Official Title: A Phase Ib/II, Open-Label, Multicenter, Randomized Platform Study Evaluating the Efficacy and Safety of Neoadjuvant Immunotherapy Combinations in Patients with Surgically Resectable Hepatocellular Carcinoma (MORPHEUS-NEO HCC)

NCT Number: NCT05908786

Document Date: Protocol Amendment Version 5: 09-Jul-2024

PROTOCOL

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED PLATFORM STUDY EVALUATING THE EFFICACY AND SAFETY OF NEOADJUVANT IMMUNOTHERAPY COMBINATIONS IN PATIENTS WITH SURGICALLY RESECTABLE HEPATOCELLULAR CARCINOMA (MORPHEUS-NEO HCC)**
PROTOCOL NUMBER:	GO44457
VERSION NUMBER:	5
TEST COMPOUNDS:	Atezolizumab (RO5541267), Bevacizumab (RO4876646), Tiragolumab (RO7092284), and Tobemstomig (RO7247669)
STUDY PHASE:	Phase Ib/II
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: IND 164122 EU CT Number: 2022-502840-11-00 NCT Number: NCT05908786
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.

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PROTOCOL HISTORY

Protocol	
Version	**Date Final**
5	See electronic date stamp on final page of this document.
4	02 November 2023
3	20 September 2023
2	1 June 2023
1	8 December 2022

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol GO44457 has been amended based on updated information from Study IMbrave050, where it was found that the benefit-risk assessment does not support [redacted] in patients with completely resected or ablated hepatocellular carcinoma (HCC) who are at a high risk for disease recurrence. Consequently, patients who have had curative resection in Study GO44457 will no longer have the option to start [redacted] and will move into surveillance following liver resection. The corresponding text has been removed in the following sections:

- Synopsis
- 3.1.1 (Figures 1 and 2)
- 3.1.2
- 4.3.1
- 4.5.8.3
- 4.6.1
- 5.3.1.
- Appendix 12 (Sections 4.1.2, 6, and Tables A12-5 and A12-7)
- Appendix 13 (Sections 4, 6, and Table A13-6)
- Appendix 14 (Sections 4.1.2, 6, and Table A14-5)
- Tables 5 (in Section 3.1.2), A12-6, and A12-8 (and text referring to it) have been removed
- The literature reference Chow et al 2023 has been removed where listed.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED PLATFORM STUDY EVALUATING THE EFFICACY AND SAFETY OF NEOADJUVANT IMMUNOTHERAPY COMBINATIONS IN PATIENTS WITH SURGICALLY RESECTABLE HEPATOCELLULAR CARCINOMA (MORPHEUS-NEO HCC)**
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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 as instructed by LabCorp.

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED PLATFORM STUDY EVALUATING THE EFFICACY AND SAFETY OF NEOADJUVANT IMMUNOTHERAPY COMBINATIONS IN PATIENTS WITH SURGICALLY RESECTABLE HEPATOCELLULAR CARCINOMA (MORPHEUS-NEO HCC)**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: IND 164122 EU CT Number: 2022-502840-11-00 NCT Number: NCT05908786

STUDY RATIONALE

This study will evaluate the efficacy and safety of immunotherapy-based treatment combinations, administered as neoadjuvant treatment, in patients with resectable hepatocellular carcinoma (HCC). Specific objectives and corresponding endpoints for the study are outlined below.

OBJECTIVES AND ENDPOINTS

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of neoadjuvant immunotherapy-based treatment combinations	• MPR rate, defined as the proportion of participants with ≤10% residual viable tumor in the tumor bed at the time of surgery, as assessed by central pathological review
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of neoadjuvant immunotherapy-based treatment combinations	• pCR rate, defined as the proportion of participants with an absence of residual tumor at the time of surgery, as assessed by central pathological review • RFS, defined as the time from surgery to the first documented recurrence of disease (intrahepatic or extrahepatic) according to EASL and/or RECIST v1.1, or death from any cause • EFS, defined as the time from randomization to any of the following events (whichever occurs first): disease progression that precludes surgery, as assessed by the investigator according RECIST v1.1; local, regional, or distant disease recurrence as measured by EASL and/or RECIST v1.1; or death from any cause • OS, defined as the time from randomization to death from any cause • OS rate at 24 months and 36 months, defined as the proportion of patients who have not experience death from any cause at 24 months and 36 months after randomization, respectively

Table 1 Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objective (cont.)	Corresponding Endpoints (cont.)
• To evaluate the efficacy of neoadjuvant immunotherapy-based treatment combinations	• ORR, defined as the proportion of participants with a radiographic CR or PR prior to surgery, as determined by the investigator according to RECIST v1.1 and HCC mRECIST – Responses will be assessed and determined according to RECIST v1.1 and HCC mRECIST, but are not required to be confirmed by subsequent imaging assessments. • Proportion of participants down staged to within Milan criteria (for participants beyond criteria at randomization) – Within Milan criteria is defined as single tumor ≤ 5 cm or 2 to 3 nodules all ≤ 3 cm. • R0 resection rate (proportion of resected participants obtaining an R0 resection). – R0 resection is defined as a microscopically margin-negative resection, in which no tumor (gross or microscopic) remains in the primary tumor bed.
Safety Objectives	**Corresponding Endpoints**
• To evaluate the safety and tolerability of neoadjuvant immunotherapy-based treatment combinations	• Incidence, nature, and severity of adverse events, serious adverse events, and immune-related adverse events (severity determined according to NCI CTCAE v5.0; severity of CRS determined according to the ASTCT CRS Consensus Grading Scale)
• To assess surgical feasibility, outcomes, morbidity, and mortality in participants receiving neoadjuvant immunotherapy-based treatment combinations	• Proportion of participants with delayed or canceled surgery due to treatment-related adverse events (defined as >28 days from surgical restaging visit), as well as length of surgical delay, duration of surgery, length of hospital stay, surgical approach, extent of surgery, intraoperative blood loss, and need for intraoperative blood transfusion • Post-operative surgical complication rates according to the Clavien-Dindo surgical classification – Clinically relevant complications are defined as Clavien-Dindo Grade $\geq$ IIIa. • Post-operative mortality, defined as death within 90 days after surgery

ASTCT = American Society for Transplantation and Cellular Therapy; CR = complete response; CRS = cytokine release syndrome; EASL = European Association for the Study of the Liver; EFS = event-free survival; HCC = hepatocellular carcinoma; HCC mRECIST = HCC-specific modified RECIST; MPR = major pathologic response; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; pCR = pathologic complete response; PR = partial response; R0 = negative surgical margins; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RFS = relapse-free survival.
Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 and HCC mRECIST.

OVERALL DESIGN AND STUDY POPULATION

This is a Phase Ib/II, open-label, multicenter, randomized platform study to evaluate neoadjuvant immunotherapy combinations in patients with resectable HCC. The study is designed with the flexibility to open new treatment arms as new agents become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modify the patient population.

