk Assessment

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy, impact the incidence or severity of SARS-CoV-2 infection.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy.

Severe SARS-CoV-2 infection appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from SARS-CoV-2 infection.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab treatment to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential

complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

The SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4.1).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of adjuvant therapy with atezolizumab plus bevacizumab compared with active surveillance in patients with completely resected or ablated HCC who are at high risk for disease recurrence. Patients randomized to the active surveillance arm who recur during the active surveillance period or during the follow-up period may cross over to treatment with atezolizumab plus bevacizumab (see Section 3.1). Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., atezolizumab and bevacizumab).

Table 3 Objectives and Corresponding Endpoints

Primary Efficacy Objective (Primary Objective)	Corresponding Endpoint
• To evaluate the efficacy of atezolizumab plus bevacizumab compared with active surveillance	• RFS after randomization, defined as the time from randomization to the first documented occurrence of intrahepatic or extrahepatic HCC as determined by an IRF, or death from any cause (whichever occurs first)
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of atezolizumab plus bevacizumab compared with active surveillance	• OS after randomization, defined as the time from randomization to death from any cause • RFS after randomization as determined by the investigator • TTR after randomization, defined as the time from randomization to first documented occurrence of intrahepatic or extrahepatic HCC, as determined by the investigator and by an IRF • IRF-assessed RFS and investigator-assessed RFS rate at 24 months and 36 months after randomization • OS rate at 24 months and 36 months, defined as the proportion of patients who have not experienced death from any cause at 24 and 36 months after randomization, respectively • Time to EHS or macrovascular invasion after randomization, defined as the time from randomization to the first appearance of EHS or macrovascular invasion, as determined by the investigator • RFS after randomization as determined by the investigator and by an IRF, among patients in the PD-L1–high subgroup

Table 3 Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of atezolizumab plus bevacizumab compared with active surveillance	• Change from baseline in physical functioning, emotional functioning, role functioning, social functioning, and global health status/quality of life scores as assessed by the IL42–EORTC QLQ-C30 (Reduced) at specified timepoints (including post-treatment (Arm A) or surveillance (Arm B) and post-recurrence) • OS among patients in the PD-L1–high subgroup • For patients randomized to active surveillance who recur and cross over to treatment with atezolizumab plus bevacizumab and have NED at the time of crossover: – RFS after first HCC recurrence, defined as the time first exposure to any dose of crossover treatment to the second documented HCC recurrence as determined by the investigator, or death from any cause (whichever occurs first). HCC recurrence is defined as occurrence of intrahepatic or extrahepatic HCC. • For patients randomized to active surveillance who recur and cross over to treatment with atezolizumab plus bevacizumab and who have measurable disease at the time of crossover: – PFS after first HCC recurrence, defined as the time from first exposure to any dose of crossover treatment to the first documented occurrence of disease progression beyond the initial unresectable disease recurrence as determined by the investigator according to RECIST v1.1 or death from any cause (whichever occurs first), – ORR, defined as the proportion of patients with a complete or partial response, as determined by the investigator according to RECIST v1.1
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of atezolizumab plus bevacizumab compared with active surveillance	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK profile of atezolizumab when given in combination with bevacizumab	• Serum concentration of atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to atezolizumab	• Prevalence of ADAs to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study

Table 3 Objectives and Corresponding Endpoints (cont.)

Exploratory Immunogenicity Objective	Corresponding Endpoint
• To evaluate potential effects of ADAs	• Relationship between treatment-emergent ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To identify and/or evaluate biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to study treatment, can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	• Relationship between biomarkers in blood, serum, plasma, and tumor tissue (see Section 4.5.6) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
Exploratory Health Status Utility Objective	**Corresponding Endpoint**
• To evaluate health status utility scores of patients treated with atezolizumab plus bevacizumab compared with active surveillance	• Change from baseline in EQ-5D-5L index-based and VAS scores at specified timepoints (including post-treatment (Arm A) or surveillance (Arm B) and post-recurrence)

ADA = anti-drug antibody; EHS = extrahepatic spread; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; HCC=hepatocellular carcinoma; IL42–EORTC QLQ-C30 (Reduced) = IL42–European Organisation for Research and Treatment of Cancer QLQ-C30 (Reduced); IRF = Independent Review Facility; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NED = no evidence of disease; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; RFS = recurrence-free survival; TTR = time to recurrence; VAS = visual analog scale.

3. STUDY DESIGN

3.1 OVERVIEW OF STUDY DESIGN

This is a Phase III, global, multicenter, open-label, two-arm, randomized study designed to evaluate the efficacy and safety of adjuvant therapy with atezolizumab plus bevacizumab compared with active surveillance in patients with completely resected or ablated HCC who are at high risk for disease recurrence.

Patients who have undergone surgical resection may have received 1 cycle of adjuvant TACE prior to study entry (randomization), if deemed appropriate by the investigator and if consistent with local standards of care (see Section 4.1.1 for details).

The definition of high risk is based on composite criteria including size of the largest tumor, number of tumors, and presence of either microvascular invasion (defined as the presence of microscopic tumor emboli within the central vein, the portal vein, or large capsular vessels), minor macrovascular invasion of the portal vein (Vp1 or Vp2, see Appendix 5), or poorly differentiated microscopic appearance (histologic Grade 3 or 4). The criteria for high risk of HCC recurrence used in this study are presented by type of curative treatment in Table 4. In the event that the pathology and the pre-curative procedure radiology report are discordant with regards to tumor size and number, the modality demonstrating the largest tumor size and number should be used to determine eligibility. Pathological findings should be used to assess microvascular invasion and/or poor tumor differentiation. If macrovascular invasion of Vp1 or Vp2 is detected on either the pre-operative computed tomography (CT)/magnetic resonance imaging (MRI) scan or the pathology report, this should be a high risk feature.

Table 4 High Risk Criteria for This Study

Curative Treatment	Criteria for High Risk of HCC Recurrence
Resection	• Up to three tumors, with largest tumor > 5 cm regardless of vascular invasion (microvascular invasion or minor macrovascular portal vein invasion of the portal vein —Vp1/Vp2), or poor tumor differentiation (Grade 3 or 4) [a] • Four or more tumors, with largest tumor ≤ 5 cm regardless of vascular invasion (microvascular invasion or minor macrovascular invasion of the portal vein—Vp1/Vp2), or poor tumor differentiation (Grade 3 or 4) [a] • Up to three tumors, with largest tumor ≤ 5 cm with vascular invasion (microvascular invasion or minor macrovascular invasion of the portal vein—Vp1/Vp2), and/or poor tumor differentiation (Grade 3 or 4) [a]
Ablation [b]	• Single tumor > 2 cm but ≤ 5 cm • Multiple tumors (up to four tumors), all ≤ 5 cm

HCC = hepatocellular carcinoma; MWA = microwave ablation; RFA = radiofrequency ablation.

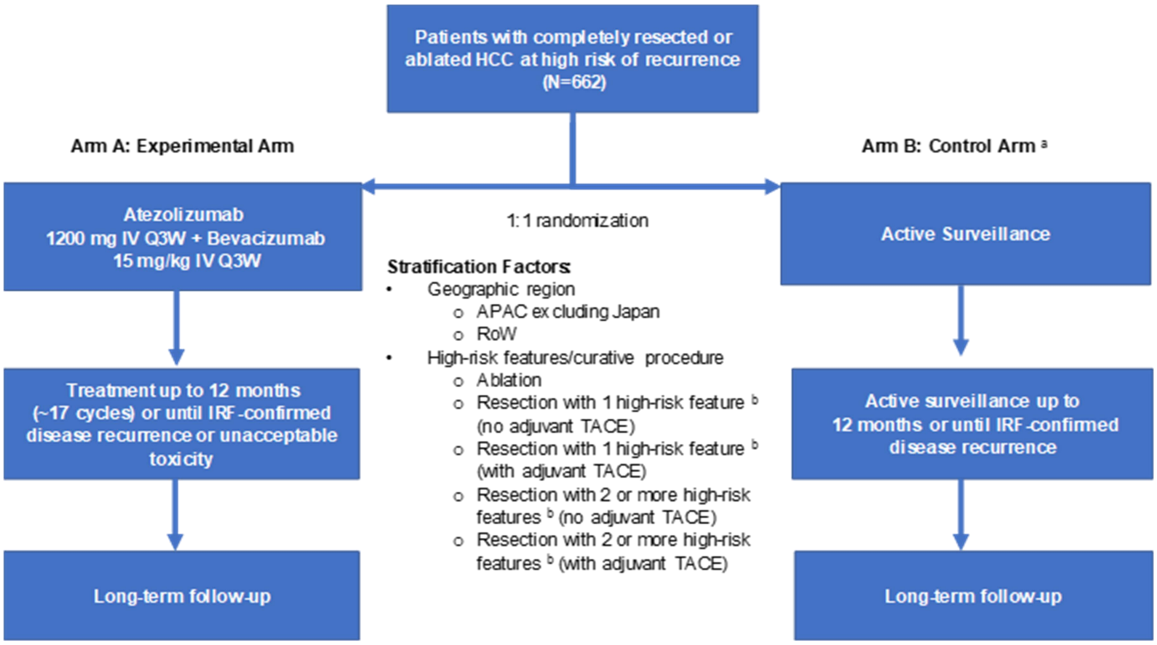
[a] In cases where a patient has evidence of mixed tumor differentiation, the worst differentiation status rather than the predominant differentiation status should be used to characterize high risk criteria.

[b] Ablation must be RFA or MWA.

An overview of the study design is shown in Figure 1. A schedule of activities is provided in Appendix 1, and a schedule of activities specifically for patients in the active surveillance arm that cross over to atezolizumab plus bevacizumab following recurrence is provided in Appendix 2. A schedule for collection of pharmacokinetic (PK), anti-drug antibody (ADA), and biomarker samples is provided in Appendix 3. Samples for PK, ADA, and biomarker analyses will not be collected from patients in the active

surveillance arm who cross over to treatment with atezolizumab plus bevacizumab following recurrence.

Figure 1 Study Schema



APAC = Asia Pacific; HCC = hepatocellular carcinoma; IRF = Independent Review Facility; Q3W = every 3 weeks; ROW = rest of world; TACE = transarterial chemoembolization.

[a] Patients who are enrolled in Arm B who have documented recurrence during the active surveillance period or during follow-up and meet the criteria outlined in Section 4.1.1.1 will have the option to cross over to treatment with atezolizumab 1200 mg Q3W plus bevacizumab 15 mg/kg Q3W.

[b] Risk features for resection include tumor size >5 cm, tumor number >3, vascular invasion (microvascular invasion or macrovascular invasion—Vp1/Vp2—of the portal vein, see Appendix 5), and poor tumor differentiation (defined as Grade 3 or 4).

This study will enroll approximately 662 patients across approximately 175 sites in the United States, Europe, and Asia Pacific (including China) in a global enrollment phase. After completion of the global enrollment phase, additional patients may be enrolled in China in an extended China enrollment phase to ensure a minimum of approximately 250 patients in a China subpopulation. The global population will include all patients enrolled during the global enrollment phase (including patients enrolled at sites in China during that phase), and the China subpopulation will include all patients enrolled at sites in China (i.e., during both the global enrollment phase and the extended China enrollment phase).

Patients who withdraw from the study will not be replaced. If necessary, the Sponsor may choose to limit the number of patients with specific curative treatment procedures (resection or ablation). In the event that this cap is implemented, sites will be notified with a letter.

Patients who fail their first screening for study eligibility may qualify for one re-screening opportunity (for a maximum of two screenings per patient) at the investigator's discretion. The investigator will maintain a record of reasons for screen failure (see Section 4.5.1).

Eligible patients will be randomized within 4−12 weeks of surgical resection or ablation (only RFA or MWA) in a 1:1 ratio to one of the following two arms:

- Arm A (experimental arm): atezolizumab 1200 mg and bevacizumab 15 mg/kg, both administered by IV infusion on Day 1 of each 21-day cycle
- Arm B (control arm): active surveillance

Randomization will be stratified according to the following stratification factors:

- Geographic region
  - Asia Pacific excluding Japan
  - Rest of World
- High risk features/curative procedure
  - Ablation
  - Resection with 1 high risk feature (no adjuvant TACE)
  - Resection with 1 high risk feature (with adjuvant TACE)
  - Resection with 2 or more high risk features (no adjuvant TACE)
  - Resection with 2 or more high risk features (with adjuvant TACE)

  Risk features for resection include tumor size > 5 cm, tumor number > 3, vascular invasion (microvascular invasion or macrovascular invasion—Vp1/Vp2—of the portal vein, see Appendix 5), and poor tumor differentiation (defined as Grade 3 or 4)

Treatment with atezolizumab plus bevacizumab or active surveillance will continue for up to 12 months (or 17 cycles, whichever occurs first) or until IRF-confirmed disease recurrence or unacceptable toxicity (for patients receiving atezolizumab + bevacizumab), whichever occurs first. Patients may continue treatment beyond 12 months due to delayed or missed visits if deemed in the best interest of the patient by the investigator. After 12 months (or 17 cycles, whichever occurs first), information on recurrence, survival, and subsequent anti-cancer therapies will be collected every 12 weeks until death (unless the patient withdraws consent or the Sponsor terminates the study).

Patients randomized to Arm A who transiently withhold or permanently discontinue bevacizumab for adverse events may continue on single-agent atezolizumab as long as they have not met the criteria for HCC recurrence. If atezolizumab is discontinued, bevacizumab should also be discontinued. If atezolizumab is transiently withheld for adverse events, bevacizumab should also be held.

Patients will undergo imaging assessments at scheduled intervals during the study (see Section 4.5.5 and Appendix 1 for details).

Patients are required to undergo tumor biopsy sample collection at the time of radiographic confirmation of disease recurrence unless not clinically feasible as assessed and documented by the investigator to evaluate tumor tissue biomarkers related to mechanisms of acquired resistance and disease recurrence and clinical benefit of atezolizumab plus bevacizumab. Examples of when tumor biopsy sample collection may be considered not clinically feasible include, but are not limited to, cases where the location of the tumor renders tumor biopsy unsafe or not clinically feasible per the investigator due to patient concerns or is prohibited by the institution or country.

Treatment with Atezolizumab plus Bevacizumab following Recurrence for Patients in Arm B

Patients randomized to Arm B who experience documented IRF-assessed HCC recurrence per protocol-defined criteria (see Section 4.5.5) either during the 12-month active surveillance period or during long-term follow-up and meet all eligibility criteria (see Section 4.1.1.1) will be offered the option of crossing over to treatment with atezolizumab 1200 mg IV and bevacizumab 15 mg/kg IV on Day 1 of each 21-day cycle. Patients can cross over directly after the first recurrence or after resection or ablation for the first recurrence (resulting in no evidence of disease [NED]). Patients undergoing resection are allowed to have 1 cycle of adjuvant TACE prior to crossover, if deemed appropriate by the investigator and if consistent with local standards of care (see Section 4.1.1 for details). Day 1 of Cycle 1 of crossover treatment must be no later than 12 weeks after documentation of recurrence. Results of tests or examinations performed for crossover and per the relevant protocol-defined window may be used for screening assessments rather than repeating such tests.

Patients who cross over to treatment with atezolizumab plus bevacizumab may continue study treatment until unacceptable toxicity or second disease recurrence (for patients with NED at the time of crossover), or 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 (e.g., symptomatic deterioration such as pain secondary to disease) (for patients with measurable disease at crossover). In the absence of unacceptable toxicity, patients with measurable disease at crossover who meet criteria for disease progression per RECIST v1.1 while receiving atezolizumab and bevacizumab or atezolizumab alone will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease

- Absence of decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Patients who transiently withhold or permanently discontinue bevacizumab for adverse events may continue on single-agent atezolizumab as long as they have not met the criteria for HCC recurrence (for patients with NED at crossover) or are experiencing clinical benefit in the opinion of the investigator (for patients with measurable disease at crossover). If atezolizumab is discontinued, bevacizumab should also be discontinued. If atezolizumab is transiently withheld for adverse events, bevacizumab should also be held.

Patients who cross over will undergo imaging assessments at scheduled intervals during the study (see Section 4.5.5 and Appendix 2 for details).

3.1.1 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will evaluate safety and efficacy data during the study. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC roles and responsibilities.

Unblinded safety data will be reviewed on a periodic basis, approximately every 6 months from the time of enrollment of the first patient. Unblinded efficacy data will be reviewed as part of the interim analysis of IRF-assessed RFS, scheduled to occur when approximately 236 RFS events have occurred (see Section 6.10). All summaries and analyses for the iDMC review will be prepared by an independent Data Coordinating Center.

After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC Charter. Final decisions will rest with the Sponsor.

Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards or Ethics Committees (IRBs/ECs).

3.1.2 Independent Review Facility

An IRF will be used to enable centralized, independent reviews of images and other clinical data (e.g., histopathology, tumor markers etc.) used for assessment of HCC recurrence. The IRF reviews will be performed prior to the pre-specified efficacy analyses. The IRF membership and procedures will be detailed in an IRF Charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when approximately 319 OS events have been observed for the final analysis of OS in the ITT population.

In addition, the Sponsor may decide to terminate the study at any time. The total length of the study, from randomization of the first patient to the end of the study, is projected to be approximately 91 months.