Several key aspects of the study design and study population are summarized below.

Table 2 Study Design

Phase:	Phase Ib/II	**Population Type:**	Adult patients
Control Method:	None	**Population Diagnosis or Condition:**	Patients with resectable HCC
Interventional Model:	Parallel group	**Population Age:**	≥ 18 years
Test Compounds:	Atezolizumab (RO5541267), Bevacizumab (RO4876646), Tiragolumab (RO7092284), and Tobemstomig (RO7247669)	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not Applicable	**Study Intervention Assignment Method:**	Randomization
Number of Arms:	3	**Number of Participants to Be Enrolled:**	Approximately 90–150

STUDY TREATMENT

Table 3 Treatment Regimens

Arm Name	Study Treatment [b]	Number of Participants [a]		
		Safety Evaluation Phase [c]	Preliminary Phase	Optional Expansion Phase [d]
Atezo + Bev	Atezolizumab plus bevacizumab	10	20	20
Atezo + Bev + Tira	Atezolizumab plus bevacizumab plus tiragolumab	10	20	20
Tobe + Bev	Tobemstomig plus bevacizumab	10	20	20

Atezo = atezolizumab; Bev = bevacizumab; Tira = tiragolumab; Tobe = tobemstomig.

[a] The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase).

[b] The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Thus, all listed experimental arms may not be open for enrollment at the same time.

[c] Enrollment will be suspended in the Atezo + Bev, Atezo + Bev + Tira, and Tobe + Bev arms to allow for a safety evaluation in approximately 10 participants.

[d] The study design includes an optional expansion phase. It is not planned to expand the experimental arms upfront. However, in each experimental arm, if clinical activity is observed in the absence of concerning safety issues during the preliminary phase, and the Sponsor requires additional data to interpret, up to approximately 20 additional participants may be enrolled in that arm during the expansion phase. The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion.

Atezolizumab + Bevacizumab

Participants in the atezolizumab plus bevacizumab (Atezo + Bev) arm will receive up to three cycles of treatment as outlined in Table 4 until surgery or unacceptable toxicity, whichever occurs first. It is recommended that treatment be initiated no later than 7 calendar days after randomization. However, the first dose of study treatment should not occur within 3 days after a core biopsy or other surgical procedure.

Table 4 Treatment Regimen for Atezo + Bev Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg by IV infusion on Day 1 • Bevacizumab 15 mg/kg by IV infusion on Day 1 [a]

Atezo + Bev = atezolizumab plus bevacizumab.

[a] On Day 1 of each cycle, bevacizumab will be administered at least 5 minutes after completion of the atezolizumab infusion.

Atezolizumab + Bevacizumab + Tiragolumab

Participants in the atezolizumab plus bevacizumab plus tiragolumab (Atezo + Bev + Tira) arm will receive up to three cycles of treatment as outlined in Table 5 until surgery or unacceptable toxicity, whichever occurs first. It is recommended that treatment be initiated no later than 7 calendar days after randomization. However, the first dose of study treatment should not occur within 3 days after a core biopsy or other surgical procedure.

Table 5 Treatment Regimen for Atezo + Bev + Tira Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg by IV infusion on Day 1 • Bevacizumab 15 mg/kg by IV infusion on Day 1 [a] • Tiragolumab 600 mg by IV infusion on Day 1 [b]

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab;
IRR = infusion-related reaction.

[a] On Day 1 of each cycle, bevacizumab will be administered at least 5 minutes after completion of the atezolizumab infusion.

[b] On Day 1 of Cycle 1, tiragolumab will be administered at least [redacted] minutes after completion of the bevacizumab infusion. The interval between subsequent infusions will be at least [redacted] minutes if the previous bevacizumab infusion was given without premedication and tolerated without an IRR or [redacted] minutes if the participant experienced an IRR with the previous bevacizumab infusion.

Tobemstomig + Bevacizumab

Participants in the Tobe + Bev arm will receive up to three cycles of treatment as outlined in Table 6 until surgery or unacceptable toxicity, whichever occurs first. It is recommended that treatment be initiated no later than 7 calendar days after randomization. However, the first dose of study treatment should not occur within 3 days after a core biopsy or other surgical procedure.

Table 6 Treatment Regimen for Tobe + Bev Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Tobemstomig 600 mg by IV infusion on Day 1 • Bevacizumab 15 mg/kg by IV infusion on Day 1 [a]

IRR = infusion-related reaction; Tobe + Bev = tobemstomig plus bevacizumab.

[a] On Day 1 of Cycle 1, bevacizumab will be administered at least 90 minutes after completion of the tobemstomig infusion. If the first infusion is tolerated without an IRR, bevacizumab will be administered at least 60 minutes after the tobemstomig infusion. If the second infusion is tolerated without an IRR, bevacizumab will be administered at least 30 minutes after all subsequent tobemstomig infusions.

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

DURATION OF PARTICIPATION

Participants will receive up to three cycles of neoadjuvant treatment until surgery or unacceptable toxicity, whichever occurs first. The total duration of study participation for each individual is expected to range from 1 day to approximately 2 to 3 years.

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Scientific Oversight Committee Internal Monitoring Committee

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
ADA	anti-drug antibody
ASTCT	American Society for Transplantation and Cellular Therapy
Atezo	Atezolizumab
BEN	benign ethnic neutropenia
Bev	Bevacizumab
BP	blood pressure
CD	cluster of differentiation
CIT	cancer immunotherapy
COVID-19	coronavirus disease 2019
CRLM	colorectal liver metastasis
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte–associated protein 4
EASL	European Association for the Study of the Liver
EBV	Epstein-Barr virus
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EGD	esophagogastroduodenoscopy
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
EDC	electronic data capture
FFPE	formalin-fixed, paraffin-embedded
G-CSF	granulocyte colony-stimulating factor
GI	Gastrointestinal
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (cont.)

Abbreviation	Definition
HCC	hepatocellular carcinoma
HCC mRECIST	HCC-specific modified RECIST
[redacted]	[redacted]
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICH	International Council for Harmonisation
IL	Interleukin
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
IxRS	interactive voice or web-based response system
LMWH	low-molecular–weight heparin
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease Study
MPR	major pathologic response
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NGS	next-generation sequencing
NSAID	non-steroidal anti-inflammatory drug
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
pCR	pathologic complete response
PFS	progression-free survival
PK	Pharmacokinetic

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (cont.)

Abbreviation	Definition
PPD	purified protein derivative
PSA	prostate-specific antigen
R0	negative surgical margins
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RFS	relapse-free survival
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SITC	Society for Immunotherapy of Cancer
SOC	Scientific Oversight Committee
TACE	transarterial chemoembolization
TB	tuberculosis
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
Tira	tiragolumab
TME	tumor microenvironment
TnI	troponin I
TnT	troponin T
Tobe	tobemstomig
TTE	transthoracic echocardiogram
ULN	upper limit of normal
VCA	viral capsid antigen
VEGF	vascular endothelial growth factor
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON LIVER CANCER

Primary liver cancer is the fifth most common cancer 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) accounts for 75%–90% of all primary liver cancers and typically arises in the setting of chronic liver disease, including alcohol consumption, chronic viral hepatitis (B or C), and nonalcoholic fatty liver disease. An estimated 72% of HCC cases arise in Asia, with more than half occurring in China. The incidence and mortality of HCC is rising in the United States and Europe (Singal et al. 2020).

1.1.1 Atezolizumab Combined with Bevacizumab in Hepatocellular Carcinoma

Immunotherapy with monoclonal antibodies blocking the PD-1/PD-L1 and cytotoxic T lymphocyte–associated protein 4 (CTLA-4) pathways have reshaped the therapeutic landscape across a broad spectrum of malignancies. Alternate immune checkpoints can also play a role, such as PD-1, LAG-3, and T-cell immunoreceptor with Ig and ITIM domains (TIGIT).

Vascular endothelial growth factor (VEGF) inhibition is believed to synergize with PD-1/PD-L1 blockade by potentiating anti-tumor immunity and attenuating critical immunosuppressive mechanisms in the tumor microenvironment (TME). The immune composition of the TME is a key determinant of HCC recurrence following liver resection, with many of the relevant immunosuppressive mechanisms being regulated directly or indirectly by VEGF.

The combination of atezolizumab (anti–PD-L1) and bevacizumab (anti-VEGF) was the first major breakthrough for immunotherapy in HCC based on the IMbrave150 Phase III study (Study YO40245, NCT03434379). In IMbrave150, first-line treatment with atezolizumab in combination with bevacizumab significantly improved overall survival (OS) (hazard ratio [HR]: 0.66; 95% CI: 0.52 to 0.85; $p < 0.001$) and progression-free survival (PFS) (HR: 0.65; 95% CI: 0.53 to 0.81; $p < 0.001$) compared with sorafenib. Furthermore, response rates defined according to Response Evaluation Criteria in Solid Tumors, Version 1.1 ([RECIST v1.1], 27% vs. 12%) or HCC-specific modified RECIST (HCC mRECIST) (33% vs. 13%) were also significantly increased with combination treatment relative to sorafenib. In an updated analysis of IMbrave150 conducted 12 months after the primary analysis, the OS, PFS, and objective response rate (ORR) benefit of atezolizumab in combination with bevacizumab compared with sorafenib were maintained (Cheng et al. 2022).

1.1.2 Potentially Curative Liver Resection

Surgical resection is a mainstay of curative treatment for patients diagnosed with HCC. However, only 15%–30% of patients are considered candidates for surgery. For patients who undergo potentially curative resection, the risk of post-operative recurrence is unacceptably high (70%–80% within 5 years), even in patients considered optimal candidates for surgery (Lee et al. 2020a). For high-risk patients with large tumors, multinodular disease, or vascular invasion, the risk of recurrence is further amplified (Lim et al. 2012). Globally, approximately 50%–60% of curative-intent liver resections are undertaken in patients at high risk of tumor recurrence. In most cases, HCC recurrence occurs "early," within 2 years of resection, and post-recurrence survival among patients with early recurrence tends to be worse compared with patients who recur late.

The vast majority (approximately 80%) of post-operative HCC recurrences are intrahepatic, and most liver resections result in microscopically negative surgical margins (R0), collectively indicating that HCC recurrence is primarily attributable to intrahepatic micrometastases that persist after surgery. Adjuvant (after surgery), neoadjuvant (before surgery), or perioperative (before and after surgery) therapeutic strategies that can effectively target micrometastatic disease and/or improve resectability through tumor downstaging have the potential to improve outcomes for patients with HCC.

1.1.3 Neoadjuvant Treatment for Hepatocellular Carcinoma

Unlike other major cancer types, no effective perioperative treatment is available to patients with HCC. The potential benefit of neoadjuvant therapy in improving HCC resectability and eliminating micrometastases has been recognized for decades, but the development of neoadjuvant therapy for HCC has been hindered by a lack of effective systemic treatments. Until recently, sorafenib was the standard of care for unresectable HCC, but its low response rate (<10%) and lack of benefit in the adjuvant setting limited its application as a neoadjuvant therapy (Llovet et al. 2008a; Bruix et al. 2015). Preoperative locoregional interventions such as transarterial chemoembolization (TACE) have generally failed to show evidence of clinical benefit (Zhou et al. 2013). High response rates with immunotherapy-based treatment in advanced disease have bolstered interest in their evaluation in the neoadjuvant setting.

1.2 STUDY RATIONALE

Moving immune checkpoint inhibitor–based treatments forward from the advanced to the early HCC setting is logical both clinically and biologically. Neoadjuvant administration of PD-1/PD-L1 inhibitors combined with standard-of-care chemotherapy significantly improved event-free survival (EFS) and/or pathologic response rates in patients with early-stage triple-negative breast cancer or non–small cell lung cancer (Garufi et al. 2022; Forde et al. 2022). In contrast, the study of neoadjuvant therapy in HCC is at a more nascent stage of development. Nonetheless, the anti-tumor activity and survival benefit observed with immunotherapies in unresectable HCC, coupled with a manageable safety profile, provide a rationale for evaluating them in the neoadjuvant setting.

This Phase Ib/II umbrella study is designed to enable the development of neoadjuvant cancer immunotherapy (CIT) combinations by identifying preliminary efficacy and safety signals in patients with resectable HCC. The study is designed with the flexibility to open new treatment arms as new treatment combinations become available and close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity.

This study will assess the importance of simultaneously targeting multiple mechanisms of immune escape through immune cell priming and activation, tumor infiltration, and/or recognition of tumor cells for elimination.

The target and proposed mechanism-of-action classification for each experimental investigational medicinal product (IMP) are summarized in Table 1. The experimental treatment regimens are described in Section 3.1.2 (see Table 4). Background information and a rationale for each treatment combination, including a benefit–risk assessment for experimental agents, are provided in the respective appendix for that treatment arm, as outlined in Table 4.

Table 1 Target and Proposed Mechanism-of-Action Classification for Experimental Investigational Medicinal Products

Experimental IMP	Target	Proposed Mechanism-of-Action Classification
Atezolizumab	PD-L1	Checkpoint inhibitor
Bevacizumab	VEGF	Angiogenesis inhibitor; recruitment of T cells to the tumor microenvironment [a]
Tiragolumab	TIGIT	TIGIT antagonist; improvement in the activation and effectiveness of T-cell and NK-cell tumor-killing activity [b]
Tobemstomig (also known as RO7247669)	PD-1, LAG-3	Bispecific, dual immune checkpoint inhibitor [c]

IMP = investigational medicinal product; NK = natural killer; TIGIT = T-cell immunoreceptor with Ig and ITIM domains; VEGF = vascular endothelial growth factor.
[a] Wallin et al. 2016.
[b] Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014.
[c] Deak et al. 2019.