3.3 *DURATION OF PARTICIPATION*

The total duration of study participation for each individual is expected to range from 1 day up to approximately 91 months.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is an 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 dose-limiting toxicities 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 PK, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

3.4.2 Rationale for Bevacizumab Dose and Schedule

Bevacizumab will be administered at a dose of 15 mg/kg Q3W (15 mg/kg on Day 1 of each 21-day cycle), which is the approved dosage for bevacizumab (Avastin® U.S. Package Insert). This dose schedule aligns with the atezolizumab dose schedule highlighted above and is the dose used in combination with atezolizumab in Study GO30140. In that study, the combination of atezolizumab plus bevacizumab was generally safe and well tolerated and no new safety signals related to the combination therapy were identified beyond the established safety profile for each individual agent.

3.4.3 Rationale for Patient Population

The target population has been chosen to address patients with HCC who have a high risk of disease recurrence following curative resection or ablation.

The risk of HCC recurrence after curative intervention is primarily related to tumor characteristics at the time of surgery or ablation, such as size, number, degree of differentiation, and the presence of vascular invasion. The prevalence of these high risk factors is highly interrelated. In general, larger tumors (>5 cm) or multiple tumors are more likely to exhibit vascular invasion than single small lesions (Pawlik et al. 2005).

For patients harboring one or more of these high risk features, the prognosis following curative intervention with surgery or ablation is particularly poor (see Section 1.1.2). For these high risk patients, effective and well-tolerated adjuvant therapies are needed in order to prevent disease recurrence and to increase cure rates.

There are no preexisting criteria to define high risk patients for adjuvant trials because available HCC staging criteria (i.e., Barcelona Clinic Liver Cancer and Hong Kong Liver Cancer) do not include all key risk factors for HCC recurrence and there are no validated tools for risk stratification in HCC that can be incorporated into clinical trials. Multiple and co-existing risk factors are involved in determining prognosis following curative treatment and because no single factor is powerful enough to independently predict outcomes, composite criteria integrating key variables are required in order to identify patients at high risk of recurrence.

3.4.4 Rationale for the Active Surveillance Control Arm (Arm B)

There is no standard adjuvant treatment after resection or ablation for HCC. For the most part, treatment guidelines do not recommend adjuvant therapy for HCC because to date no treatment has been proven effective in randomized studies after potentially curative treatment (EASL 2018; Heimbach et al. 2018).

Active surveillance with imaging (with or without α-fetoprotein [AFP]) following resection or ablation is currently the standard of care represented in treatment guidelines (European Association for the Study of the Liver [EASL] 2018; Heimbach et al, 2018). The EASL and American Association for the Study of Liver Diseases (AASLD) guidelines recommend screening with imaging with or without AFP every 3–6 months following surgery.

This study will employ an open-label, rather than double-blind placebo-controlled, study design because of ethical concerns and the burden of giving mock IV infusions Q3W for up to 1 year to patients in Arm B.

3.4.5 Rationale for Crossover from Active Surveillance to Treatment with Atezolizumab plus Bevacizumab

Patients randomized to Arm B will be offered the chance to cross over to treatment with atezolizumab plus bevacizumab upon documented IRF-confirmed recurrence if deemed clinically appropriate by the investigator, to both allow access to atezolizumab and bevacizumab and to derive additional data on the combination in the recurrent HCC setting.

3.4.6 Rationale for Recurrence-Free Survival as Primary Endpoint

Treatment benefit will be measured in this trial using RFS as the primary efficacy endpoint. The RFS is an endpoint that quantifies clinically meaningful benefit to patients with HCC and is recommended by HCC experts as a primary endpoint for adjuvant studies (EASL 2018). Further, RFS, unlike OS, would not be confounded by potential use of subsequent treatments in the recurrence and metastatic settings.

3.4.7 Rationale for Choice of Randomization Stratification Factors

To balance the clinical risk factors between the two study arms, randomization will be stratified using a permuted-block randomization scheme. The stratification factors are as follows:

- Geographic region
  - Asia Pacific excluding Japan
  - Rest of World
- High risk features/curative procedure
  - Ablation
  - Resection with 1 high risk feature (no adjuvant TACE)
  - Resection with 1 high risk feature (with adjuvant TACE)
  - Resection with 2 or more high risk features (no adjuvant TACE)
  - Resection with 2 or more high risk features (with adjuvant TACE)
- Risk features for resection include tumor size > 5 cm, tumor number > 3, vascular invasion (microvascular invasion or macrovascular invasion—Vp1/Vp2—of the portal vein, see Appendix 5), and poor tumor differentiation (defined as Grade 3 or 4)

The reasons for using these factors are provided below.

Geographic Region

Although HCC is a global disease, there is significant geographic heterogeneity in terms of treatment outcomes. Differences in outcome may be attributed to several potential causes that include regional differences in disease etiology and clinical practice patterns. The geographic distribution of HCC reflects the distribution of HBV and HCV, which currently are the two major etiologic risk factors worldwide. The majority of cases of HCC worldwide are caused by HBV, which is endemic in Africa and East Asia except Japan. HCV is the most common cause of HCC in Japan, most of Europe, and the United States. Other non-viral causes of cirrhosis are more prevalent in Japan and the West compared with Asia. Based on the close association between geography and HCC etiology, geographic region represents a reasonable surrogate for disease etiology. Several studies have reported that patients with HCC arising in the context of HBV or HCV infections have different characteristics and outcomes (Omata et al. 2017). With respect to long-term surgical outcomes, several studies have reported that HCV infection was associated with worse oncological outcomes compared with HBV infection. For example, Sasaki et al. (2017) reported that HCV-related HCC had a higher cumulative recurrence rate compared with HBV-related HCC, with HCV infection representing an independent predictor of recurrence even after accounting for potential

confounders. A similar association between outcomes and viral etiology has been noted for patients treated with ablation (Huang et al. 2011).

High Risk Features/Curative Procedure

Three different components contribute to this stratification factor including curative procedure, number of risk factors, and adjuvant TACE.

Ablation is considered a high risk factor because available data indicate that liver resection is typically associated with better outcomes compared with ablation in patients with HCC (Gravante et al. 2011). Although no randomized trials are available comparing outcomes using the high risk criteria in this study, a large retrospective analysis ($n = 1061$) reported that resection was superior to ablation with respect to both RFS and OS in patients with HCC who have either single tumors > 3 cm but < 5 cm or 2–3 tumors each < 5 cm (Huang et al. 2011).

Resected patients, can have multiple risk factors that are outlined in Section 3.1. The impact of harboring high risk clinicopathologic features on risk of recurrence is summarized in Section 3.4.3. While the presence of a single high risk feature confers a negative impact on prognosis, the presence of multiple risk factors imposes significant additional risk (Pawlik et al. 2005; Noh et al. 2016).

The study will allow resected patients to have undergone 1 cycle of post-operative TACE prior to study entry (randomization; see Section 4.1.1). Given the potential positive impact of adjuvant TACE on RFS following resection (Wang et al. 2018; Wei et al. 2018), use of adjuvant TACE will contribute to the stratification factor High Risk Features/Curative Procedure for randomization.

3.4.8 Rationale for Biomarker Assessments

The PD-L1 expression in tumor tissues has been shown to be correlated with the clinical benefits from anti–PD-1 and anti–PD-L1 therapy across many tumor indications (Topalian et al. 2012; Herbst et al. 2014, 2016; Borghaei et al. 2015; Fehrenbacher et al. 2016; Rosenberg et al. 2016). Emerging data from published HCC studies (El-Khoueiry 2017; Zhu et al. 2018) and preliminary findings from the Sponsor's study of first-line treatment in patients with HCC (Study GO30140; unpublished observations) also suggest that PD-L1 expression may be correlated with the clinical benefits from anti–PD-L1/PD-1 agents. A more comprehensive analysis of the association between PD-L1 expression and clinical outcomes will be conducted in the upcoming clinical readouts for both Studies GO30140 and YO40245 (IMbrave150) studies of first-line therapy in patients with HCC. These results will further inform the role of PD-L1 in the study design of this adjuvant HCC trial.

In this study, submission of surgical tumor tissues at baseline will be mandated and the expression of PD-L1 will be examined by the central laboratory using a PD-L1 (SP263) immunohistochemistry assay. In addition to assessing the status of PD-L1, other exploratory biomarkers (such as potential predictors and prognostic biomarkers associated with clinical benefits of atezolizumab + bevacizumab), tumor immunobiology, drug resistance mechanisms, or tumor types may also be analyzed.

Tissue samples will be collected for DNA extraction to enable whole genome sequencing (WGS) or whole exome sequencing (WES) to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Genomics is increasingly informing researchers' understanding of disease pathobiology. The WGS and the WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

Blood samples will be collected at baseline and during the study to evaluate changes in surrogate biomarkers, which may include circulating-tumor DNA (ctDNA). The ctDNA is extracellular DNA that is present in a number of bodily fluids, including blood, synovial fluid and cerebrospinal fluid. Compared with performing a tissue biopsy, ctDNA examination has the advantages of minimal invasion and greater convenience. Detection of minimal residual disease through ctDNA analysis in plasma has been shown to identify patients at high risk of recurrence in early stage breast cancer and colorectal cancer (Wang et al. 2017; Gabriel and Bagaria 2018) among other indications. Detection of ctDNA-positive patients following primary liver cancer surgery may help to identify patients at high risk for disease recurrence in the adjuvant setting. Due to detection of ctDNA preceding the established clinical parameters (i.e., imaging), assessment of ctDNA positivity at benchmark timepoints post-treatment may be used as a potential surrogate endpoint for RFS and OS.

Changes in biomarkers may provide evidence of biologic activity of atezolizumab in humans. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood-based biomarkers that might predict which patients are more likely to benefit from atezolizumab in combination with bevacizumab.

3.4.9 Rationale for Patient-Reported Outcomes

Early stage HCC is largely asymptomatic, with the majority of patients exhibiting no disease-specific, discernable symptoms. Instead, it is the impact of treatment and the associated burden, rather than disease burden, that defines the patient experience. Therefore, in this setting it is most important to document the burden associated with adjuvant HCC treatment and understand the impact of therapy as reported by patients to inform benefit–risk assessment and treatment decision making. This is especially critical in the adjuvant HCC setting, as there is limited information about the impact of treatments on patients' lives in this setting.

A fit-for-purpose assessment of function and Health Related Quality of Life (HRQoL) will be collected in the study. The validated physical function, role function, emotional function, social functioning, and global health status (GHS)/HRQoL scales of the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 will be administered throughout the study (Aaronson et al. 1993; Fitzsimmons et al. 1999). The original EORTC QLQ-C30 has been modified to reduce patient burden of additional questions while capturing the most likely impacts of the combination treatment under study. This reduced version will be hereafter referred to as the item list 42 (IL42)–EORTC QLQ-C30 (Reduced). In addition, the EQ-5D-5L will be completed to inform pharmacoeconomic models. See Section 4.5.8 for details.

Both the IL42–EORTC QLQ-C30 (Reduced) and the EQ-5D-5L measures will be administered at specified timepoints as indicated in Appendix 1.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 662 patients with completely resected or ablated HCC who are at high risk for disease recurrence will be enrolled during the global enrollment phase of this study (see Table 4). After completion of the global enrollment phase, additional patients may be enrolled in China in an extended China enrollment phase to ensure a total of a minimum of 250 patients from mainland China in a China subpopulation.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Participants with a first diagnosis of HCC who have undergone either a curative resection or ablation (RFA or MWA only) within 4–12 weeks prior to randomization
  - Multimodality treatment is not permitted, for example resection and ablation.

- Combination treatments (with the exception of one TACE after resection) is not allowed.
- Patients may receive a second ablation procedure if this is part of the initial curative treatment plan and not due to disease recurrence following the first procedure. In cases where there is more than one ablation procedure, the time between the first and the second ablation procedures should not exceed 1 week. The time between the second ablation procedure and randomization should not exceed 12 weeks.

- Documented diagnosis of HCC that has been completely resected or ablated (RFA or MWA only) as described below:
  - Patients with resected HCC must have documented histological confirmation of negative surgical margins (R0) which is documented in a pathology report (patients with microscopically positive [R1] or grossly positive [R2] resection margins or unknown margins will be excluded from the study).
  - Patients with ablated HCC must have documented evidence of complete radiological response, including disappearance of any intratumoral arterial enhancement in all ablated lesions.
  - All patients must have disease-free status documented within 4 weeks prior to randomization by a complete physical examination, radiographic images, and pathology (resection only), with no subsequent evidence of residual or recurrent disease prior to randomization.

    A complete set of baseline (post-curative procedure) radiographic images and accompanying report must be available prior to randomization.
- Absence of major macrovascular (gross vascular) invasion of the portal vein (Vp3 or Vp4) or any grade of macrovascular invasion in the hepatic vein or inferior vena cava.

  Note: Patients undergoing resection with minor vascular invasion of the portal vein (Vp1 or Vp2) as detected by either imaging or pathological examination are allowed (see Appendix 5).
- Absence of extrahepatic spread as confirmed by CT or MRI scan of the chest abdomen, pelvis, and head prior to and following curative procedure
- Full recovery from surgical resection or ablation within 4 weeks prior to randomization
- High risk for HCC recurrence after resection or ablation as defined in Table 4

  In the event that the pathology and the pre–curative procedure radiology report are discordant with regards to tumor size and number, the modality demonstrating the largest tumor size and number should be used to determine high risk features. Pathological findings should be used to assess for microvascular invasion and/or poor tumor differentiation. If macrovascular invasion of Vp1 or Vp2 is detected on either the pre-operative CT/MRI scan or the pathology report, this should be a high risk feature.

- For patients who received post-operative TACE: full recovery from the procedure within 4 weeks prior to randomization, including:
  - AST and ALT $\leq 5 \times$ 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 (NCI CTCAE), Version 5.0 Grade 1
  - No significant medical events (e.g., gastrointestinal [GI] bleeding, cardiac events, hepatorenal syndrome) during or after the TACE procedure
- For patients with resected HCC, availability of a representative baseline tumor tissue sample that meets the following criteria:
  - A formalin-fixed, paraffin-embedded (FFPE) resected tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections should be submitted along with an associated pathology report within 4 weeks after randomization. For patients in China, tissue samples may be submitted retrospectively upon Human Genetic Resources Administration of China (HGRAC) approval of sample submission.

    Note: For patients with ablated HCC, submission of a tumor specimen is encouraged but not mandated (see Section 4.5.6).
- Negative HIV test at screening
- Documented virology status of hepatitis, as confirmed by screening HBV and HCV tests
  - For patients with active HBV: HBV DNA < 500 IU/mL during screening, initiation of anti-HBV treatment at least 14 days prior to randomization and willingness to continue anti-HBV treatment during the study (per local standard of care; e.g., entecavir)
  - Patients with HCV, either with resolved infection (as evidenced by detectable antibody) or chronic infection (as evidenced by detectable HCV RNA), are eligible
  - For patients with detectable HCV RNA and for whom HCV treatment is deemed appropriate by the investigator, treatment should begin no sooner than 6 months following curative procedure consistent with AASLD guidelines
- For patients enrolled in the extended China enrollment phase: current resident of mainland China and of Chinese ancestry
- Performance of an esophagogastroduodenoscopy either before resection or ablation as part of pre-procedure work-up or during screening (i.e., following resection or ablation), and assessment and treatment of varices of all sizes per local standard of care prior to randomization
- ECOG Performance Status of 0 or 1
- Child–Pugh Class A status (see Appendix 4)

- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to randomization unless otherwise specified:
  - AST, ALT, and ALP $\leq 5 \times$ ULN
  - Serum bilirubin $\leq 3 \times$ ULN
  - Albumin $\geq$ 28 g/L (2.8 g/dL)
  - Serum creatinine $\leq$ 1.5 × ULN or creatinine clearance $\geq$ 30 mL/min (calculated using the Cockcroft-Gault formula)
  - Hemoglobin $\geq$ 90 g/L (9 g/dL)

    Patients may be transfused to meet this criterion.
  - Platelet count $\geq 75 \times 10^9$/L (75,000/μL) without transfusion
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 2 \times$ ULN
  - Urine dipstick for proteinuria $< 2+$ (within 7 days prior to Day 1 of Cycle 1)

    Patients discovered to have $\geq 2+$ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection (or an alternative method such as protein:creatinine ratio, per local guidance) and must demonstrate $<$ 1 g of protein in 24 hours.

- 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 must remain abstinent or use contraceptive methods with a failure rate of $<$ 1% per year while they are receiving atezolizumab and bevacizumab and for 5 months after the final dose of atezolizumab and for 6 months after the final dose of bevacizumab. Women must refrain from donating eggs during the same period.