1.3 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). 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 immune checkpoint inhibition may be the modulation of the host-immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses (Wykes and Lewin 2018). In nonclinical models, the 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 CIT.

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 interferon-γ (Merad and Martin 2020). Although it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops SARS-CoV-2 infection while receiving immune checkpoint inhibitor therapies (e.g., atezolizumab). At this time, there is insufficient evidence for causal association between immune checkpoint inhibitor therapies 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 immune checkpoint inhibitor therapies 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 CITs 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 CIT (SITC 2020). For participants enrolling in this study and receiving CIT, a decision to administer the vaccine to a participant should be made on an individual basis by the investigator in consultation with the participant.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for participants receiving CIT 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 participant and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of the COVID-19 outbreak in a given area or region.

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 (as described for each treatment arm in Appendix 12, Appendix 13, and Appendix 14).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of immunotherapy-based treatment combinations, administered as neoadjuvant treatment, in patients with resectable HCC. Specific objectives and corresponding endpoints for the study are outlined below in Table 2.

Table 2 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of neoadjuvant immunotherapy-based treatment combinations	• MPR rate, defined as the proportion of participants with ≤10% residual viable tumor in the tumor bed at the time of surgery, as assessed by central pathological review
Secondary Efficacy Objective	**Corresponding Endpoint**
• To evaluate the efficacy of neoadjuvant immunotherapy-based treatment combinations	• pCR rate, defined as the proportion of participants with an absence of residual tumor at the time of surgery, as assessed by central pathological review • RFS, defined as the time from surgery to the first documented recurrence of disease (intrahepatic or extrahepatic) according to EASL and/or RECIST v1.1, or death from any cause • EFS, defined as the time from randomization to any of the following events (whichever occurs first): disease progression that precludes surgery, as assessed by the investigator according RECIST v1.1; local, regional, or distant disease recurrence as measured by EASL and/or RECIST v1.1; or death from any cause • OS, defined as the time from randomization to death from any cause • OS rate at 24 months and 36 months, defined as the proportion of patients who have not experience death from any cause at 24 months and 36 months after randomization, respectively

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CR = complete response; CRS = cytokine release syndrome; EASL = European Association for the Study of the Liver; EFS = event-free survival; HCC = hepatocellular carcinoma; HCC mRECIST = HCC-specific modified RECIST; MPR = major pathologic response; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; pCR = pathologic complete response; PK = pharmacokinetic; PR = partial response; R0 = negative surgical margins; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RFS = relapse-free survival.
Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1) and HCC mRECIST (see Appendix 2).

Table 2 Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objective (cont.)	Corresponding Endpoints (cont.)
• To evaluate the efficacy of neoadjuvant immunotherapy-based treatment combinations	• ORR, defined as the proportion of participants with a radiographic CR or PR prior to surgery, as determined by the investigator according to RECIST v1.1 and HCC mRECIST – Responses will be assessed and determined according to RECIST v1.1 and HCC mRECIST, but are not required to be confirmed by subsequent imaging assessments. • Proportion of participants downstaged to within Milan criteria (for participants beyond criteria at randomization) – Within Milan criteria is defined as single tumor ≤5 cm or 2 to 3 nodules all ≤3 cm. • R0 resection rate (proportion of resected participants obtaining an R0 resection) – R0 resection is defined as a microscopically margin-negative resection, in which no tumor (gross or microscopic) remains in the primary tumor bed.
[redacted]	[redacted]

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CR = complete response; CRS = cytokine release syndrome; EASL = European Association for the Study of the Liver; EFS = event-free survival; HCC = hepatocellular carcinoma; HCC mRECIST = HCC-specific modified RECIST; MPR = major pathologic response; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; pCR = pathologic complete response; PK = pharmacokinetic; PR = partial response; R0 = negative surgical margins; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RFS = relapse-free survival.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1) and HCC mRECIST (see Appendix 2).

Table 2 Objectives and Corresponding Endpoints (cont.)

Safety Objectives	Corresponding Endpoints
• To evaluate the safety and tolerability of neoadjuvant immunotherapy-based treatment combinations	• Incidence, nature, and severity of adverse events, serious adverse events, and immune-related adverse events (severity determined according to NCI CTCAE v5.0; [redacted]
• To assess surgical feasibility, outcomes, morbidity, and mortality in participants receiving neoadjuvant immunotherapy-based treatment combinations	• Proportion of participants with delayed or canceled surgery due to treatment-related adverse events (defined as >28 days from surgical restaging visit), as well as length of surgical delay, duration of surgery, length of hospital stay, surgical approach, extent of surgery, intraoperative blood loss, and need for intraoperative blood transfusion • Post-operative surgical complication rates according to the Clavien-Dindo surgical classification – Clinically relevant complications are defined as Clavien-Dindo Grade ≥ IIIa (see Appendix 6). • Post-operative mortality, defined as death within 90 days after surgery
[redacted]	[redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted] • [redacted]

[redacted]

CR = complete response; CRS = cytokine release syndrome; EASL = European Association for the Study of the Liver; EFS = event-free survival; HCC = hepatocellular carcinoma; HCC mRECIST = HCC-specific modified RECIST; MPR = major pathologic response; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; pCR = pathologic complete response; PK = pharmacokinetic; PR = partial response; R0 = negative surgical margins; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RFS = relapse-free survival.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1) and HCC mRECIST (see Appendix 2).

Table 2 Objectives and Corresponding Endpoints (cont.)

[redacted]

CR = complete response; CRS = cytokine release syndrome; EASL = European Association for the Study of the Liver; EFS = event-free survival; HCC = hepatocellular carcinoma; HCC mRECIST = HCC-specific modified RECIST; MPR = major pathologic response; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; pCR = pathologic complete response; PK = pharmacokinetic; PR = partial response; R0 = negative surgical margins; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RFS = relapse-free survival.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1) and HCC mRECIST (see Appendix 2).

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

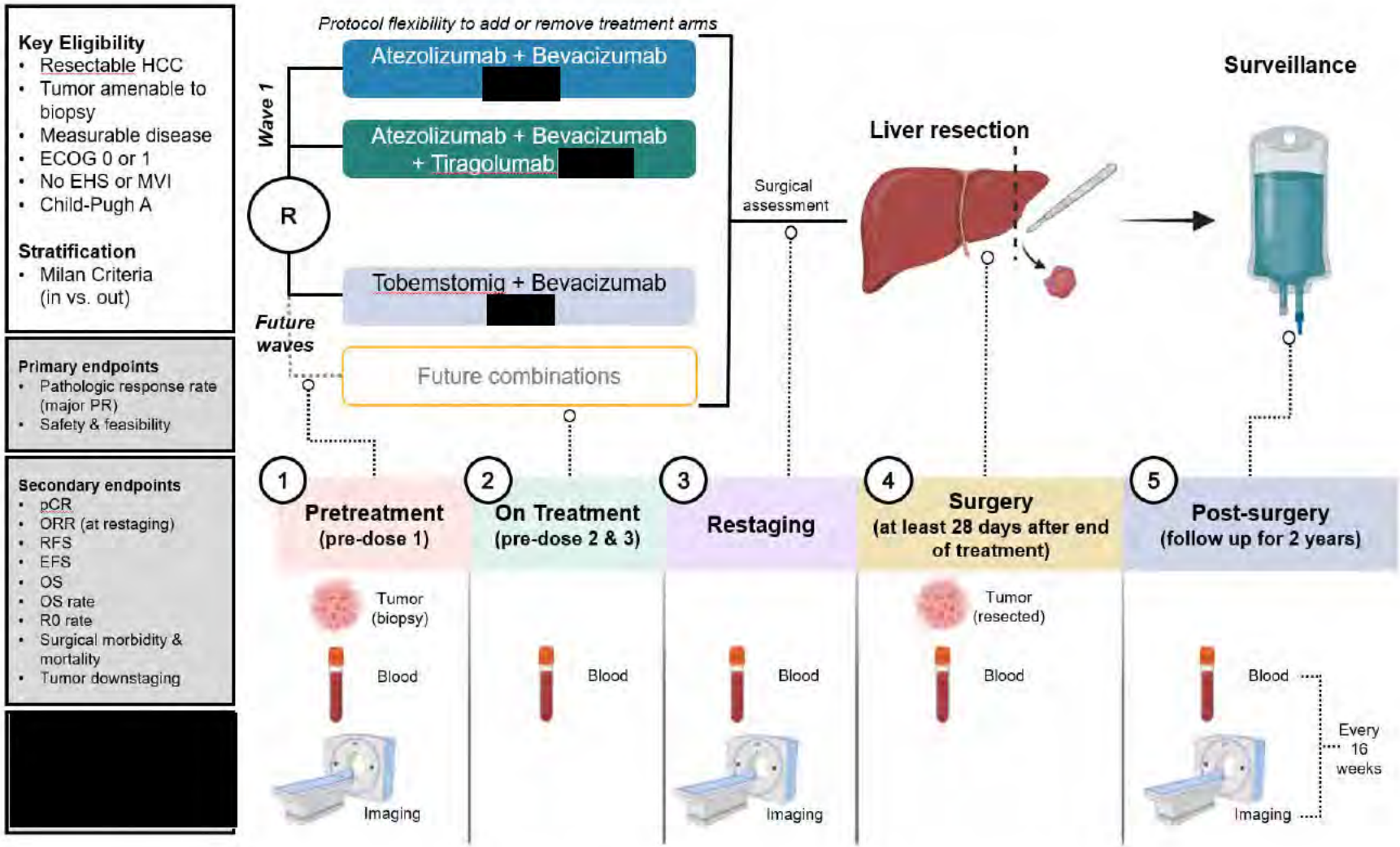
This is a Phase Ib/II, open-label, multicenter, randomized platform study to evaluate neoadjuvant immunotherapy combinations in patients with resectable HCC. The study is designed with the flexibility to open new treatment arms as new agents become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modify the patient population.

A study schema is provided in Figure 1 and a detailed study design is shown in Figure 2. A schedule of activities and a sample collection schedule for each arm are provided in Appendix 12, Appendix 13, and Appendix 14.

Approximately 90–150 participants will be enrolled during the study, with approximately [redacted] participants enrolled into each arm. Approximately [redacted] participants will be enrolled in each treatment arm during the safety evaluation. If no new safety signals are detected, up to approximately [redacted] additional participants may be enrolled in each treatment arm during the preliminary phase. The study design includes an optional expansion phase. It is not planned to expand the experimental arms upfront. However, in each experimental arm, if clinical activity is observed in the absence of concerning safety issues during the preliminary phase, and the Sponsor requires additional data to interpret, up to approximately [redacted] additional participants may be enrolled in that arm during the expansion phase. The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion. Additional participants may be enrolled to ensure balance among treatment arms with respect to demographic and baseline characteristics, including potential predictive biomarkers, to enable further subgroup analyses. New experimental arms may be added during the course of the study by amending the protocol.

The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added). Patients will be ineligible if they meet any of the exclusion criteria outlined in Section 4.1.2. Details on treatment assignment and randomization are provided in Section 4.2.

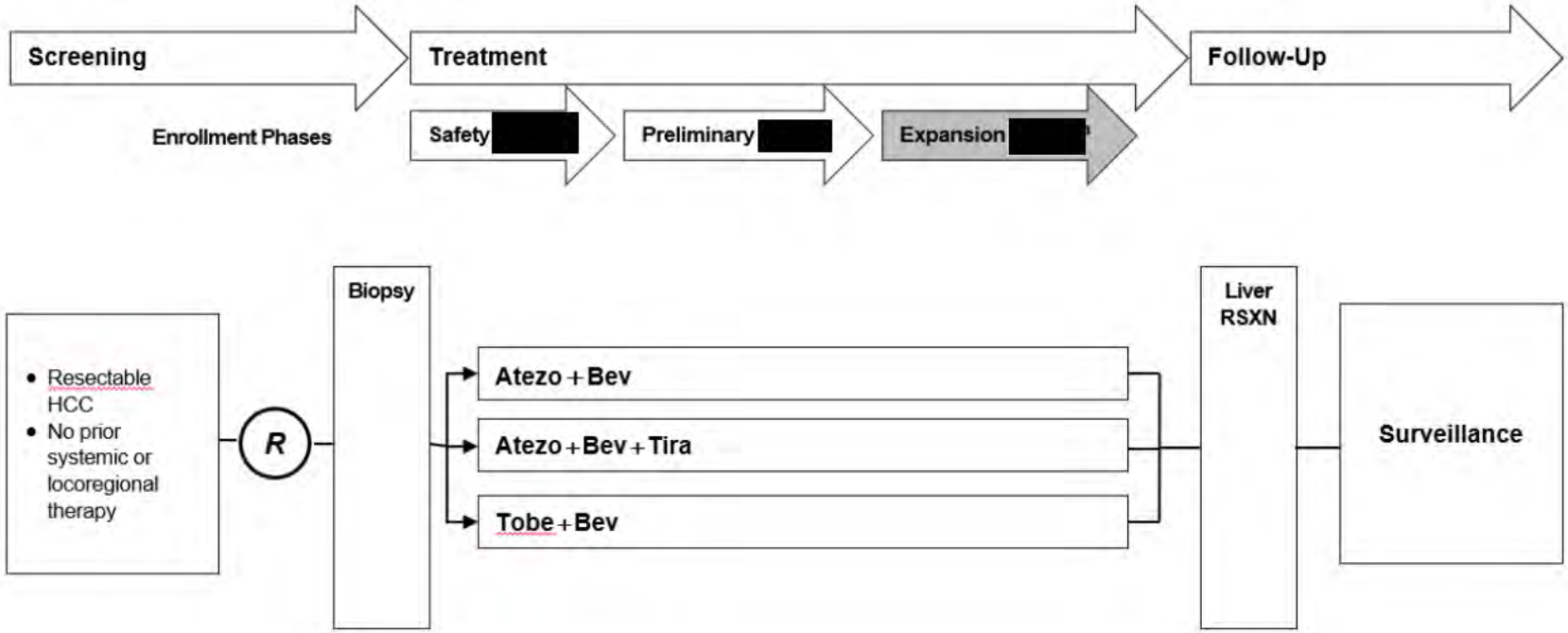
Figure 1 Study Schema



ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; EHS = extrahepatic spread; HCC = hepatocellular carcinoma; MVI = macroscopic vascular invasion; ORR = objective response rate; OS = overall survival; pCR = pathologic complete response; PR = partial response; R = randomization; R0 = negative surgical margins; RFS = relapse-free survival.