  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 is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With 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 bevacizumab to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.1.1 Additional Inclusion Criteria for Crossover for Patients in Arm B

Patients randomized to Arm B must meet the following criteria to qualify for crossover to treatment with atezolizumab plus bevacizumab:

- Patient meets all other eligibility criteria in Sections 4.1.1 and 4.1.2. However the following criteria are not applicable for crossover:
  - Inclusion criteria: signed informed consent, a first diagnosis of HCC, documented diagnosis of HCC that has been completely resected or ablated, absence of major macrovascular invasion and extrahepatic spread, high risk for HCC recurrence after resection or ablation
  - Exclusion criteria: evidence of residual, recurrent, or metastatic disease; any treatment for HCC prior to resection or ablation is still excluded except for patients who received TACE for initial curative procedure
- Documentation of unequivocal recurrence as defined by EASL Clinical Practice Guidelines (Appendix 6 and the radiology interpretation guide from Calyx) or RECIST v1.1 (Appendix 7) criteria that is confirmed by the IRF

- For Arm B patients who undergo surgical resection or ablation for first recurrence: full recovery from surgical resection or ablation within 4 weeks prior to Day 1 of Cycle 1
- Availability of a representative tumor specimen obtained at the time of recurrence for exploratory biomarker research (see Section 4.5.6 for information on tumor specimens)

4.1.2 Exclusion Criteria

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

- Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
- Evidence of residual, recurrent, or metastatic disease at randomization
- Clinically significant ascites
- History of hepatic encephalopathy
- Prior bleeding event due to untreated or incompletely treated esophageal and/or gastric varices within 6 months prior to randomization
- Have received more than 1 cycle of adjuvant TACE following surgical resection
- 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, *granulomatosis with Polyangiitis*, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  – Rash must cover $<$ 10% of body surface area.
  – Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
  – There is 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 12 months prior to Day 1 of Cycle 1.
- 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 CT scan

- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to Day 1 of Cycle 1, unstable arrhythmia, or unstable angina
- History of malignancy other than HCC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>$ 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Active tuberculosis
- Severe infection within 4 weeks prior to Day 1 of Cycle 1, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that in the opinion of the investigator, could impact patient safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to Day 1 of Cycle 1

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Prior allogeneic stem cell or solid organ transplantation
- On the waiting list for liver transplantation
- 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
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 5 months after the final dose of atezolizumab or within 6 months after the final dose of bevacizumab

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to Day 1 of Cycle 1.
- Co-infection with HBV and HCV

  Patients with a history of HCV infection but who are negative for HCV RNA by polymerase chain reaction will be considered to be negative for HCV infection.
- Co-infection with HBV and hepatitis D viral infection
- Clinically significant uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected serum calcium $>$ ULN)
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or bevacizumab formulations

- Any treatment for HCC prior to resection or ablation, including systemic therapy (including investigational agents) and locoregional therapy such as TACE

  Prior use of herbal therapies or traditional Chinese medicines with anti-cancer activity included in the label is allowed, but such therapies must be discontinued at least 7 days prior to randomization and are prohibited during the study.

  Portal vein embolization used to increase the functional liver remnant prior to surgery is permitted.
- Treatment with a live, attenuated vaccine within 4 weeks prior to Day 1 of Cycle 1, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Treatment with investigational therapy within 4 weeks prior to Day 1 of Cycle 1
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-cytotoxic T lymphocyte–associated protein 4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, IFN and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to Day 1 of Cycle 1
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-α [TNF-α] agents) within 2 weeks prior to Day 1 of Cycle 1, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible.
  - Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- Inadequately controlled arterial hypertension (defined as systolic blood pressure [BP] $>$ 150 mmHg and/or diastolic BP $>$ 100 mmHg), based on an average of at least three BP readings at two or more sessions

  Anti-hypertensive therapy to achieve these parameters is allowed.
- History of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1 of Cycle 1
- History of hemoptysis ($\geq$ 2.5 mL of bright red blood per episode) within 1 month prior to Day 1 of Cycle 1
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)

- Current or recent (within 10 days of Day 1 of Cycle 1) use of aspirin ($>$325 mg/day) or current or recent treatment with dipyramidole, ticlopidine, clopidogrel, and cilostazol
- Current or recent (within 10 days prior to Day 1 of Cycle 1) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose

  Prophylactic anticoagulation for the patency of venous access devices is allowed provided the activity of the agent results in an INR $<1.5\times$ ULN and aPTT is within normal limits (according to institutional standards) within 14 days prior to Day 1 of Cycle 1.

  Prophylactic use of low-molecular-weight heparin (LMWH; i.e., enoxaparin 40 mg/day) is allowed. However, the use of direct oral anticoagulant therapies such as dabigatran (Pradaxa®) and rivaroxaban (Xarelto®) is not recommended due to bleeding risk. Benefits and risks should be assessed and caution exercised for use of direct oral anticoagulants. The investigator should consider switching to other approved anticoagulants due to the risk of upper GI bleeding in patients with HCC.
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to Day 1 of Cycle 1
- History of GI fistula, GI perforation, or intra-abdominal abscess within 6 months prior to Day 1 of Cycle 1
- Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Major surgical procedure within 4 weeks prior to Day 1 of Cycle 1 or anticipation of need for a major surgical procedure during the study
- History of clinically significant intra-abdominal inflammatory process within 6 months prior to Day 1 of Cycle 1, including, but not limited to, peptic ulcer disease, diverticulitis, or colitis
- Chronic daily treatment with a non-steroidal anti-inflammatory drug (NSAID)

  Occasional use of NSAIDs for the symptomatic relief of medical conditions such as headache or fever is allowed.

  Chronic use of low dose aspirin ($<$ 325 mg/day) is allowed.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a randomized, open-label study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from the interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of two study arms: Arm A (atezolizumab + bevacizumab) or Arm B (active surveillance). Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each study arm. Randomization will be stratified according to the criteria outlined in Section 3.1.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are atezolizumab and bevacizumab. Appendix 14 *identifies all IMPs.*

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

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

4.3.1.2 Bevacizumab

The bevacizumab drug product will be supplied by the Sponsor as a sterile liquid in single-use, 16-mL, preservative-free glass vials that contain 400 mg of bevacizumab (25 mg/mL).

For information on the formulation and handling of bevacizumab, see the pharmacy manual and the Bevacizumab Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1. Atezolizumab will be administered first followed by bevacizumab, with a minimum of 5 minutes between dosing. Patients will receive treatment as described in Sections 4.3.2.1 and 4.3.2.2. Treatment must be initiated no later than 3 business days after randomization, with the exception of the emergence of an adverse event for which dosing may be postponed.

If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule, with one exception:
If treatment was postponed for fewer than 3 days, the patient can resume the original schedule.

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

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 12 and Appendix 13.

4.3.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Treatment duration is described in Section 3.1.

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 11. Atezolizumab infusions will be administered per the instructions outlined in Table 5.

Table 5 Administration of First and Subsequent Atezolizumab Infusions

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

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 12.

No dose modification for atezolizumab is allowed.

4.3.2.2 Bevacizumab

Bevacizumab will be administered by IV infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle. Treatment duration is described in Section 3.1.

Administration of bevacizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 11. Bevacizumab infusions will be administered per the instructions outlined in Table 6.

Table 6 Administration of First and Subsequent Bevacizumab Infusions

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

[a] For patients with borderline blood pressure, repeated measurements can be used to obtain an average blood pressure.

Guidelines for medical management of IRRs are provided in Appendix 12.

No dose modification for bevacizumab is allowed.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab and bevacizumab) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate

documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Atezolizumab and Bevacizumab

The Sponsor will offer continued access to Roche IMPs (atezolizumab and bevacizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMPs (atezolizumab and bevacizumab) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMPs (atezolizumab and bevacizumab) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for HCC
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for HCC
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

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 Day 1 of Cycle 1 to the treatment/surveillance discontinuation visit. All such

medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

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

- Oral contraceptives with a failure rate of < 1% per year (see Section 4.1.1)
- Hormone-replacement therapy
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section 4.4.3)
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Low-dose aspirin (< 325 mg/day).

  Co-administration of proton-pump inhibitors is strongly recommended to reduce potential GI damage.

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

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.3) 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 12).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor-α Inhibitors

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

corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 12 and Appendix 13 for details).

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies, including traditional Chinese medicine, 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 4.4.3) may be used during the study at the discretion of the investigator. Prior use of herbal therapies or traditional Chinese medicines with anti-cancer activity included in the label is allowed, but such therapies must be discontinued at least 7 days prior to randomization.

4.4.3 Prohibited Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority–approved or experimental, is prohibited for various time periods prior to Day 1 of Cycle 1 (depending on the anticancer agent; see Section 4.1.2), during study treatment/active surveillance, and during long-term follow-up until IRF-confirmed disease recurrence. This includes but is not limited to the following:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy [e.g., Xiao Chai Hu Tang, Kanglaite]), whether health authority–approved or experimental, is prohibited for various time periods prior to Day 1 of Cycle 1, depending on the agent (see Section 4.1.2), during study treatment/active surveillance, and during long-term follow-up until IRF-confirmed disease recurrence is documented.
- Investigational therapy is prohibited within 4 weeks prior to Day 1 of Cycle 1, during study treatment/active surveillance, and during long-term follow-up until IRF-confirmed disease recurrence.

The following medications are prohibited for patients receiving atezolizumab plus bevacizumab, unless otherwise noted:

- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the final dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, IFNs and IL-2) are prohibited within 4 weeks or 5 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.

- Current use of full dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purposes or anti-platelet therapy are prohibited within 10 days prior to Day 1 of Cycle 1 and during study treatment.
  - Local label recommended doses for prophylactic use of anticoagulants or thrombolytic therapies are allowed. Benefits and risks should be assessed and caution exercised for use of direct oral anticoagulants. Other approved anticoagulants should be considered due the risk of upper GI bleeding in patients with HCC.
  - Low-dose aspirin (<325 mg/day) is permitted. Co-administration of proton-pump inhibitors is strongly recommended to reduce potential GI damage.
  - However, if a patient experiences a venous thromboembolism event while still receiving study treatment, it may still be possible for the patient to remain on study medication despite anticoagulation treatment (see Section 4.1.2).
- Use of warfarin or warfarin-like products is not permitted at all (includes for prophylactic use)

  Prophylactic use of low-dose anticoagulation, unfractionated heparin or LMWH is permitted. The preferred choice for anticoagulation treatment should be LMWH as per American Society of Clinical Oncology guidelines (Lyman et al. 2015).
- Concomitant chronic use of NSAIDs while receiving study treatment is prohibited, with the exception of chronic low-dose aspirin (<325 mg/day). However, for the symptomatic relief of medical conditions (e.g., headache, fever), sporadic or short-term intake of oral NSAIDs is allowed, when co-administered with proton-pump inhibitors to reduce potential GI damage.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed in the study is provided in Appendix 1. A schedule of activities for patients randomized to Arm B who cross over to treatment with atezolizumab plus bevacizumab is provided in Appendix 2. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

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 detailed record of all patients screened and to document eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, 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 Day 1 of Cycle 1 will be recorded. At the time of each follow-up physical examination, or patient contact by means of telephone or telemedicine, 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.

4.5.3 Physical Examinations

A complete physical examination, performed at screening, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, GI, genitourinary, and neurologic systems.
Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

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 on the Adverse Event eCRF.

Physical examinations should include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic BP, and temperature. Abnormalities observed at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits, any new or worsened clinically significant abnormalities should be recorded on the Adverse Event eCRF.

4.5.5 Imaging Assessments

Patients will undergo imaging assessments at screening, every 12 weeks for the first 3 years following randomization and every 24 weeks thereafter, regardless of treatment delays, until IRF-confirmed disease recurrence or until the end of Year 7 after

randomization, whichever occurs first even if the patient starts a new anti-cancer therapy. Thus, imaging assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease recurrence, even if they start new anti-cancer therapy. At the investigator's discretion, imaging assessments may be repeated at any time if clinically indicated.

Screening assessments must include CT scans with IV contrast (and oral contrast per site standard of care) or MRI scans of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen and pelvis should be performed. If a CT scan with contrast is not contraindicated, it is mandatory to obtain a dual-phase imaging scan of the liver, and every effort should be made to time the contrast administration so that high-quality arterial-phase imaging is obtained throughout the liver on the first run, and high-quality portal venous-phase imaging is obtained throughout the liver on the second run. A CT scan with contrast or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also be performed if clinically indicated.

If a CT scan is performed in a positron emission tomography/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

All postbaseline imaging assessments will include CT scans with IV contrast (and oral contrast per site standard of care) or MRI scans of the chest, abdomen, and pelvis; scans of the head will be included per local practice or as clinically indicated.

The same radiographic procedures used at screening should be used for subsequent imaging assessments (e.g., the same contrast protocol for CT scans). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

Diagnosis of intrahepatic recurrence will be based on non-invasive criteria and/or biopsy-proven pathologic confirmation of recurrence as defined by the EASL Clinical Practice Guidelines 2018 (see Appendix 6 as well as the radiology interpretation guide from Calyx). Intrahepatic recurrence is defined by the appearance of one or more intrahepatic lesions with a longest diameter of >1 cm and a typical vascular pattern of HCC on dynamic imaging (i.e., hypervascularization in the arterial phase with washout in the portal venous or late venous phase). Lesions that do not show a typical vascular pattern can be diagnosed as HCC recurrence by evidence of a growth interval of at least 1 cm in subsequent scans. Extrahepatic recurrence will be defined as per RECIST v1.1 (see Appendix 7).

Sites will provide any CT, MRI, or PET/CT scans used for assessments of HCC recurrence to an IRF for central review. Contrast-enhanced ultrasound and AFP changes cannot be reviewed by the IRF to evaluate recurrence. Any biopsy results that have been done to diagnose HCC recurrence or to investigate suspicious lesions, should be entered in RAVE so that the IRF can review. Baseline screening scans performed after curative procedure will be submitted to the IRF only after the patient has been randomized.

Imaging for Patients in Arm B Who Cross Over to Treatment with Atezolizumab plus Bevacizumab

Patients randomized to Arm B who cross over to treatment with atezolizumab plus bevacizumab after documented IRF-assessed recurrence will undergo imaging assessments every 12 weeks from the Crossover Cycle 1 Day 1 visit, regardless of treatment delays, until a second disease recurrence (for patients with NED at the time of crossover) or loss of clinical benefit as determined by the investigator (for patients with measurable disease at the time of crossover). Thus, imaging assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease recurrence or loss of clinical benefit (as appropriate), even if they start new anti-cancer therapy. At the investigator's discretion, imaging assessments may be done more frequently or repeated at any time if clinically indicated. Images collected following confirmation of disease recurrence by the IRF do not need to be submitted to the IRF for central review.

An imaging assessment is not required during screening for crossover. For crossover patients not undergoing a second resection or ablation, the scan confirming recurrence can serve as the baseline imaging assessment assuming chest, abdomen, and pelvis imaging has been obtained. For patients undergoing a second resection or ablation procedure, imaging of chest, abdomen, and pelvis following resection or ablation is needed and should represent baseline.

The same radiographic procedures used to assess disease sites prior to crossover should be used during crossover (e.g., the same contrast protocol for CT scans). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

For patients with measurable disease at crossover, all measurable and evaluable lesions identified at the time of documented recurrence should be re-assessed at each subsequent tumor evaluation. Objective response at a single timepoint will be determined by the investigator according to RECIST v1.1 (see Appendix 7).

For patients with NED at the time of crossover, diagnosis of intrahepatic and extrahepatic recurrence will be made as described above.

4.5.6 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, and other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and lactate dehydrogenase
- Coagulation: INR and aPTT
- Thyroid function testing: TSH, free T3 (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- AFP
- HIV serology
- HBV serology: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody, total hepatitis B core antibody (HBcAb), HBV DNA

  If a patient has a positive HBsAg test and/or a positive total HBcAb test at screening, an HBV DNA test and quantitative HBsAg test must also be performed during screening to determine if the patient has an HBV infection, as well as at Cycles 5, and 9, and at the discontinuation visit. If local quantitative HBsAg test is not available, a qualitative HBsAg followed by quantitative HBV DNA can be performed as an alternative.
- 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 at screening, Cycles 5, and 9, and at the discontinuation visit.
- C-reactive protein
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test within 14 days before Day 1 of Cycle 1. Urine pregnancy tests will be performed at specified subsequent visits (see Appendix 1 and Appendix 2). 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 postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

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

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Serum samples for atezolizumab PK analysis through use of a validated immunoassay
- Serum samples for assessment of ADAs to atezolizumab through use of a validated immunoassay
- Blood, serum, and plasma samples for exploratory research on biomarkers
- For patients with resected HCC and only if available for patients with ablated HCC, an archival tumor tissue sample obtained at baseline for exploratory research on biomarkers and biomarker assay development

    For patients with resected HCC (mandatory), an FFPE resected tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections should be submitted along with an associated pathology report within 4 weeks after randomization. For patients in China, tissue samples may be submitted retrospectively upon HGRAC approval of sample submission.

    For patients with ablated HCC (if available), biopsy is not mandated. Although any available tumor tissue sample can be submitted, sites are strongly encouraged, if available, to submit a representative FFPE tumor specimen in a paraffin block (preferred) or approximately 10−15 slides containing unstained, freshly cut, serial sections along with an associated pathology report. Samples collected via resection, core-needle biopsy, or excisional, incisional, punch, or forceps biopsy are preferred. However, all specimen types (e.g., fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples) are acceptable.
- Tumor tissue sample obtained at the time of radiographic confirmation of disease recurrence unless not clinically feasible as assessed and documented by the investigator for exploratory research on biomarkers and biomarker assay development

    Biopsies at the time of recurrence should be performed within 12 weeks after recurrence or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

Exploratory biomarker research may include, but will not be limited to, PD-L1, ctDNA, tumor-immune phenotypes, molecular subtypes of HCC, mutations, tumor mutation burden, copy number variations, T-effector signature, immune subsets, and pathway signatures. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of next-generation sequencing of a comprehensive panel of genes.

DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.10), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, serum, plasma, and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.7 Electrocardiograms

An ECG is required at screening and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. 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. Paper copies of ECG tracings will be kept as part of the patient's permanent

study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.8 Patient-Reported Outcomes

To more fully characterize the clinical profile of atezolizumab in combination with bevacizumab, patient-reported outcome (PRO) data will be obtained through use of the following instruments: the IL42–EORTC QLQ-C30 (Reduced) and the EQ-5D-5L.

Refer to Appendix 1 for the frequency and timing of PRO assessments.

4.5.8.1 Data Collection Methods for Patient-Reported Outcomes

The PRO instruments will be completed at the clinic or by means of a telephone call at specified timepoints during the study (see Appendix 1). To ensure instrument validity and that data standards meet health authority requirements, questionnaires must be completed by the patient at the start of the clinic visit before any discussion with the investigator of the patient's health state, laboratory results, or health record; before administration of study treatment; and prior to the completion of all other study assessments. If the patient is unable to complete the measure on her or his own, interviewer assessment is allowed but may only be conducted by a member of the clinic staff. With interviewer assessment, questionnaire items must be read to the patient verbatim; no interpretation, rephrasing, or rewording of the questions is allowed during interview-assisted completion.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.
- Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

After treatment (Arm A) or surveillance (Arm B) discontinuation, the IL42–EORTC QLQ-C30 (Reduced) and EQ-5D-5L instruments will be administered at the first four long-term follow-up assessments for approximately 1 year at clinic visits or by means of a telephone call. Patients who experience disease recurrence should complete the PRO questionnaires at the visit when disease recurrence is determined by the investigator if operationally feasible, at the treatment/surveillance discontinuation visit, and then at the first four long-term follow-up assessments at clinic visits or by means of a telephone call. For patients who experience disease recurrence after the collection of the first four long-term follow-up PRO assessments, PROs do not need to be collected again.

Patients in Arm B who cross over to treatment with atezolizumab plus bevacizumab will not complete PRO instruments after they cross over.

4.5.8.2 Description of Patient-Reported Outcomes Instruments

IL42–EORTC QLQ-C30 (Reduced)

The IL42–EORTC QLQ-C30 (Reduced) is a reduced version of the validated, reliable EORTC QLQ-C30, self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999). This reduced version contains the validated patient functioning (physical, emotional, role, and social) and GHS/quality of life (QoL) scales and was created for this study from the EORTC Quality of Life Group Item Library (https://www.eortc.be/itemlibrary/). The measure consists of 15 questions in total and will employ the same recall period of the EORTC-QLQ-C30 of the previous week (see Appendix 8). The IL42–EORTC QLQ-C30 (Reduced) will follow the original scoring for each scale as is specified in the EORTC Scoring manual (Fayers et al. 2001). The functioning items are scored on a 4-point scale that ranges from "not at all" to "very much," and the GHS/QoL scale is scored on a 7-point scale that ranges from "very poor" to "excellent." It takes less than 10 minutes to complete the measure.

EQ-5D-5L

The EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013; (see Appendix 9). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a Visual Analog Scale (VAS) that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

4.5.9 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study drug, are associated

with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. The DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.9) will not be applicable at that site. If collection of the WES sample is missed at Cycle1 Day 1, this sample may be collected at any other time during the study (See Appendix 3).

Genomics is increasingly informing researchers' understanding of disease pathobiology. The WGS and the WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Refer to Section 4.5.6 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. The RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to atezolizumab and bevacizumab, HCC, diseases, or drug safety:

- Leftover blood, serum, plasma, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides).

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researchers' understanding of disease pathobiology. The WGS and the WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

The RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.10.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from Study WO41535.

4.5.10.7 Monitoring and Oversight

The RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment 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
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy

- Pregnancy
- For patients in Arm A and crossover patients with NED at the time of crossover: disease recurrence (confirmed by IRF for patients in Arm A), as determined by EASL Clinical Practice Guidelines for intrahepatic recurrence or RECIST v1.1 for extrahepatic recurrence
- For crossover patients with measurable disease at the time of crossover: 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 3.1 for details)

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

Patients will return to the clinic for a treatment/surveillance discontinuation visit $\leq$ 30 days after the final dose of study treatment (Arm A) or final visit or telephone contact (Arm B).

After treatment/surveillance discontinuation, information on survival follow-up and new anti-cancer therapy will be collected by telephone calls, patient medical records, and/or clinic visits approximately every 12 weeks until death (unless the patient withdraws consent or the Sponsor terminates the study). The first long-term follow-up should occur approximately 12 weeks from the last scheduled imaging assessment (for patients who have experienced disease recurrence and discontinued from surveillance/treatment period) or at the next scheduled imaging assessment (for patients who have not experienced disease recurrence and have discontinued from the surveillance/treatment period).

4.6.2 Patient Discontinuation from the 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 patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

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

4.6.3 Study Discontinuation

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

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

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 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 Sections 5.1.1–5.1.3).

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 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 criteria for treatment interruption or discontinuation, are provided in Appendix 12 and

Appendix 13. Refer to Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

Patients with active infection that in the opinion of the investigator could impact patient safety are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines 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 SARS-CoV-2 infection, 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 SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, *facial paresis, myelitis,* myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 13 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: GI perforations, all-bladder perforation, hemorrhage, pulmonary hemorrhage, arterial thromboembolic events (ATE), fistulae, wound-healing complications, hypertension, congestive heart failure (CHF), cardiac disorders (excluding CHF and ATE), neutropenia, infections, necrotizing fasciitis, thrombocytopenia, venous thromboembolism, posterior reversible encephalopathy syndrome, pulmonary hypertension, ovarian failure, embryo-fetal development disturbance, hypersensitivity reactions/infusion reactions, peripheral sensory neuropathy, osteonecrosis of the jaw, non-mandibular osteonecrosis, thrombotic microangiopathy, and proteinuria.

Refer to Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for Bevacizumab.

5.1.3 Risks Associated with Combination Use of Atezolizumab and Bevacizumab

The risk of overlapping toxicities between atezolizumab and bevacizumab is anticipated to be minimal based on the known safety profile of each agent and available data from clinical studies. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hemorrhage, hypothyroidism, and GI toxicity) may be ambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with bevacizumab could be exacerbated by the immunostimulatory activity of atezolizumab.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. For patients in the active surveillance arm, an adverse event is any untoward medical occurrence.

An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

For patients receiving active treatment with atezolizumab plus bevacizumab, adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- 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 (see Section 5.3.5.7)

- 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.
- Pneumonitis
- Colitis
- Endocrinopathies: (e.g., diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis)
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: e.g., Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, CRS, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- *Myelitis*
- *Facial paresis*
- Grade ≥ 3 hypertension
- Grade ≥ 3 proteinuria
- Any grade GI perforation, abscess, or fistula
- Grade ≥ 2 non-GI fistula or abscess
- Grade ≥ 3 wound-healing complication
- Hemorrhage
  - Any grade CNS bleeding
  - Grade ≥ 2 hemoptysis

  - Other Grade ≥ 3 hemorrhagic event
- Any ATE
- Grade ≥3 venous thromboembolic event
- Any grade posterior reversible encephalopathy syndrome
- Grade ≥3 CHF

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact (at clinic visits or using telemedicine). All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment or surveillance on Day 1 of Cycle 1, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment or surveillance on Day 1 of Cycle 1, all adverse events will be reported until 30 days after the final cycle (i.e., final cycle of treatment or surveillance) or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final cycle or until initiation of new systemic anti-cancer therapy, whichever occurs first.

In patients in Arm B crossing over to treatment with atezolizumab and bevacizumab, after the end of the reporting period for serious adverse events (i.e., 90 days after the final cycle of surveillance) but prior to initiation of study treatment, if applicable, only serious adverse events caused by a protocol-mandated intervention (e.g., resection or ablation to treat disease recurrence, invasive procedures such as biopsies) should be reported. If an adverse event occurs prior to crossover and the frequency, severity, or character of the adverse event worsens after initiation of the crossover treatment , a separate adverse event should be reported with an onset date after initiation of the

crossover treatment. When recording the separate adverse event, it is important to convey the concept that the prior adverse event has changed after initiation of crossover treatment by including applicable descriptors (e.g., “more frequent headaches” or “worsening of hypertension”).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 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?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 8):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 8 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

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

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction". Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF 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, each individual event should be recorded on the Adverse Event

eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high BP), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of HCC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). The iDMC will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should

be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study.
When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Hepatocellular Carcinoma

Events that are clearly consistent with the expected pattern of disease recurrence should not be recorded as adverse events. These data will be captured as efficacy assessment data only. However, in situations in which there is no confirmation of disease recurrence, the underlying symptoms should be captured as adverse events and assessed accordingly for seriousness, severity, and causality until a diagnosis or cause for such events is established or until confirmation of HCC recurrence. If the symptoms are later confirmed to be due to recurrence of disease, symptoms reported as adverse events should be retracted.

For patients with measurable disease at the time of crossover, events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not experienced an adverse event.
- Hospitalization due solely to recurrence or progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter referred to as “special situations”) are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For atezolizumab and bevacizumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with atezolizumab and bevacizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest for patients receiving active treatment (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest in patients receiving active treatment and serious events in all patients, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.

The Emergency Medical Call Center will *also* be available 24 hours per day, 7 days per week. *The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.*

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment or surveillance on Day 1 of Cycle 1, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment or surveillance on Day 1 of Cycle 1, serious adverse events and adverse events of special interest will be reported until 90 days after the final cycle (i.e., final cycle of treatment or surveillance) or until initiation of new systemic anti-cancer therapy, whichever occurs first. For adverse events of special interest in patients receiving active treatment and for serious adverse events in all patients, investigators should record all case details that can be gathered immediately (i.e., within

24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab or 6 months after the final dose of bevacizumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the final dose of bevacizumab. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been

signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the final cycle or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Atezolizumab	Atezolizumab Investigator's Brochure
Bevacizumab	Bevacizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An iDMC will monitor the incidence of the adverse events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The statistical considerations and analysis plan are summarized below. Further details will be provided in the Statistical Analysis Plan (SAP) as part of the Data Analysis Plan.

The global population will include all patients enrolled during the global enrollment phase (including patients enrolled in China during that phase), and the China subpopulation will include all patients enrolled at sites in China (i.e., during both the global enrollment phase and the extended China enrollment phase). Separate analyses will be performed for the global population (see Sections 6.1–6.10) and the China subpopulation (see Section 6.11).

6.1 DETERMINATION OF SAMPLE SIZE

A total of approximately 662 patients will be randomized in the global enrollment phase of this study using a 1:1 randomization ratio to allocate patients to either the atezolizumab plus bevacizumab arm (Arm A) or the active surveillance arm (Arm B). The primary efficacy endpoint for this study is IRF-assessed RFS, defined as the time from randomization to the first documented occurrence of intrahepatic or extrahepatic HCC, or death from any cause (whichever occurs first).

The sample size of this study is based on the number of RFS events required to demonstrate efficacy with regard to the primary efficacy endpoint of IRF-assessed RFS. To detect an improvement in RFS using a log-rank test at a two-sided significance level of 0.05, approximately 323 RFS events will be required to achieve 80% overall power assuming a target HR of 0.73 (median RFS improvement over active surveillance of 7.4 months). The minimum detectable difference (MDD) for RFS is a HR of 0.8 (median RFS improvement of 5 months).

The calculation of sample size and estimates of the RFS analysis timelines are based on the following assumptions:

- Patients will be randomized to Arm A and Arm B in a 1:1 ratio.
- RFS follows a one-piece exponential distribution.
- The median RFS in Arm B is 20 months.
- The O'Brien–Fleming boundaries approximated by the Lan–DeMets method (Lan and DeMets 1983) will be used as stopping boundaries for the interim and final analyses of RFS.
- The dropout rate is 15% for Arm A and 20% for Arm B over 12 months.

The recruitment of approximately 662 patients will take place over approximately 17 months.

See Section 6.11 for sample size considerations for the China subpopulation.

6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, study treatment administration, reasons for discontinuation from the study treatment, and reasons for study discontinuation will be summarized by study arm for all randomized patients (the ITT population). Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by study arm for the ITT population.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic characteristics such as age, sex, race/ethnicity, and baseline disease characteristics (e.g., ECOG Performance Status) will be summarized by study arm for the ITT population. Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

Baseline measurements are the last available data obtained prior to initiation of treatment or surveillance on Day 1 of Cycle 1.

6.4 EFFICACY ANALYSES

The analyses of RFS, OS, time to recurrence (TTR), and time to extrahepatic spread (EHS) or macrovascular invasion will be performed on the basis of all randomized patients (the ITT population), with patients grouped according to the treatment assigned at randomization, regardless of whether they receive any assigned study drug.

Hypotheses will be formally tested on primary (IRF-assessed RFS) and the key secondary endpoints (OS). Implementation of the statistical testing procedure will strongly control the overall Type 1 error at 5% (two-sided). Additional details will be provided in the SAP.

The analysis of RFS after the first HCC recurrence will be performed on the basis of patients in Arm B who cross over to treatment with atezolizumab plus bevacizumab after documented HCC recurrence with NED at the time of crossover. The analyses of PFS and ORR will be performed on the basis of patients in Arm B who cross over to treatment with atezolizumab plus bevacizumab after documented HCC recurrence with measurable disease at the time of crossover.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is IRF-assessed RFS, defined as the time from randomization to the first documented occurrence of intrahepatic or extrahepatic HCC, or death from any cause (whichever occurs first). Patients who have not experienced disease recurrence or death at the time of analysis will be censored at the date of the last assessment for HCC occurrence. Patients with no postbaseline radiographic

assessment will be censored at the date of randomization. For the purposes of analysis of RFS in the ITT population, in the rare event that the IRF identifies baseline disease, this patient will be assessed as having a recurrence event at the time of randomization.

Analysis of RFS will be performed on basis of the ITT population using the ITT principle: with patients grouped according to the study arm assigned at randomization, regardless of whether they receive any assigned study drug, cause of going off protocol treatment, crossover from Arm B to treatment with atezolizumab plus bevacizumab etc.

RFS will be tested with the overall type I error controlled at a two-sided significance level of 0.05. The null and alternative hypotheses regarding RFS can be phrased in terms of survival functions $S_A(t)$ and $S_B(t)$ for Arm A (atezolizumab + bevacizumab) and Arm B (active surveillance), respectively:

$$H_0: S_A(t) = S_B(t) \text{ versus } H_1: S_A(t) \neq S_B(t)$$

The two-sided stratified log-rank test, stratified by the same stratification factors specified for randomization, will be used as the primary analysis to compare RFS between the two arms. The stratification factor leading to the largest number of empty cells may be excluded from the analysis. The unstratified log-rank test will be used to check the robustness of the results of the stratified log-rank test.

The Kaplan–Meier method will be used to estimate the median RFS for each study arm. The Brookmeyer–Crowley method will be used to construct the 95% CI for the median RFS for each study arm. Stratified Cox proportional-hazards models will be used to estimate the HR and its 95% CI. The unstratified HR will also be estimated.

A group sequential design will be implemented for testing the RFS primary endpoint to account for the conduct of one interim analysis, which is to be conducted when approximately 236 RFS events have occurred (see Section 6.10). The overall type I error rate of 0.05 for testing of the RFS primary efficacy endpoint will be controlled through use of an α-spending function that utilizes the Lan–DeMets method approximating the O'Brien–Fleming boundaries (O'Brien and Fleming 1979).

The final analysis of RFS will be conducted when approximately 323 IRF-assessed RFS events have occurred, which is expected to take place approximately 39 months after the first patient is randomized.

Sensitivity analyses to assess the robustness of the analysis of RFS will be pre-specified in the SAP.

To assess the homogeneity of the treatment effect with respect to the primary efficacy endpoint of RFS across important subgroups, Forest plots (including the estimated HRs)

will be provided. A full list of all pre-specified exploratory subgroup analyses for RFS for this study will be provided in the SAP.

Further details regarding the primary efficacy analysis will be provided in the SAP.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are OS, investigator-assessed RFS, investigator-assessed and IRF-assessed TTR, , investigator- and IRF-assessed RFS rate at 24 months and 36 months, OS rate at 24 months and 36 months, investigator-assessed time to EHS or macrovascular invasion, and investigator-assessed and IRF-assessed RFS among patients in the PD-L1–high subgroup. OS will be a key secondary endpoint of this study.

6.4.2.1 Overall Survival

The OS will be defined as the time from randomization to death from any cause. Patients who are alive at the time of the analysis will be censored at the last date the patient was known to be alive. Patients with no postbaseline information will be censored at the date of randomization. The analysis performed for OS will follow the methods described for the primary endpoint.