Note: See Table 4 for a summary of available treatment regimens.

Figure 2 Detailed Study Design



Atezo = atezolizumab; Bev = bevacizumab; HCC = hepatocellular carcinoma; R = randomization; RSXN = resection; Tira = tiragolumab; Tobe = tobemstomig.

[a] The study design includes an optional expansion phase. It is not planned to expand the experimental arms upfront. However, in each experimental arm, if clinical activity is observed in the absence of concerning safety issues during the preliminary phase, and the Sponsor requires additional data to interpret, up to approximately [redacted] additional participants may be enrolled in that arm during the expansion phase.

3.1.2 Treatment Assignment

Participants will be randomly assigned to receive one of three experimental neoadjuvant treatments:

- Atezolizumab plus bevacizumab (Atezo + Bev);
- Atezolizumab plus bevacizumab plus tiragolumab (Atezo + Bev + Tira);
- Tobemstomig plus bevacizumab (Tobe + Bev).

Randomization will be stratified according to the Milan criteria status [redacted] Treatment regimens are summarized in Table 3 and Table 4.

Participants in the experimental arms will receive up to three cycles (21 days each) of neoadjuvant treatment (see Table 3) until surgery or unacceptable toxicity, whichever occurs first. Participants must receive the first dose of neoadjuvant treatment within 7 calendar days of randomization.

After completion of neoadjuvant treatment, or in case of discontinuation due to toxicity and in the absence of disease progression, participants will undergo curative-intent liver resection. Liver resection must take place at least 28 days after the final dose of neoadjuvant treatment. Participants will move into the surveillance phase following liver resection.

Table 3 Dose and Schedule for Neoadjuvant Treatment Regimens

Treatment Arm	Cycle Length (days)	Number of Pre-Operative Cycles Administered	Dose, Route, and Regimen (drugs listed in order of administration by IV infusion on Day 1)
Atezo + Bev	21	3	Atezolizumab 1200 mg Bevacizumab 15 mg/kg
Atezo + Bev + Tira	21	3	Atezolizumab 1200 mg Bevacizumab 15 mg/kg Tiragolumab 600 mg
Tobe + Bev	21	3	Tobemstomig 600 mg Bevacizumab 15 mg/kg

Atezo = atezolizumab; Bev = bevacizumab; Tira = tiragolumab; Tobe = tobemstomig.

Table 4 Treatment Regimens

Arm Name	Study Treatment [b]	Number of Participants [a]			
		Safety Evaluation Phase [c]	Preliminary Phase	Optional Expansion Phase [d]	Appendix
Atezo + Bev	Atezolizumab plus bevacizumab	[redacted]	[redacted]	[redacted]	Appendix 12
Atezo + Bev + Tira	Atezolizumab plus bevacizumab plus tiragolumab	[redacted]	[redacted]	[redacted]	Appendix 13
Tobe + Bev	Tobemstomig plus bevacizumab	[redacted]	[redacted]	[redacted]	Appendix 14

Atezo = atezolizumab; Bev = bevacizumab; Tira = tiragolumab; Tobe = tobemstomig.

[a] The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase; see Section 4.2 for details).

[b] The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Thus, all listed experimental arms may not be open for enrollment at the same time.

[c] Enrollment will be suspended in the Atezo + Bev, Atezo + Bev + Tira, and Tobe + Bev arms to allow for a safety evaluation in approximately 10 participants.

[d] The study design includes an optional expansion phase. It is not planned to expand the experimental arms upfront. However, in each experimental arm, if clinical activity is observed in the absence of concerning safety issues during the preliminary phase, and the Sponsor requires additional data to interpret, up to approximately [redacted] additional participants may be enrolled in that arm during the expansion phase. The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion.

3.1.3 Safety Evaluation Phase

To evaluate the toxicities of the experimental treatments in the neoadjuvant setting, enrollment will be suspended after approximately [redacted] participants have been enrolled in to each treatment arm to allow for a safety evaluation.

The safety evaluation will be based on safety data from approximately [redacted] participants who have received at least one dose of treatment (i.e., one dose of each agent for a given combination) and who have completed safety follow-up assessments until surgery. Notably, timely conduct of liver resection is an indicator of treatment feasibility and tolerability. Surgical feasibility will be assessed based on the number of participants who fail to undergo surgery as a result of a treatment-related adverse event resulting in an extended delay in surgery [redacted] Delays in surgery as a result of factors not associated with treatment, such as scheduling or logistical issues, will not be included in the evaluation of surgical feasibility.

In addition, during the [redacted] or at any time following the safety evaluation phase, [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

If no new safety signals are detected, enrollment will be resumed in that arm.

3.1.4 Assessments and Monitoring

All participants will be closely monitored for safety and tolerability throughout the study. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) [redacted]

Participants will undergo pathologic tumor assessments at the time of surgery based on the resected tumor mass. Radiologic response will be assessed and determined by the

investigator in accordance with RECIST v1.1 and HCC mRECIST, but confirmation by subsequent imaging assessments is not required (see Appendix 1 and Appendix 2).

Pretreatment baseline tumor tissue samples will be collected from all participants, preferably by means of a biopsy performed at study entry. [redacted] prior to enrollment and the participant has not received any anti-cancer therapy, including locoregional liver-directed therapy, since the time of the biopsy. Post-treatment surgical tissue samples will be collected from all participants.

These samples will be utilized for biomarker research (see rationale for biomarker assessments in Section 3.4.6 and details on tissue sample collection in Section 4.5.10).

To characterize the pharmacokinetic (PK) properties and/or immunogenicity of atezolizumab and the other therapeutic agents, blood samples will be taken at various timepoints before and during study treatment administration.

On the basis of a review of real-time safety data and available PK data, treatment regimens may be modified by the Sponsor as deemed appropriate.