To detect an improvement in OS using a log-rank test at a two-sided significance level of 0.05, approximately 319 deaths will be required to achieve 80% overall power assuming a target HR of 0.73 (median OS improvement over active surveillance of 22 months).

The final OS analysis will be conducted when approximately 319 deaths have occurred and is expected to take place approximately 91 months after the first patient is randomized. Formal statistical treatment comparison for OS will only be performed after IRF-assessed RFS results have reached statistical significance. See Section 6.10 for additional details.

6.4.2.2 Investigator–Assessed Recurrence Free Survival

The analysis methods for investigator-assessed RFS are analogous to those described for IRF-assessed RFS (see Section 6.4.1).

6.4.2.3 Time to Recurrence

The TTR is defined as the time from randomization to first documented occurrence of intrahepatic or extrahepatic HCC. Patients who have not experienced disease recurrence at the time of the analysis will be censored at the date of the last assessment for HCC occurrence. Patients with no postbaseline information will be censored at the date of randomization. The analysis of TTR will be conducted separately based on investigator-assessed and IRF-assessed data and will follow the methods described for the primary endpoint (see Section 6.4.1).

6.4.2.4 IRF-Assessed and Investigator-Assessed RFS at 24-Month and 36-Month Landmark Analysis

The IRF- and investigator-assessed RFS rates at 24 months and 36 months will be estimated for each study arm through use of the Kaplan-Meier method, with 95% CIs calculated through use of Greenwood's formula.

6.4.2.5 Overall Survival 24-Month and 36-Month Landmark Analysis

The OS rates at 24 months and 36 months will be estimated for each study arm through use of the Kaplan-Meier method, with 95% CIs calculated through use of Greenwood's formula.

6.4.2.6 Time to Extrahepatic Spread or Macrovascular Invasion

Time to EHS or macrovascular invasion is defined as the time from randomization to the first appearance of EHS or macrovascular invasion. The analysis of time to EHS or macrovascular invasion will be conducted for the study period prior to crossover. Events that occurred in the study period post-crossover will not be considered. Patients who have not experienced either EHS or macrovascular invasion at the time of the analysis or before crossover will be censored at the date of the last assessment for HCC occurrence prior to the analysis data cutoff date and before crossover when applicable. Patients with no postbaseline information will be censored at the date of randomization. The analysis of time to EHS or macrovascular invasion will be conducted based on investigator-assessed data and will follow the methods described for the primary endpoint (see Section 6.4.1).

6.4.2.7 Recurrence-Free Survival among Patients with PD-L1–High Tumors

The RFS among patients in the PD-L1–high subgroup is defined in an analogous manner to the primary endpoint and will be analyzed through use of same methods described for the primary endpoint (see Section 6.4.1). The analysis of RFS in the PD-L1–high subgroup will be conducted separately based on investigator-assessed RFS data and IRF-assessed data.

6.4.3 Exploratory Efficacy Endpoints

Exploratory Overall Survival Analyses

The OS among patients in the PD-L1–high subgroup is defined in an analogous manner to OS in the ITT population and will be analyzed through use of the same methods described for OS in the ITT population (see Section 6.4.2.1). The cutoff to define PD-L1–high tumors will be informed by association of clinical outcome with PD-L1 status in Studies GO30140 and YO40245 (IMbrave150) and will be pre-specified in the SAP.

Exploratory Patient-Reported Outcome Analyses

Change from baseline in physical functioning, emotional functioning, role functioning, social functioning, and GHS/QoL scores as assessed by the IL42–EORTC QLQ-C30 (Reduced). Summary statistics (number of patients, mean, mean change, standard

deviation, median, minimum, maximum, and 95% CI) of linearly transformed scores (per the EORTC scoring manual, Fayers et al. 2001) will be calculated at all assessment timepoints for each study arm. Published minimally important differences (e.g., 10 points) will be used to identify meaningful changes for each scale within each treatment group (Osoba et al. 1998).

Completion rates and reasons for missing data will be summarized for the IL42–EORTC QLQ-C30 (Reduced) questionnaire at each assessment timepoint for both arms. Details of the analysis, including methods for handling missing data, will be specified in the SAP.

Exploratory Efficacy Analyses in Arm B Patients Who Cross Over to Treatment with Atezolizumab Plus Bevacizumab

The following exploratory efficacy endpoints will be analyzed in patients in Arm B who cross over to treatment with atezolizumab plus bevacizumab after documented HCC recurrence:

- For patients with NED at the time of crossover:
  - RFS after the first HCC recurrence, defined as the time from first exposure to any dose of crossover treatment to the second documented HCC recurrence or death from any cause (whichever occurs first), as determined by the investigator. HCC recurrence is defined as occurrence of intrahepatic or extrahepatic HCC.
- For patients with measurable disease at the time of crossover:
  - PFS after first HCC recurrence, defined as the time from first exposure to any dose of crossover treatment to the first documented occurrence of disease progression beyond the initial unresectable disease recurrence as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first)
  - ORR, defined as the proportion of patients with a CR or PR as determined by the investigator according to RECIST v1.1

The 95% CI for ORR will be calculated using the Clopper-Pearson method (Clopper and Pearson 1934).

Methodological details will be provided in the SAP.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all patients randomized to Arm A who received at least one full or partial dose of study treatment (atezolizumab and/or bevacizumab) and all patients randomized to Arm B who underwent at least one safety assessment.

Safety analyses will be conducted separately for the study periods prior to crossover and post-crossover.

Verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0.

Drug exposure will be summarized by descriptive statistics to include treatment duration, number of doses, and dose intensity.

The following events occurring during or after initiation of study treatment or surveillance on Day 1 of Cycle 1 will be summarized by study arm and NCI CTCAE grade:

- All adverse events
- All adverse events leading to death
- Serious adverse events
- Grade $\geq$ 3 adverse events
- Adverse event of special interest
- Adverse events leading to study drug discontinuation or interruption

Multiple occurrences of the same event will be counted once at the maximum severity. Laboratory data with values outside the normal ranges will be identified. In addition, selected laboratory data will be summarized by study arm and grade.

Descriptive statistics will be used to summarize changes in vital signs by study arm.

Deaths and causes of death reported during the study treatment period and those reported during the follow-up period after treatment or surveillance completion/discontinuation will be summarized by arm.

Additional analyses may be performed as indicated.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of all patients with at least one PK assessment.

Serum concentrations of atezolizumab will be reported as individual values and summarized (geometric mean and geometric mean coefficient of variation) by cycle, when appropriate and as data allow. Individual and median serum atezolizumab concentrations will be plotted for PK-evaluable patients by day.

Atezolizumab concentration data may be pooled with data from other studies using an established population PK model to derive PK parameters such as clearance, volume of distribution, and area under the curve, as warranted by the data. Potential correlations of relevant PK parameters with dose, safety, efficacy, or biomarker outcomes may be explored.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized for ADA-evaluable patients. When determining postbaseline incidence, patients are considered to be postbaseline ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be postbaseline ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported.

6.8 BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, biomarker data may be analyzed in the context of this study and in aggregate with data from other studies.

6.9 HEALTH UTILITY ANALYSES

Health utility data from the EQ-5D-5L will be evaluated in pharmacoeconomic models. The results from the health economic data analyses will be reported separately from the clinical study report.

6.10 INTERIM ANALYSES

6.10.1 Interim Analyses of RFS

One interim analysis of IRF-assessed RFS will be performed. The interim analysis will be performed when approximately 236 RFS events have occurred, which is expected to take place approximately 26 months after the first patient is randomized. For the interim analysis, the MDD for RFS is a HR of 0.734 (median RFS improvement over active surveillance of 7.2 months).

For the interim analysis, efficacy stopping boundaries will be determined through use of the Lan–DeMets method to approximate the O'Brien–Fleming boundaries. Analysis timing and stopping boundaries for the interim and final RFS analyses are summarized in Table 9.

The planned interim analysis of RFS will be conducted by an independent Data Coordinating Center and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

6.10.2 Interim Analyses of OS

A group sequential design will be implemented for testing OS to account for the conduct of up to two interim analyses. The boundary for statistical significance at each interim analysis and the final analysis will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming function (Lan and DeMets 1983) to maintain the overall type 1 error rate at 0.05 level. The O'Brien-Fleming boundary for statistical significance is provided in Table 10. Formal statistical treatment comparison for OS will only be performed after IRF-assessed RFS results have reached statistical significance at either the interim or final RFS analyses.

If RFS is statistically significant at the interim analysis, then three analyses of the key secondary endpoint of OS are planned (see Table 10). The two interim analyses of OS will be conducted at the time of the planned interim and final analyses of the primary efficacy endpoint of IRF-assessed RFS. The final OS analysis will be conducted when approximately 319 deaths occurs.

If RFS is not statistically significant at the interim analysis, the study will continue to the RFS final analysis without conducting an interim analysis for OS. If RFS is statistically significant at the final analysis, then only one interim analysis of the secondary endpoint of OS is planned at the time of the IRF-assessed RFS final analysis (see Table 11). The final OS analysis will be conducted when approximately 319 deaths occurs.

If RFS is not statistically significant in either interim or final analysis, the secondary endpoint of the OS will not be formally tested and will be descriptive only.

The boundaries for statistical significance at the planned IRF-assessed RFS and OS interim and final analyses will be determined based on the actual number of events observed.

Further details will be provided in the SAP.

Table 9 Analysis Timing and Stopping Boundaries for Recurrence-Free Survival Analyses

Analysis Timing [a]	Planned Information Fraction	Required No. of Events (Estimated)	Estimated Analysis Timing	Stopping Boundary (Two-Sided p-Value) [b]
RFS interim analysis	73%	236	26 months after first patient is randomized	MDD HR $\leq$0.734 (p-value $\leq$0.017)
RFS final analysis	100%	323	39 months after first patient is randomized	MDD HR $\leq$0.8 (p-value $\leq$0.045)

HR = hazard ratio; ITT = intent-to-treat; MDD = minimum detectable difference (based on an exponential distribution); RFS = recurrence-free survival.

[a] Analysis timing is estimated on the basis of protocol assumptions. Actual timing depends on the exact time that the required events have accrued.

[b] The actual stopping boundaries will be calculated at the time of the interim and final RFS analysis on the basis of the observed information fraction, that is, the actual number of RFS events observed at the time of analysis over the total planned target number of RFS events in the ITT population.

Table 10 Projected Interim and Final OS Analysis Characteristics When Statistical Significance is Reached at the Interim Analysis for RFS

Analysis	No. of events	% information	Event to Patient Ratio	Cutoff Date [a]	MDD [b]	Boundary (p-value) [c]
First OS interim (Performed at time of RFS interim analysis)	107	33.5%	16%	Month 26	0.489	$p \leq 0.0002$
Second OS interim (Performed at time of RFS final analysis)	164	51.4%	25%	Month 39	0.634	$p \leq 0.0035$
Final OS (Event driven)	319	100%	48%	Month 91	0.802	$p \leq 0.0488$

MDD = minimally detectable difference; OS = overall survival; RFS = recurrence free survival.

Note: Assumes 5% dropout rate over 12 months for OS analyses.

[a] Study month at which required number of events are projected to occur, where Study Month 1 is the month the first patient is enrolled. Analysis results will be available after data cleaning.

[b] The largest observed hazard ratio that is projected to be statistically significant.

[c] The projected boundary for statistical significance for the number of events shown (actual boundary to be calculated at time of analysis based on actual number of events).

Table 11 Projected Interim and Final OS Analysis Characteristics When Statistical Significance is Reached at the Final Analysis for RFS

Analysis	No. of events	% information	Event to Patient Ratio	Cutoff Date [a]	MDD [b]	Boundary (p-value) [c]
First OS interim (performed at time of RFS final analysis)	164	51.4%	25%	Month 39	0.634	$p \leq 0.0035$
Final OS (Event driven)	319	100%	48%	Month 91	0.802	$p \leq 0.0488$

MDD = minimally detectable difference; OS = overall survival; RFS = recurrence free survival.

Note: Assumes 5% dropout rate over 12 months for OS analyses.

[a] Study month at which required number of events are projected to occur, where Study Month 1 is the month the first patient is enrolled. Analysis results will be available after data cleaning.

[b] The largest observed hazard ratio that is projected to be statistically significant.

[c] The projected boundary for statistical significance for the number of events shown (actual boundary to be calculated at time of analysis based on actual number of events).

6.11 CHINA SUBPOPULATION ANALYSES

The Sponsor is targeting a total enrollment of a minimum of 250 patients from mainland China. The sample size of the China subpopulation was determined by characterizing the efficacy and safety profile of atezolizumab plus bevacizumab. After approximately 662 patients have been randomized into the global portion of the study, in the event that fewer than 250 patients from mainland China are enrolled, additional patients in China may be subsequently randomized into the two study arms in a 1:1 ratio in an extended China enrollment phase to ensure a total of approximately 250 patients from mainland China for the China subpopulation.

The primary efficacy objective of the China subpopulation analysis is to assess efficacy, as measured by the primary endpoint of IRF-assessed RFS of atezolizumab plus bevacizumab compared with active surveillance in the Chinese patients. The China subpopulation is not powered to demonstrate statistical significance in terms of efficacy, and no formal hypothesis testing will be performed.

The China subpopulation analyses will be conducted when sufficient RFS events have occurred to demonstrate approximately 80% probability of maintaining 50% of RFS risk reduction compared with that estimated from the global population. The exact timing of analyses will be specified in the SAP.

The analysis methods for China subpopulation will be the same as for the global population unless elsewhere noted. The results of the China subpopulation analyses will be summarized in a separate report from the clinical study report for the global population. The statistical details for such analyses in the China subpopulation will be documented in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and any other externally generated electronic study data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

The eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

The eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. The eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. The eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for

the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) or Clinical Trial Regulation (536/ 2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study- related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, 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.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will

permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 175 sites globally will participate to randomize approximately 662 patients. Screening and enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will evaluate patient safety and efficacy during the study. An IRF will be used to enable centralized, independent reviews of images.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/ or other summaries of clinical study results may be available in the health authority database for public access, as required by local regulation, and will be made available upon request. For more information, refer to the Roche Global Policy on Sharing or Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only.

10. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

Antonia SJ, Villegas A, Daniel D, at al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med. 2017;377:1919–1929.

Avastin® (bevacizumab) U.S. Package Insert, Genentech, Inc.

Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med 2015;373;1627–39.

Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.

Bruix J, Takayama T, Mazzaferro V, at al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2015;16:1344–54.

Chen DS and Hurwitz H. Combinations of bevacizumab with cancer immunotherapy. Cancer J. 2018 Jul/Aug;24(4):193-204.

Chen DS and Mellman I. Nature. Elements of cancer immunity and the cancer-immune set point. 2017;541:321–30.

Chen Q, Shu C, Laurence AD, et al. Effect of Huaier granule on recurrence after curative resection of HCC: a multicentre, randomised clinical trial. Gut. 2018;67:2006–16.

Cheng AL, Qin S, Ikeda M, et al. Mbrave150: Efficacy and Safety Results From a Ph 3 Study Evaluating Atezolizumab (atezo) + Bevacizumab (bev) vs Sorafenib (Sor) as First Treatment (tx) for Patients (pts) With Unresectable Hepatocellular Carcinoma (HCC). Proceedings of ESMO Asia 2019: 22–24 November 2019 [cited: 27 November 2019]; Singapore. Available from: https://www.esmo.org/Oncology-News/Atezolizumab-in-Combination-with-Bevacizumab-Provides-Superior-Outcome-Compared-with-Sorafenib-in-Unresectable-HCC.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404–13.

Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs 2016;8:593–603.

[EASL] European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.

Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018;378:1789–801.

El-Khoueiry A. The promise of immunotherapy in the treatment of hepatocellular carcinoma. Am Soc Clin Oncol Educ Book 2017;37:311–17.

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Finn RS, Qin S, Ikeda, M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894–905.

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer 1999;35:939–41.

Frebel H, Nindl V, Schuepbach RA, et al. Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice. J Exp Med 2012;209:2485–99.

Gabriel E, Bagaria SP. Assessing the Impact of Circulating Tumor DNA (ctDNA) in Patients With Colorectal Cancer: Separating Fact From Fiction. Front Oncol 2018;8:297.

Gabrielson A, Wu Y, Wang H, et al. Intratumoral CD3 and CD8 T-cell densities associated with relapse-free survival in HCC. Cancer Immunol Res 2016;4:419–30.

Gravante G, Overton J, Sorge R, et al. Radiofrequency ablation versus resection for liver tumours: an evidence-based approach to retrospective comparative studies. J Gastrointest Surg 2011;15:378–87.

Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358–80.

Herbst RS, Baas P, Kim D-W, et al. Pembrollizumab versus docetaxel for previously treated PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387;1540–50.

Herbst RS, Soria JC, Kowanetz M et al. Predictive correlates of response to the anti-PD-L1 antibody atezolizumab in cancer patients. Nature 2014; 515: 563–7.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.

Huang J, Hernandez-Alejandro R, Croome KP, et al. Radiofrequency ablation versus surgical resection for hepatocellular carcinoma in Childs A cirrhotics-a retrospective study of 1,061 cases. J Gastrointest Surg 2011;15:311–20.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27.

Lan KKG and DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659–63.