3.1.5 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will monitor participant safety throughout the study. The IMC will include representatives from clinical science, safety science, and biostatistics. In addition to the ongoing assessment of the incidence, nature, and severity of adverse events, serious adverse events, deaths, and laboratory abnormalities performed by the investigator and the Medical Monitor, the IMC will review all necessary cumulative data at regular intervals during the study. At the time of each review, the IMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, a treatment regimen should be modified, the protocol should be amended, or enrollment should be held pending further safety evaluations). Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities will be detailed in an IMC Charter.

3.1.6 Scientific Oversight Committee

A Scientific Oversight Committee (SOC) will act as a consultative body to the Sponsor, providing external expert opinions on the [redacted] data collected during the study. This committee will consist of an external group of at least [redacted] experts in CIT who will advise the Sponsor on the interpretation of study data. For this purpose, the SOC will evaluate [redacted] data on a periodic basis, approximately every 6 months from the time the first participant is enrolled in the study. Members will

follow a charter that outlines their roles and responsibilities. [redacted] The Sponsor will retain all decision-making authority for this study.

3.1.7 Central Pathology Review

Pathologic response will be assessed centrally by both manual and digital evaluations. Additional details about the central pathology review facility and procedures will be detailed in the Central Pathology Review Facility Charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient completes the last visit (LPLV), including survival follow-up visits conducted by telephone or in the clinic. The total length of the study, from screening of the first participant to the end of the study, is expected to be approximately 2 to 3 years.

3.3 DURATION OF PARTICIPATION

Participants will receive up to three cycles of neoadjuvant treatment until surgery or unacceptable toxicity, whichever occurs first. The total duration of study participation for each individual is expected to range from 1 day to approximately 2 to 3 years.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Study Population

Liver resection is the cornerstone of curative treatment for HCC. However, only 15%–30% of newly diagnosed patients undergo potentially curative liver resection. Despite surgical and technological advances, patients with HCC are at high risk for post-operative tumor recurrence and cancer-related death. For patients with early-stage HCC within Milan criteria, who are considered ideal candidates for curative-intent hepatectomy, post-operative 5-year disease-free survival is only 37% (Lim et al. 2012). For patients presenting with higher tumor burden and/or clinicopathologic risk features such as vascular invasion, the risk of tumor recurrence is further amplified (Chan et al. 2018). The majority of HCC recurrences occur within 2 years of surgery due to residual micrometastatic tumor deposits.

Unlike other major tumor types, no perioperative (neoadjuvant or adjuvant) treatment is currently available to patients with HCC. Consequently, outcomes for patients with early-stage HCC who undergo surgery are generally poorer in comparison to other early-stage gastrointestinal (GI) tumors for which effective perioperative therapy is available.

This study will enroll patients with HCC who are deemed to be candidates for R0 liver resection with curative intent. As outlined above, these patients are at high risk of post-operative recurrence and would potentially benefit from neoadjuvant treatment.

3.4.2 Rationale for Neoadjuvant Immunotherapy-Based Treatment for Hepatocellular Carcinoma

Across oncology, there is considerable interest in developing neoadjuvant immunotherapies. Nonclinical and early clinical data suggest that neoadjuvant use of immunotherapy may be more effective than adjuvant treatment (Topalian et al. 2020). Neoadjuvant administration of PD-1/PD-L1 inhibitors combined with standard-of-care chemotherapy significantly improved EFS and/or pathologic response rates in patients with early-stage triple-negative breast cancer or non–small cell lung cancer (Schmid et al. 2020; Forde et al. 2022).

Although negative margins (R0) are usually observed at the time of surgical resection, HCC recurrence typically occurs within the liver and is believed to originate from occult micrometastases that persist after resection. This pattern of recurrence suggests that neoadjuvant treatment that can reduce the burden of micrometastic disease prior to resection has the potential to improve clinical outcomes.

Neoadjuvant immunotherapy has several possible advantages, including reduced tumor burden before surgery ("downstaging") leading to either less extensive surgery with fewer complications or conversion of unresectable patients to surgical candidates, as well as the ability to assess therapeutic response upon surgical resection of the tumor ("pathologic response"), which could be a surrogate marker for recurrence-free and OS. Immunotherapy prior to surgery may also attenuate the immunosuppressive effects of surgery and enhance T-cell priming leading to increased expansion of anti-tumor T cells, allowing for continued immunosurveillance of micrometastatic tumor deposits following resection (Krishnamoorthy et al. 2021). The apparent inverse relationship between tumor burden and clinical benefit for immunotherapy suggests that response could be enhanced in early disease (Topalian et al. 2020). In support of this, ORRs for atezolizumab in combination with bevacizumab are higher in patients with liver-confined HCC compared with those with extrahepatic disease (53% vs. 28%) (Lee et al. 2020b). Tumor downstaging or downsizing prior to surgery that enables liver resection and/or limits the extent of the operation is a potential benefit of neoadjuvant treatment (Pinato et al. 2021). In the liver transplant setting, patients with HCC who are successfully downstaged with neoadjuvant interventions to meet Milan criteria with neoadjuvant locoregional treatments have similar outcomes to patients who are initially within Milan criteria (Mazzaferro et al. 2020). Neoadjuvant conversion therapy using chemotherapy with or without targeted agents is an accepted approach for the treatment of patients with initially unresectable colorectal liver metastases (CRLMs) (Van Cutsem et al, 2016). It remains to be seen if a downstaging paradigm using immunotherapy can similarly improve outcomes in the context of HCC liver resection.

A series of small single-arm Phase II studies have investigated PD-1/PD-L1 inhibitor–based regimens as neoadjuvant therapy in patients with HCC, which collectively provide some preliminary insights into safety, efficacy, and immune modulation (Ho et al. 2021; Xia et al. 2022; Kaseb et al. 2022; Marron et al. 2022). Despite differences between the trials in terms of patient population (resectable vs. borderline resectable) and investigational treatments (monotherapy and in combination), all studies consistently demonstrated that neoadjuvant treatment could be given safely without compromising surgery and induced pathologic responses in a subset of patients. Evaluation of pre- and post-treatment tissue demonstrated that neoadjuvant treatment promoted local and systemic T cell-mediated immunity, tumoral infiltration of immune effectors, as well as other positive changes in the TME. The preliminary data from these trials support further investigations of neoadjuvant immunotherapy in HCC, including evaluation of novel combinations.

3.4.3 Rationale for Neoadjuvant Use of Bevacizumab

The ability of bevacizumab to augment anti-cancer immunity and potentiate the clinical benefit of atezolizumab in HCC make it a critical component of therapy (Lee et al. 2020b; Zhu et al. 2022). However, neoadjuvant administration of anti-VEGF agents has not been widely studied in the setting of HCC, and the potential for anti-VEGF therapy to induce bleeding or compromise wound healing and post-operative liver regeneration could theoretically complicate use in the neoadjuvant setting. However, preliminary clinical data suggest that pre-operative use of bevacizumab in the context of HCC resection can be deployed safely. Details on the rationale for neoadjuvant use of tiragolumab and tobemstomig are provided in the respective appendices, Appendix 13 and Appendix 14.