Lee M, Ryoo BY, Hsu CH, et al. Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study. Lancet Oncol 2020;21:808–20.

Lee M, Ryoo BY, Hsu CH, et al. LBA39 Randomised efficacy and safety results for atezolizumab (Atezo)+ bevacizumab (Bev) in patients (pts) with previously untreated, unresectable hepatocellular carcinoma (HCC). Ann Oncol 2019;30(Supplement_5):mdz394-030.

Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American society of clinical oncology clinical practice guideline update 2014. J Clin Oncol 2015;33:654–6.

Martins-Filho SN, Paiva C, Azevedo RS, et al. Histological grading of hepatocellular carcinoma—a systematic review of literature. Front Med (Lausanne) 2017;4:193.

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.

[NCCN] National Comprehensive Cancer Network. Recommendations of the NCCN COVID-19 Vaccination Advisory Committee [resource on the Internet]. 2021 [cited: 28 May 2021]. Available from: https://www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v2-0.pdf?sfvrsn=b483da2b_2.

Noh JH, Kim TS, Ahn KS, et al. Prognostic factors after hepatic resection for the single hepatocellular carcinoma larger than 5 cm. Ann Surg Treat Res 2016;91:104–11.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549–56.

Okrah K, Tarighat S, Liu B, Koeppen H, et al. Transcriptomic analysis of hepatocellular carcinoma reveals molecular features of disease progression and tumor immune biology. NPJ Precis Oncol 2018;2:25.

Omata M, Cheng AL, Kokudo N, Kudo M, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11:317–370.

Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in healthrelated quality-of-life scores. J Clin Oncol 1998;16:139–44.

Pawlik TM, Poon RT, Abdalla EK, at al. Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. Arch Surg 2005;140:450–7; discussion 457–8.

Rini BI, Powles T, Atkins MB, et al. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. Lancet 2019;393:2404–15.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Sasaki K, Shindoh J, Nishioka Y, et al. Impact of viral etiology on postoperative de novo recurrence after hepatectomy for hepatocellular carcinoma in cirrhotic patients. J Gastrointest Surg 2017;21:487–95.

Sia D, Jiao Y, Martinez-Quetglas I, et al. Identification of an immune-specific class of hepatocellular carcinoma, based on molecular features. Gastroenterology 2017;153:812–26.

[SITC] Society for Immunotherapy of Cancer. Society for Immunotherapy of Cancer statement on SARS-CoV-2 vaccination and cancer immunotherapy [resource on the Internet]. Press release: 23 December 2020 [cited: 28 May 2021]. Available from: https://www.sitcancer.org/aboutsitc/press-releases/2020/sitc-statement-sars-cov-2-vaccination-cancer-immunotherapy.

Shen J, Wen J, Li C, et al. The prognostic value of microvascular invasion in early-intermediate stage hepatocelluar carcinoma: a propensity score matching analysis. BMC Cancer 2018;18:278.

Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 2018;378:2288–301.

Tecentriq® (atezolizumab) U.S. Package Insert, Genentech.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012;366:2443–54.

Villanueva A. Hepatocellular carcinoma. N Engl J Med 2019;380:1450–62.

Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017;377:1824–35. Villanueva A. Hepatocellular Carcinoma. N Engl J Med 2019;380:1450–62.

Wang R, Li X, Zhang H, et al. Cell-free circulating tumor DNA analysis for breast cancer and its clinical utilization as a biomarker. Oncotarget 2017;8:75742–55.

Wang Z, Ren Z, Chen Y, et al. Adjuvant Transarterial Chemoembolization for HBV-Related Hepatocellular Carcinoma After Resection: A Randomized Controlled Study. Clin Cancer Res 2018;24:2074–81.

Wei W, Jian PE, LiSH, et al. Adjuvant transcatheter arterial chemoembolization after curative resection for hepatocellular carcinoma patients with solitary tumor and microvascular invasion: a randomized clinical trial of efficacy and safety. Cancer Commun (Lond) 2018;10:61.

Zhong JH, Rodríguez AC, Ke Y, et al. Hepatic resection as a safe and effective treatment for hepatocellular carcinoma involving a single large tumor, multiple tumors, or macrovascular invasion. Medicine (Baltimore) 2015;94:e396.

Zhao RC, Zhou J, Wei YG, et al. Cost-effectiveness analysis of transcatheter arterial chemoembolization with or without sorafenib for the treatment of unresectable hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2017;16:493–98.

Zhou J, Sun HC, Wang Z, et al. Guidelines for diagnosis and treatment of primary liver cancer in China (2017 edition). Liver Cancer 2018;7:235–60.

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.

Appendix 1
Schedule of Activities

	Both Arms		Arm A (Atezolizumab + Bevacizumab)	Arm B (Active Surveillance)		Both Arms	Both Arms
	Screening [a]			Day 1 of Cycles 1, 3, 5, 7, 9, 11, 13, 15, 17 [b]	Day 1 of Cycles 2, 4, 6, 8, 10, 12, 14, 16 [b]	Treatment/ Surveillance Discon.[c]	
Assessment Timing	Days –28 to –1	Days –7 to –1	Day 1 of Each Cycle [b]			≤ 30 Days after Final Cycle	Long-Term Follow-Up
Informed consent [a]	x						
Review of eligibility criteria	x						
Demographic data	x						
Medical history and baseline conditions	x						
ECOG Performance Status		x	x [d]	x [d]		x	
Patient-reported outcomes			Odd Cycles only, starting at Cycle 1 [d, e]	x [d, e]		x [f]	x [f]
Complete physical examination [g]	x						
Limited physical examination [h]			x [d]	x [d]		x	
Weight	x [i]		x [i]	x		x	
Height	x						
Vital signs [j]	x		x	x		x	
12-lead ECG [k]	x		Perform as clinically indicated				

Appendix 1: Schedule of Activities (cont.)

	Both Arms		Arm A (Atezolizumab + Bevacizumab)	Arm B (Active Surveillance)		Both Arms	Both Arms
	Screening [a]					Treatment/ Surveillance Discon.[c]	
Assessment Timing	Days –28 to –1	Days –7 to –1	Day 1 of Each Cycle [b]	Day 1 of Cycles 1, 3, 5, 7, 9, 11, 13, 15, 17 [b]	Day 1 of Cycles 2, 4, 6, 8, 10, 12, 14, 16 [b]	≤30 Days after Final Cycle	Long-Term Follow-Up
EGD [l]	x						
HIV, HBV, HCV serology [m]	x						
Quantitative HBsAg, HBV DNA, HCV RNA [n]	x		Cycles 5 and 9 only [d]	Cycles 5 and 9 only [d]		x	
Hematology [o]		x	x [d, p]	x [d]		x	
Serum chemistry [q]		x	x [d, p]	x [d]		x	
Coagulation (aPTT, INR)		x	x [d, p]	x [d]		x	
Child-Pugh assessment [r]		x	x [d]	x [d]		x	
Pregnancy test [s]	x		x [d]			x [t]	x [s]
Urinalysis [u]		x [v]	x [d, p, v]	x [d]		x	
C-reactive protein			Cycle 1 only [d]	Cycle 1 only [d]			
α-fetoprotein	x		x [d]	x [d]			
TSH, free T3 (or total T3), free T4 [w]	x		Cycles 5, 9, 13, and 17 only [d]				
Tumor tissue sample for biomarker analysis [x]	x						

Appendix 1: Schedule of Activities (cont.)

	Both Arms		Arm A (Atezolizumab + Bevacizumab)	Arm B (Active Surveillance)		Both Arms	Both Arms
	Screening [a]					Treatment/ Surveillance Discon.[c]	
Assessment Timing	Days –28 to –1	Days –7 to –1	Day 1 of Each Cycle [b]	Day 1 of Cycles 1, 3, 5, 7, 9, 11, 13, 15, 17 [b]	Day 1 of Cycles 2, 4, 6, 8, 10, 12, 14, 16 [b]	≤30 Days after Final Cycle	Long-Term Follow-Up
Serum PK sample			See Appendix 3			See Appendix 3	
Serum ADA sample			See Appendix 3			See Appendix 3	
Blood, serum, and plasma biomarker samples	See Appendix 3						
Blood sample for WES [y]			Cycle 1 only. See Appendix 3	Cycle 1 only. See Appendix 3			
Study treatment infusion [z]			X				
Adverse events [aa]	x		x [bb]	x [bb]	x [bb, cc]	x	
Concomitant medications [dd]		x	x [bb]	x [bb]	x [bb, cc]	x	
Imaging assessments [ee]	x		Every 12 weeks (±7 days) for the first 3 years following randomization and every 24 weeks (±10 days) thereafter, regardless of treatment delays, until the end of Year 7 after randomization or until IRF-confirmed disease recurrence [ff], whichever occurs first				
Tumor tissue sample, if clinically feasible			At the time of radiographic confirmation of disease recurrence [gg]				
Survival and anti-cancer therapy follow-up [hh]							x

ADA = anti-drug antibody; CT = computed tomography; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; EGD = esophagogastroduodenscopy; FFPE = formalin-fixed, paraffin-embedded; GI = gastrointestinal; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HGRAC = Human Genetic Resources Administration of China; IL42–EORTC = IL42–European Organisation for the Research and Treatment of Cancer; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetic; PRO = patient-reported outcome; WES = whole exome sequencing.

Notes: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted. Each cycle is 21 days in length. If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule, with one exception: If treatment was postponed for fewer than 3 days, the patient can resume the original schedule.

[a] Written informed consent may be obtained more than 28 days prior to randomization and is required before performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and per the relevant protocol-defined window may be used for screening assessments rather than repeating such tests. Screening local laboratory assessments obtained ≤96 hours prior to Day 1 of Cycle 1 do not have to be repeated for Cycle 1. Test results should be reviewed prior to administration of study treatment.

[b] Day 1 of Cycle 1 should occur within 3 business days from randomization, with the exception of the emergence of an adverse event for which dosing may be postponed. Day 1 of subsequent cycles should occur within a window of ±3 days.

[c] Patients will return to the clinic for a treatment/surveillance discontinuation visit not more than 30 days after the final dose of study treatment (patients who receive active treatment) or final visit or telephone contact (patients who do not receive active treatment), or at the end of the 12-month treatment/surveillance period.

[d] Indicated assessments may be obtained ≤96 hours before Day 1 of each cycle. C-reactive protein may be obtained ≤96 hours before Day 1 of Cycle 1.

[e] PRO assessments (IL42–EORTC QLQ-C30 [Reduced] and EQ-5D-5L questionnaires) will be completed at the site or by means of telephone call at each odd cycle visit before the patient receives any information on disease status, and prior to the completion of all other study assessments and the administration of study treatment. Patients who experience disease recurrence will complete PRO assessments at the visit when disease recurrence is determined by the investigator if operationally feasible, at the treatment/surveillance discontinuation visit, and at the first four LTFU visits. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. If the patient is unable to complete the measure on her or his own, interview assessment is allowed but can only be conducted by site staff (see Section 4.5.8.1).

[f] PRO assessments (IL42–EORTC QLQ-C30 [Reduced] and EQ-5D-5L questionnaires) will be administered by trained staff at the treatment/surveillance discontinuation visit, and at the first four LTFU visits. In scenarios where PRO assessments cannot be done on scheduled LTFU visits, PRO assessments may be done ≤ 96 hours prior to the scheduled LTFU visits; when imaging assessments are

done at a different day or location than the LTFU visit, PRO assessments may be done after imaging assessments, as long as results have not been discussed with patients. For patients who experience disease recurrence after the collection of the first four LTFU PRO assessments, PRO assessments do not need to be collected again.

[g] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat and cardiovascular, dermatologic, musculoskeletal, respiratory, GI, genitourinary, and neurologic systems.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated.

[i] The dose of bevacizumab will be based on the patient's weight (in kilograms) measured $\leq$14 days prior to baseline (the initiation of study treatment) and will remain the same throughout the study unless there is a weight change of $>$10% from the baseline body weight, in which case the bevacizumab dose should be modified. Body weight will be re-baselined at the time of dose change, and dose modifications should occur if the patient's weight changes $>$10% from the new baseline.

[j] Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure, and temperature. For patients receiving active treatment, vital signs should be measured within 60 minutes prior to each infusion. Vital signs will be measured at the end of bevacizumab infusion and 2 ($\pm$1) hours after end of the infusion and will also be collected during and at 30 ($\pm$10) minutes after every infusion of atezolizumab if clinically indicated.

[k] Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[l] EGD is required only for patients who did not undergo an EGD prior to surgical resection or ablation.

[m] At screening, patients will be tested for HIV, HBsAg, HBcAb, and HBsAb. HBV DNA test must be performed during screening in patients who have positive serology for HBsAg and/or positive serology for HBcAb.

[n] If patient tests positive for HBsAg and/or HBcAb, quantitative HBsAg and HBV DNA will be tested at screening, Day 1 of Cycles 5 and 9, and at the discontinuation visit. If patient tests positive for HCV antibody at screening, quantitative HCV RNA must be tested locally at screening, on Day 1 of Cycles 5 and 9, and at the discontinuation visit. If local quantitative HBsAg test is not available, a qualitative HBsAg followed by quantitative HBV DNA can be performed as an alternative.

[o] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells). A manual differential can be done if clinically indicated.

[p] The indicated local laboratory assessments from each cycle must be reviewed prior to study treatment administration for each cycle.

[q] Serum chemistry includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and lactate dehydrogenase.

[r] Patients will undergo assessment of Child-Pugh status at screening and Day 1 of each cycle for patients in Arm A and Day 1 of each odd cycle for patients in Arm B (see Appendix 4) as well as at the Treatment/Surveillance discontinuation visit.

[s] All women of childbearing potential will have a serum pregnancy test within 14 days before Day 1 of Cycle 1. Urine pregnancy tests will be performed at specified subsequent visits for patients in Arm A including prior to Day 1 of each cycle and at the treatment discontinuation visit. An additional pregnancy test should be performed 6 months after last administration of study drug. Pregnancy test results should be reviewed and confirmed as negative prior to administration of treatment at each cycle. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[t] A pregnancy test at the treatment/surveillance discontinuation visit is only required for patients in Arm A.

[u] Urine dipstick includes specific gravity, pH, glucose, protein, ketones, and blood.

[v] Patients must have $<2+$ proteinuria on dipstick within 7 days prior to Day 1 of Cycle 1. Patients with $\geq 2+$ proteinuria on dipstick urinalysis at baseline must undergo a 24-hour urine collection (or protein:creatinine ratio as an alternative per local guidance) and demonstrate <1 g of protein in 24 hours. 24 hour urine collection (or protein:creatinine ratio as an alternative per local guidance) should be done prior to bevacizumab administration according to the guidelines in Appendix 12.

[w] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycles 5, 9, 13, and 17.

[x] Mandatory for resected patients: representative FFPE tumor from the resected specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections. If available for ablated patients: a representative FFPE tumor specimen in a paraffin block (preferred) or approximately 10–15 slides containing unstained, freshly cut, serial sections along with an associated pathology report. Samples collected via resection, core-needle biopsy, or excisional, incisional, punch, or forceps biopsy are preferred. However, all specimen types (e.g., fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples) are acceptable. Tissue samples should be submitted within four weeks following randomization. For patients in China, tissue samples may be submitted retrospectively upon HGRAC approval of sample submission.

[y] Not applicable for a site that has not been granted approval for WES.

[z] For patients receiving active treatment, atezolizumab will be administered first followed by bevacizumab, with a minimum of 5 minutes between dosing. The initial dose of atezolizumab will be delivered over 60 ($\pm$15) minutes. Subsequent infusions will be delivered over 30 ($\pm$10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 ($\pm$15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. The initial dose of bevacizumab will be delivered over 90 ($\pm$15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 ($\pm$10) minutes or 90 ($\pm$15) minutes if the patient experienced an infusion-related reaction with the previous infusion. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ($\pm$15) minutes. In the absence of unacceptable toxicity, patients may continue study treatment for up to 12 months or until disease recurrence.

[aa] After informed consent has been obtained but prior to initiation of study treatment or surveillance on Day 1 of Cycle 1, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment or surveillance on Day 1 of Cycle 1, all adverse events will be reported until 30 days after the final cycle (i.e., final cycle of treatment or surveillance) or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final cycle or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment.

[bb] In the event that a patient cannot attend a clinic visit, telemedicine may be used to collect adverse event and concomitant medications.

[cc] Adverse events and concomitant medications at cycles can be assessed either via telephone call or clinic visit.

[dd] Concomitant medications includes 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 Day 1 of Cycle 1 to the treatment/surveillance discontinuation visit.

[ee] Imaging performed during screening should consist of CT and/or MRI of the chest, abdomen, pelvis, and head,and any other imaging studies (CT scan of the neck, plain films, etc.) as clinically indicated by the treating physician (see Section 4.5.5 for details). Patients will undergo imaging assessments every 12 weeks (±7 days) for the first 3 years following randomization and every 24 weeks (±10 days) thereafter, regardless of treatment delays, until the end of Year 7 after randomization or IRF-confirmed disease recurrence, whichever occurs first (see Section 4.5.5 for details). Thus, imaging assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease recurrence, even if they start new, non–protocol-specified anti-cancer therapy. The same radiographic procedures and technique should be used throughout the study for each patient (e.g., if the patient had CT chest/abdomen/pelvis performed during screening, then he or she should subsequently undergo CT performed using the same radiologic protocol throughout the remainder of the study). Results must be reviewed by the investigator before dosing at the next cycle.

[ff] Criteria for diagnosis of recurrence are described in Section 4.5.5.

[gg] Patients will undergo a mandatory tumor biopsy sample collection at the time of first evidence of clinical or radiographic disease recurrence if deemed clinically feasible by the investigator. Biopsies at the time of recurrence should be performed within 12 weeks after recurrence or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

[hh] Information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected by means of telephone calls or telemedicine, patient medical records, and/or clinic visits approximately every 12 weeks (± 21 days) until death (unless the patient withdraws consent or the Sponsor terminates the study). If the patient experiences disease recurrence during the treatment/surveillance period, the first LTFU should be done 12 weeks (± 21 days) from the last scheduled imaging assessment. If the patient has not experienced disease recurrence in the treatment/surveillance period, the first LTFU should be done at the first scheduled

imaging assessment after the treatment/surveillance period. The visit window for the LTFU is ± 21 days. 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.

Appendix 2
Schedule of Activities for Patients in Arm B Who Cross Over to Treatment with Atezolizumab plus Bevacizumab

Assessment Timing	Screening [a]		Treatment Period	Treatment Discontinuation [c]	Long-Term Follow-Up
	Days –28 to –1	Days –7 to –1	Day 1 of Each 21-Day Cycle [b]	≤30 Days after Final Dose	
Review of eligibility criteria	x				
ECOG Performance Status		x	x [d]	x	
Limited physical examination [e]	x		x [d]		
Weight [f]	x		X	x	
Vital signs [g]	x		X	x	
12-lead ECG [h]	x		Perform as clinically indicated		
EGD	x [i]				
Quantitative HBsAg, HBV DNA, HCV RNA [j]			As clinically indicated	x	
Hematology [k]		x	x [d, l]		
Serum chemistry [m]		x	x [d, l]		
Coagulation panel (aPTT, INR)		x	x [d, l]		
Child-Pugh assessment [n]		x [d]	x [d]	x [n]	
Pregnancy test [o]	x		x [d]	x	x [o]
Urinalysis [p]		x [q]	x [d, l]		
α-fetoprotein	x		x [d]		

Appendix 2: Schedule of Activities for Patients in Arm B who Cross Over to Treatment with Atezolizumab plus Bevacizumab (cont.)

Assessment Timing	Screening [a]		Treatment Period	Treatment Discontinuation [c]	Long-Term Follow-Up
	Days –28 to –1	Days –7 to –1	Day 1 of Each 21-Day Cycle [b]	≤30 Days after Final Dose	
TSH, free T3 (or total T3), free T4 [r]	x		Every 4 cycles starting at Cycle 5 [d]		
Study treatment infusion [s]			X		
Adverse events [t, u]	x		X	x	
Concomitant medications [u, v]		x	X	x	
Imaging assessments [w]	x [x]		Every 12 weeks after Crossover Day 1 of Cycle 1 (±7 days; at approximately every 4 cycles), regardless of treatment delays, until disease recurrence [y] (for patients with NED at the time of crossover) or loss of clinical benefit as determined by the investigator (for patients with measurable disease at crossover)		
Survival and anti-cancer therapy follow-up [z]					x

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EGD = esophagogastroduodenoscopy; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; NED = no evidence of disease.

Notes: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted. Each cycle is 21 days in length. If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule, with one exception: If treatment was postponed for fewer than 3 days, the patient can resume the original schedule.

[a] Results of tests or examinations performed per the relevant protocol-defined window may be used for screening assessments rather than repeating such tests. Screening local laboratory assessments obtained ≤96 hours prior to the initiation of study treatment do not have to be repeated for Cycle 1. Test results should be reviewed prior to administration of study treatment.

[b] Day 1 of Cycle 1 should occur within 3 business days from the end of screening, with the exception of the emergence of an adverse event for which dosing may be postponed. Day 1 of Cycle 1 must be no later than 12 weeks after documentation of recurrence. Day 1 of subsequent cycles should occur within a window of ±3 days.

[c] Patients will return to the clinic for a treatment discontinuation visit not more than 30 days after the final dose of study treatment.

[d] Indicated assessments may be obtained ≤96 hours before Day 1 of each cycle.

[e] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated.

[f] The dose of bevacizumab will be based on the patient's weight (in kilograms) measured ≤14 days prior to baseline (the initiation of study treatment) and will remain the same throughout the study unless there is a weight change of >10% from the baseline body weight, in which case the bevacizumab dose should be modified. Body weight will be re-baselined at the time of dose change, and dose modifications should occur if the patient's weight changes >10% from the new baseline.

[g] Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure, and temperature. Vital signs should be measured within 60 minutes prior to each infusion. Vital signs will be measured at the end of bevacizumab infusion and 2 (±1) hours after end of the infusion and will also be collected during and at 30 (±10) minutes after every infusion of atezolizumab if clinically indicated.

[h] Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[i] As clinically indicated.

[j] If patient tests positive for HBsAg and/or HBcAb at initial screening, quantitative HBsAg and HBV DNA will be tested as clinically indicated during crossover treatment and at the discontinuation visit. If patient tests positive for HCV antibody at initial screening, quantitative HCV RNA must be tested locally as clinically indicated and at the discontinuation visit. If local quantitative HBsAg test is not available, a qualitative HBsAg followed by quantitative HBV DNA can be performed as an alternative.

[k] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells). A manual differential can be done if clinically indicated.

[l] The indicated local laboratory assessments from each cycle must be reviewed prior to study treatment administration for each cycle.

[m] Serum chemistry includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and lactate dehydrogenase.

[n] Patients will undergo assessment of Child-Pugh status at screening and Day 1 of each cycle (see Appendix 4) as well as at the Treatment Discontinuation visit. Laboratory tests (bilirubin, albumin, and INR) required for Child-Pugh assessment at the Treatment Discontinuation visit can either be repeated or taken from the most recent cycle visit if ≤ 30 days from Treatment Discontinuation visit.

[o] All women of childbearing potential will have a serum pregnancy test within 14 days before Day 1 of Cycle 1. Urine pregnancy tests will be performed at specified subsequent visits including prior to Day 1 of each cycle and at the treatment discontinuation visit. An additional pregnancy test should be performed 6 months after last administration of study drug. Pregnancy test results should be reviewed and confirmed as negative prior to administration of treatment at each cycle. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[p] Urine dipstick includes specific gravity, pH, glucose, protein, ketones, and blood.

[q] Patients must have $<2+$ proteinuria on dipstick within 7 days prior to initiation of study treatment. Patients with $\geq 2+$ proteinuria on dipstick urinalysis at baseline must undergo a 24-hour urine collection and demonstrate <1 g of protein in 24 hours. 24 hour urine collection (or protein:creatinine ratio as an alternative per local guidance) should be done prior to bevacizumab administration according to the guidelines in Appendix 12.

[r] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 5 and every 4 cycles thereafter (i.e., Cycles 9, 13, etc.).

[s] Atezolizumab will be administered first followed by bevacizumab, with a minimum of 5 minutes between dosing. The initial dose of atezolizumab will be delivered over 60 ($\pm$15) minutes. Subsequent infusions will be delivered over 30 ($\pm$10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 ($\pm$15) minutes if the patient experienced an infusion–associated adverse event with the previous infusion. The initial dose of bevacizumab will be delivered over 90 ($\pm$15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 ($\pm$10) minutes, or 90 ($\pm$15) minutes if the patient experienced an infusion-related reaction with the previous infusion. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ($\pm$15) minutes. Patients may continue study treatment until unacceptable toxicity or second disease recurrence (for patients with NED at the time of crossover), or 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) (for patients with measurable disease at crossover).

[t] After the end of the reporting period for serious adverse events (i.e., 90 days after the final cycle of surveillance) but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., resection or ablation to treat disease recurrence, invasive procedures such as biopsies) should be reported. After initiation of study treatment on Day 1 of Cycle 1, all adverse events will be reported until 30 days after the final cycle or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final cycle or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment.

[u] In the event that a patient cannot attend a clinic visit, telemedicine may be used to collect adverse event and concomitant medications.

[v] Concomitant medications includes 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 Day 1 of Cycle 1 to the treatment discontinuation visit.

[w] The same radiographic procedures and technique should be used throughout the study for each patient (e.g., if the patient had CT chest/abdomen/pelvis performed during screening, then he or she should subsequently undergo CT performed using the same radiologic protocol throughout the remainder of the study). Results must be reviewed by the investigator before dosing at the next cycle.

[x] An imaging assessment at screening is optional; the first documented recurrence prior to crossover can serve as the baseline imaging assessment.

[y] Criteria for diagnosis of recurrence are described in Section 4.5.5.

[z] Information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected by means of telephone calls or telemedicine, patient medical records, and/or clinic visits approximately every 12 weeks (± 21 days) until death (unless the patient withdraws consent or the Sponsor terminates the study). 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.

Appendix 3
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Arm A Samples [a]	Arm B Samples [a]
Screening (Days −28 to −1)	At visit	Biomarker (plasma)	Biomarker (plasma)
Day 1 of Cycle 1	At visit (prior to any drug administration for Arm A	Atezolizumab PK (serum) Atezolizumab ADA (serum) Biomarker (WES) (blood) [b] Biomarker (plasma, serum) [c]	Biomarker (WES) (blood) [b] Biomarker (plasma, serum) [c]
	30 min (±10 minutes) after end of atezolizumab infusion	Atezolizumab PK (serum)	
Day 1 of Cycle 2	Prior to any drug administration	Atezolizumab PK (serum) Atezolizumab ADA (serum)	
Day 1 of Cycle 3	At visit (prior to any drug administration for Arm A)	Atezolizumab PK (serum) Atezolizumab ADA (serum) Biomarker (plasma, serum) [c]	Biomarker (plasma, serum) [c]
Day 1 of Cycle 4	Prior to any drug administration	Atezolizumab PK (serum) Atezolizumab ADA (serum)	
Day 1 of Cycle 5	At visit (prior to any drug administration for Arm A)	Biomarker (plasma, serum) [c]	Biomarker (plasma, serum) [c]
Day 1 of Cycle 7	At visit (prior to any drug administration for Arm A)	Biomarker (plasma, serum) [c]	Biomarker (plasma, serum) [c]
Day 1 of Cycle 8	Prior to any drug administration	Atezolizumab PK (serum) Atezolizumab ADA (serum)	
Day 1 of Cycle 9	At visit (prior to any drug administration for Arm A)	Biomarker (plasma, serum) [c]	Biomarker (plasma, serum) [c]
Day 1 of Cycle 11	At visit (prior to any drug administration for Arm A)	Biomarker (plasma, serum) [c]	Biomarker (plasma, serum) [c]
Day 1 of Cycle 12	Prior to any drug administration	Atezolizumab PK (serum) Atezolizumab ADA (serum)	
Day 1 of Cycle 15	At visit (prior to any drug administration for Arm A)	Biomarker (plasma, serum) [c]	Biomarker (plasma, serum) [c]
Day 1 of Cycle 16	Prior to any drug administration	Atezolizumab PK (serum) Atezolizumab ADA (serum)	

Visit	Timepoint	Arm A Samples [a]	Arm B Samples [a]
Treatment/ surveillance discontinuation (≤ 30 days after final cycle)	At visit	Atezolizumab PK (serum) Atezolizumab ADA (serum) Biomarker (plasma, serum) [c]	Biomarker (plasma, serum) [c]
Long-term follow-up period, through Year 3 after randomization [d]	At imaging assessment visits	Biomarker (plasma, serum) [c]	Biomarker (plasma, serum) [c]

ADA = anti-drug antibody; PK = pharmacokinetic; WES = whole exome sequencing.

Note: PK, ADA, and biomarker samples will not be taken in patients randomized to Arm B who cross over to treatment with atezolizumab plus bevacizumab

[a] With the exception of the PK sample to be collected 30 minutes after the infusion on Day 1 of Cycle 1, all other PK, ADA, and biomarker samples can be collected ≤ 96 hours before Day 1 of each cycle.

[b] Not applicable for a site that has not been granted approval for WES. If collection of the WES sample is missed at Cycle 1 Day 1, this sample may be collected at any other time during the study.

[c] At the time of disease recurrence (or the next visit if disease recurrence occurs at an unscheduled visit), biomarker samples will be collected either at the treatment/surveillance discontinuation visit or the imaging assessment visit. Following collection of biomarker samples at the time of disease recurrence, subsequent biomarker sample collection is not required.

[d] During the long-term follow-up period, biomarker sample will be collected at the first imaging assessment and all subsequent imaging assessments (± 6 weeks) through Year 3 after randomization or until disease recurrence, whichever comes first.

Appendix 4
Child-Pugh Classification

Scoring

Measure	Points Scored for Observed Finding		
	1 Point	2 Points	3 Points
Bilirubin (mg/dL)	< 2.0	2.0–3.0	> 3.0
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
Prothrombin time, [a] seconds over control	1.0–3.0	4.0–6.0	> 6.0
International normalized ratio	< 1.7	1.7–2.3	> 2.3
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Encephalopathy (grade)	None	Mild to moderate (Grade 1 or 2)	Severe (Grade 3 or 4)

[a] Prolonged time.

Classification

Points	Class
5–6	A
7–9	B
10–15	C

References

Child CG, Turcotte JG. Surgery and portal hypertension. In: The liver and portal hypertension. Edited by Child CG. Philadelphia, Saunders;1964:50–64.

Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–9.

Appendix 5
Classification of Hepatocellular Carcinoma with Vascular Invasion

Figure 1 shows the classification of portal vein tumor invasion according to the Liver Cancer Study Group of Japan classification (Costentin et al. 2017).

Figure 1 Classification of Portal Vein Tumor Invasion

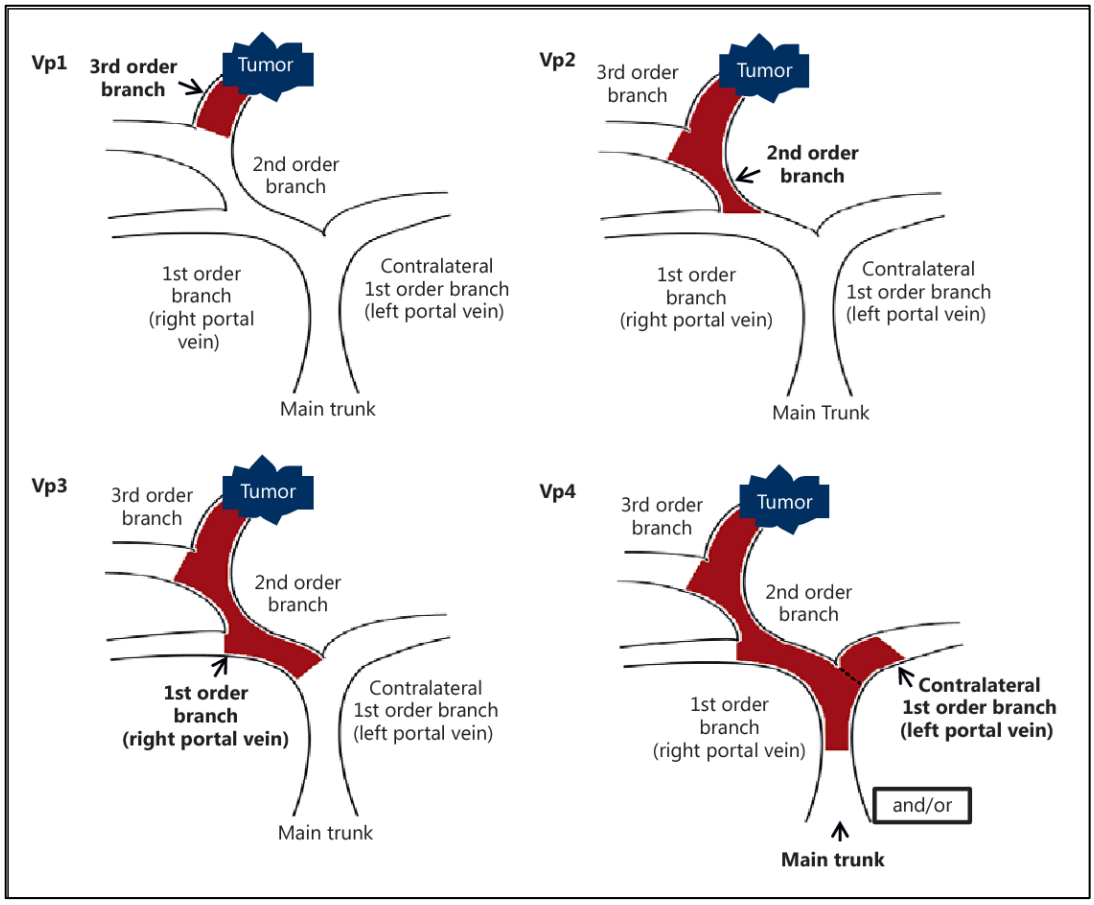


Table 1 Definition of Types of Vascular Invasion in HCC

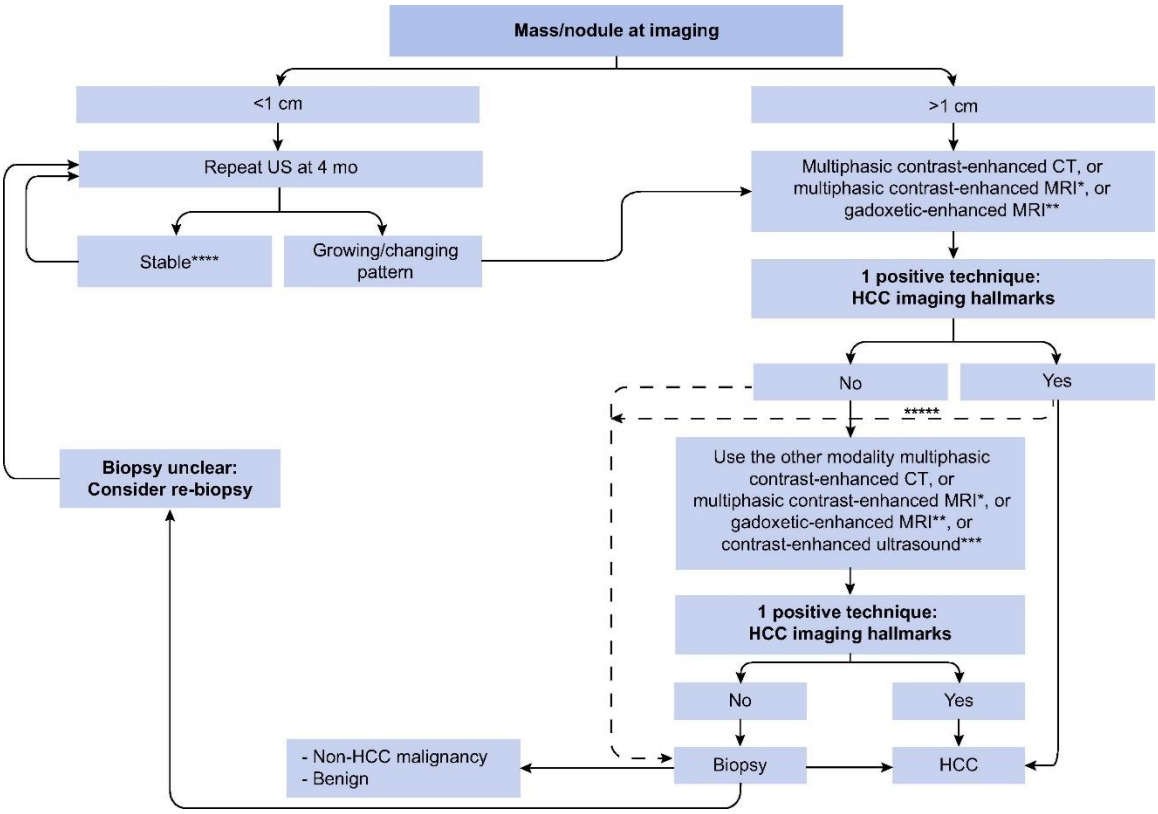
Type of vascular invasion	Classification	Definition	Eligible for IMbrave050
Portal vein	Vp0	No evidence of tumor thrombus invasion	Yes [a]
	Vp1	Tumor thrombus distal to but not in the second-order branches	Yes [a]
	Vp2	Tumor thrombus in the second-order branches	Yes
	Vp3	Tumor thrombus in the first-order branches	No
	Vp4	Tumor thrombus in the main trunk or contralateral or both	No
Hepatic vein	Vv0	Absence of tumor thrombus invasion of the hepatic vein	Yes
	Vv1	Tumor thrombus invasion of peripheral branches of the hepatic vein	No
	Vv2	Tumor thrombus invasion of the right, middle, or left hepatic vein, the inferior right hepatic vein, or the short hepatic vein	No
	Vv3	Tumor thrombus invasion of the inferior vena cava.	No
Microvascular invasion	N/A	Presence of microscopic thrombi within the central hepatic vein, the portal vein, or large capsular vessels	Yes

[a] Only allowed for patients undergoing resection.

REFERENCES

Costentin CE, Ferrone CR, Arellano RS, et al. Hepatocellular carcinoma with macrovascular invasion: defining the optimal treatment strategy. Liver Cancer 2017;6:360–74.

Appendix 6
EASL Clinical Practice Guidelines: Diagnostic Algorithm and Recall Policy in Cirrhotic Liver



APHE = arterial phase hyper-enhancement; CT = computed tomography; EASL = European Association for the Study of the Liver; HCC = hepatocellular carcinoma; IRF = Independent Review Facility; mo = months; MR = magnetic resonance; MRI = magnetic resonance imaging; US = ultrasound.

* Using extracellular MR contrast agents or gadobenate dimeglumine.

** Using the following diagnostic criteria: APHE and washout on the portal venous phase.

*** Using the following diagnostic criteria: APHE and mild washout after 60 seconds. Please note, contrast enhanced-US cannot be used by the IRF to determine recurrence.

**** Lesion < 1 cm stable for 12 months (three controls after 4 months) can be shifted back to regular 6-month surveillance.

***** Optional for center-based programmes.

REFERENCE

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69:182–236.

Appendix 7
Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (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 $\leq$ 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 $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 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.

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 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 used for objective tumor evaluation.

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 should 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 ≥ 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 $\times$ 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 ≥ 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").

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.

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 at prior timepoints (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

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.

Patients with Non-Measurable Disease Only

For patients with non-measurable disease only, the same general concepts apply as noted above. However, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-measurable disease cannot be easily quantified (by definition, if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

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.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

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.

Table 2 Criteria for Overall Response at a Single Timepoint: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

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 and Table 2.

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.

Appendix 8
IL42–European Organisation for the Research and Treatment of Cancer QLQ-C30 (Reduced)

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

ENGLISH

IL42 – EORTC QLQ-C30 (Reduced)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Did you feel tense?	1	2	3	4
9. Did you worry?	1	2	3	4
10. Did you feel irritable?	1	2	3	4
11. Did you feel depressed?	1	2	3	4
12. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
13. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

14. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

15. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 9
EQ-5D-5L

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

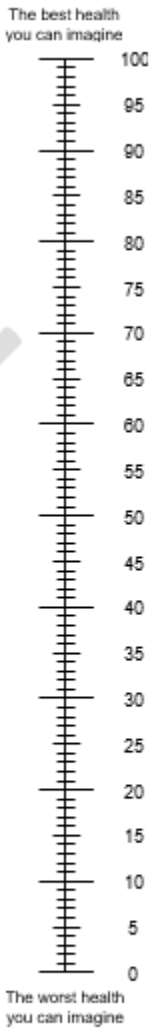
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 10
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life–threatening skin adverse reaction *or pericardial disorder* while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • *Autoimmune myelitis* • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Crohn disease	• Churg-Strauss syndrome • 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 • *Granulomatosis with Polyangiitis*

Appendix 11
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

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

PROCEDURES

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

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 12
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 patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on of the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Bevacizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. If bevacizumab is delayed due to toxicity for $>$ 42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab. Bevacizumab can be resumed after being withheld for $>$ 42 days if the patient is likely to derive clinical benefit.

Atezolizumab or bevacizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The investigator will determine the acceptable length of treatment interruption. If atezolizumab is discontinued, bevacizumab should also be discontinued. If bevacizumab is discontinued, atezolizumab can be continued. If atezolizumab is transiently withheld for adverse events, bevacizumab should also be held.

Refer to Section 4.3.2 for information on dose interruptions for reasons other than toxicity.

MANAGEMENT GUIDELINES

Guidelines for management of patients who experience specific adverse events are provided in Table 1.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab

Event	Action to Be Taken
IRRs, anaphylaxis, and hypersensitivity reactions	• Guidelines for management of IRRs for atezolizumab are provided in Appendix 13. • Guidelines for management of IRRs for bevacizumab are provided below. • For anaphylaxis precautions, see Appendix 11. • For hypersensitivity reactions and allergic reactions, permanently discontinue the causative agent.
IRR to bevacizumab, Grade 1	• Systemic intervention is not indicated. Continue bevacizumab.
IRR to bevacizumab, Grade 2	• Reduce infusion rate to ≤50% or interrupt infusion at the discretion of the investigator per medical judgment. • If the infusion is interrupted, it may be resumed at ≤50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.
IRR to bevacizumab, Grade 3 or 4	• Stop infusion and permanently discontinue bevacizumab. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen) if clinically indicated.

IRR = infusion-related reaction.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity	
GI perforation, any grade	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • Initiate treatment per institutional guidelines. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a]
Bowel obstruction, Grade 2	• Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab for partial obstruction requiring medical intervention. • Bevacizumab may be restarted upon complete resolution of event.
Bowel obstruction, Grade 3 or 4	• Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab until complete resolution. • If surgery is necessary, patient may restart bevacizumab after full recovery from surgery and at the investigator's discretion.
Posterior reversible encephalopathy syndrome	
Posterior reversible encephalopathy syndrome, any grade confirmed by magnetic resonance imaging	• Withhold atezolizumab. Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a]

GI = gastrointestinal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Hypertension [a, b]	
General guidance	• Treat with antihypertensive medication as needed.
Hypertension, Grade 1	• Continue atezolizumab and bevacizumab. • Consider increased BP monitoring.
Hypertension, Grade 2	• Continue atezolizumab. • If asymptomatic, begin or modify baseline anti-hypertensive therapy and continue bevacizumab. • If symptomatic, start or adjust anti-hypertensive therapy.
Hypertension, Grade 3	• Continue atezolizumab. • Modify existing anti-hypertensive therapy (more than one drug or more intensive therapy than previously indicated). • Withhold bevacizumab until symptoms resolve AND BP $<$ 160/90 mmHg
Hypertension, Grade 4	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Hemorrhage	
Hemorrhage, Grade 3 or 4 (excluding cerebral hemorrhage)	• Continue atezolizumab. • Permanently discontinue bevacizumab.
CNS hemorrhage, any grade	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Grade $\geq$2 hemoptysis ($\geq$2.5 mL of bright red blood per episode)	• Continue atezolizumab. • Permanently discontinue bevacizumab.
Bleeding in patients on full-dose anticoagulant therapy	• Continue atezolizumab. • Permanently discontinue bevacizumab.

BP = blood pressure.

[a] Vascular disorders (including hypertension and hypotension) are possible adverse events of atezolizumab, considering the mechanism of action.

[b] Based on an average of at least three blood pressure readings at two or more sessions.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Event	Action to Be Taken
Thromboembolic events	
Venous thromboembolic event, Grade 3	• Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be withheld 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.
Venous thromboembolic event, Grade 4	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Arterial thromboembolic event, any grade	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Event	Action to Be Taken
Proteinuria	
Proteinuria, Grade 1 (1+ by dipstick; urinary protein < 1.0 g/24 hours)	• Continue atezolizumab and bevacizumab.
Proteinuria, Grade 2 (2+ and 3+ by dipstick; urinary protein 1.0–3.4 g/24 hours)	• Continue atezolizumab. • For 2+ dipstick: Continue bevacizumab and collect 24-hour urine protein [a] prior to subsequent bevacizumab administration. • For 3+ dipstick: Obtain 24-hour urine [a] prior to administering bevacizumab. • Withhold bevacizumab for urinary protein ≥ 2 g/24 hours. • If bevacizumab is withheld and urine protein improves to < 2 g/24 hours ≤ 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab.
Proteinuria, Grade 3 (4+ by dipstick; urinary protein ≥ 3.5 g/24 hours) with no diagnosis of nephrotic syndrome	• Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab. • If urine protein improves to < 2 g/24 hours ≤ 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab.
Nephrotic syndrome, Grade 3 or 4	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Fistula	
Fistula formation involving an internal organ, any grade	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [b]
Fistula formation not involving an internal organ, Grade 4	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [b]

[a] An alternative method such as protein:creatinine ratio, per local guidance can be accepted.

[b] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Event	Action to Be Taken
Wound dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Congestive heart failure	
Congestive heart failure, Grade 3 or 4	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Bevacizumab-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab and bevacizumab.
Grade 3	• Continue atezolizumab. Withhold bevacizumab. • If event resolves to Grade 2 or better ≤42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]
Grade 4	• Withhold atezolizumab and bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a] • If event resolves to Grade 2 or better ≤42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 13. • Continue bevacizumab.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 13. • Withhold bevacizumab. • If event resolves to Grade 2 or better ≤42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit.

Appendix 13
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, when clinically indicated.

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

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections.

- Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.
- In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.
- Consider holding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5-1 mg/kg/day of prednisone or equivalent) may be administered.
- For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.
- Hold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1-2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.
- In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.

The investigator should consider the benefit–risk balance a given patient prior to further administration of atezolizumab. 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 the

investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

Guidelines for managing patients who experience selected adverse events are provided in the following sections. Management guidelines are presented by adverse event severity based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. 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. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table 1

.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • 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 with or without transbronchial biopsy. • 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 and contact Medical Monitor. [c, d] • 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 and contact Medical Monitor. [c] • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. • Bronchoscopy or BAL with or without transbronchial biopsy 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; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[d] In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.

HEPATIC EVENTS

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 and contact Medical Monitor. [c]

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

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

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
AST or ALT increases to $>10\times$ ULN or total bilirubin increases to $>3\times$ ULN	• Permanently discontinue atezolizumab and contact Medical Monitor. [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 $\geq$ 1 month.

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

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

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table 3.

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

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

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

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

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

ENDOCRINE EVENTS

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. Patients should be referred to an endocrinologist if an endocrinopathy is suspected. The TSH, free T3, and T4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• Consider withholding atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Grade3 and 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer to an endocrinologist. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism. [c]
Grade 1 hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH <0.1 mU/L:** • Follow guidelines for *Grade 2* hyperthyroidism. • Consider patient referral to endocrinologist.
Grade 2 hyperthyroidism	• Consider withholding atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Refer to an endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]
Symptomatic adrenal insufficiency, Grades 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 and contact the Medical Monitor. [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.

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 and contact the Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [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; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE 5.0.

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

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

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 and contact the Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [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.

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table 6.

IMMUNE-MEDIATED MYOCARDITIS

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.

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.

Table 6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2–4 Immune-mediated pericardial disorders, Grades 2-4	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD or pericardiocentesis 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;
NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

INFUSION-RELATED REACTIONS AND CYTOKINE RELEASE SYNDROME

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

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

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (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 the medical management of IRRs and CRS are provided in Table 7.

Severe SARS-CoV-2 infection 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 SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator's judgment. If a diagnosis of SARS-CoV-2 infection 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 for 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, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact the Medical Monitor. • 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, antipyretic medications, 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 Medical Monitor.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

Event	Management
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 and contact the Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

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

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE 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 $\geq 38°C$ 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, antipyretic medications, 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 event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, antipyretic medications, 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) for information on experimental treatments for CRS.

PANCREATIC EVENTS

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.

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 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 and contact the Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. [c]

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

Event	Management
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [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; ULN = upper limit of normal; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

DERMATOLOGIC EVENTS

The majority of cases of rash reported with the use of atezolizumab 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

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • 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 for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 9 Management Guidelines for Dermatologic Events (cont.)

Event	Management
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [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.

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

NEUROLOGIC DISORDERS

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*, with specific guidelines for myelitis provided in Table 11.*

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • *Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below*

Immune-mediated neuropathy, *including facial paresis,* 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.
	• *For general immune-mediated neuropathy*:
	  • If event resolves to Grade 1 or better, resume atezolizumab. [b]
	  • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
	• *For facial paresis:*
	  • *If event resolves fully, resume atezolizumab* [b]
	  • *If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor.* [c]

Immune-mediated neuropathy, *including facial paresis,* Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.

Table 10 Management Guidelines for Neurologic Disorders (cont.)

Event	Management
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [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.

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 11 Management Guidelines for Immune-Mediated Myelitis

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

IMMUNE-MEDIATED MENINGOENCEPHALITIS

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 12.

Table 12 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact the Medical Monitor. • 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.

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

RENAL EVENTS

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 13.

Table 13 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function closely, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

Table 13 Management Guidelines for Renal Event (cont.)

Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • 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.

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED MYOSITIS

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 14.

Table 14 Management Guidelines for Immune-Mediated Myositis

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

Table 14 Management Guidelines for Immune-Mediated Myositis (cont.)

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

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).

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

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 $\geq 38.5°C$
- 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 $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

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

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

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 15.

Table 15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

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

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

REFERENCES

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

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

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

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

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

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

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

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

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

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

Appendix 14
Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area)

Table 1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	*IMP Designation*	*Marketing Authorization Status in EEA*	*Used within Marketing Authorization*
Atezolizumab (RO5541267)	*IMP (test product)*	*Authorized*	*No*
Bevacizumab (RO4876646)	*IMP (test product)*	*Authorized*	*No*

EEA = European Economic Area; IMP = investigational medicinal product.

Signature Page for Protocol - WO41535 - TECENTRIQ - v6 - Published
System identifier: RIM-CLIN-473392

Approval Task	[redacted] Company Signatory 23-Mar-2023 17:44:02 GMT+0000