Yarchoan and colleagues conducted a single-arm Phase II study to evaluate the feasibility of neoadjuvant nivolumab in combination with cabozantinib (anti-VEGF) in high risk patients with borderline resectable HCC (Yarchoan et al. 2021). In this study 12 out of 15 participants (80%) underwent successful margin-negative resection, and 5 out of 12 participants (42%) had major pathologic responses (MPR). Importantly, no participants experienced a treatment-related adverse event that precluded continuing on to surgery. The safety and tolerability of cabozantinib and nivolumab in the 8-week neoadjuvant treatment period were generally consistent with the toxicity profile of this combination in unresectable HCC. Case studies have demonstrated that conversion therapy with atezolizumab in combination with bevacizumab can enable resection in patients with HCC considered initially inoperable (Wang et al. 2021; Hidaka et al. 2022). In both case reports, surgery was undertaken 4 weeks following the last administration of bevacizumab without significant safety issues.

Bevacizumab-based neoadjuvant regimens have been widely studied in patients with CRLMs (Bolhuis et al. 2020) and are incorporated in treatment guidelines (Van Cutsem et al. 2016). Neoadjuvant bevacizumab can be given safely in patients

with CRLMs without comprising surgery or liver regeneration. Although CRLMs are not a perfect analog for HCC where the liver is often cirrhotic, these data support the rationale for exploring neoadjuvant bevacizumab-containing immunotherapy regimens in the setting of liver resection.

3.4.4 Rationale for Major Pathologic Response as Primary Efficacy Endpoint

The pathologic response to neoadjuvant therapy is believed to be a surrogate endpoint of improved patient outcomes for multiple cancer types. The majority of neoadjuvant studies in HCC that are testing immunotherapy use pathologic response as an endpoint (Su et al. 2021).

Several early neoadjuvant immunotherapy studies in HCC have indicated that pathologic response (either major or complete) is a relevant surrogate marker for long-term benefit (Ho et al. 2021; Kaseb et al. 2022; Marron et al. 2022). Pathologic complete response (pCR; defined as the absence of viable tumor) following neoadjuvant TACE has been shown to predict a favorable post-operative prognosis in patients with HCC (Yang et al. 2019). Pathological response will be assessed by local and central review, and defined as specified in Section 4.5.8.1.

3.4.5 Rationale for Response Assessment Based on HCC Modified RECIST

Anti-angiogenic therapies reduce the vascularity of the tumor, producing necrosis without necessarily causing a change in overall tumor size. To provide a common framework for the design of clinical trials in HCC, the American Association for the Study of Liver Diseases (AASLD) developed modified criteria (HCC mRECIST), which quantify only the viable portions of the tumor to provide an improved endpoint for assessment (Llovet et al. 2008b; Lencioni and Llovet 2010; Lencioni et al. 2017).

Considering the anti-angiogenic mode of action of bevacizumab, HCC mRECIST as assessed by the investigator (Appendix 2), in addition to RECIST v1.1 as assessed by the investigator (Appendix 1), will be used for radiographic tumor response assessment.

[redacted]

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet all of the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years at the time of signing Informed Consent Form
- Ability to fully comply with the protocol, in the investigator's judgment
- Diagnosis of HCC confirmed either histologically or clinically according to AASLD criteria for patients with cirrhosis (see Appendix 3)
  - For participants without cirrhosis, histological confirmation is mandatory.
- HCC that is amenable to R0 surgical resection with curative intent in the opinion of the surgeons and oncologists or hepatologists involved in the care of the participant
  - Patients presenting with resectable HCC within or beyond Milan criteria (without extrahepatic spread or macrovascular invasion) are eligible.
- Measurable disease (at least one target lesion) according to RECIST v1.1 as determined by the investigator (see Appendix 1)
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 within 7 days prior to randomization (see Appendix 7)
- Child-Pugh Class A (see Appendix 4) within 7 days prior to randomization
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- No prior locoregional or systemic treatment for HCC

- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to initiation of study treatment:
  - [redacted] without granulocyte colony-stimulating factor (G-CSF) support, except participants with benign ethnic neutropenia (BEN): [redacted]

    BEN (also known as constitutional neutropenia) is an inherited cause of mild or moderate neutropenia that is not associated with any increased risk for infections or other clinical manifestations (Atallah-Yunes et al. 2019). BEN is referred to as ethnic neutropenia because of its increased prevalence in people of African descent and other specific ethnic groups.
  - Lymphocyte count [redacted]
  - Platelet count [redacted]
  - Hemoglobin [redacted]

    Participants must not have required transfusion during screening or within [redacted] prior to screening to meet this criterion.
  - AST, ALT, and ALP [redacted]
  - Bilirubin [redacted]
  - Adequate renal function: creatinine clearance by estimated glomerular filtration rate (eGFR) by Modification of Diet in Renal Disease Study (MDRD) formula [redacted]

    Participants with creatinine clearance by estimating eGFR by MDRD formula of [redacted] if renal function was stable for [redacted] prior to randomization.
  - Albumin [redacted] without transfusion
  - For participants not receiving anticoagulation: INR or aPTT [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- [redacted] with the following exception:
  - [redacted]
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as outlined for each specific treatment arm in Appendix 12, Appendix 13, and Appendix 14
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating sperm, as outlined for each specific treatment arm in Appendix 12, Appendix 13, and Appendix 14

4.1.2 Exclusion Criteria

Participants will be excluded from the study if they meet any of the following criteria:

- Presence of extrahepatic disease or macrovascular invasion
- Known fibrolamellar HCC, sarcomatoid HCC, mixed cholangiocarcinoma and HCC, or other rare variants of HCC
- History of hepatic encephalopathy if clinically significant within one year prior to initiation of study treatment
- Moderate or severe ascites
- [redacted]
  - [redacted]
- [redacted]
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Untreated or incompletely treated esophageal and/or gastric varices with bleeding or that are at high risk for bleeding
  - [redacted]
- A prior bleeding event due to esophageal and/or gastric varices within 6 months prior to initiation of study treatment

- Inadequately controlled hypertension, defined as systolic blood pressure (BP) >150 mmHg and/or diastolic BP >100 mmHg (average of at least three 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 initiation of study treatment
- History of hemoptysis (≥ 2.5 mL of bright red blood per episode) within 1 month prior to initiation of study treatment
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (≤ 10 days prior to initiation of study treatment) use of aspirin (>325 mg/day) or treatment with clopidogrel, dipyramidole, ticlopidine, or cilostazol
  - Chronic use of low dose aspirin (<325 mg/day) for cardioprotection is allowed.
- Current or recent (≤ 10 days prior to initiation of study treatment) 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 [redacted] and aPTT is within normal limits within 14 days prior to initiation of study treatment.
  - 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®) are not recommended due to potential 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.
  - For prophylactic use of anticoagulants or thrombolytic therapies, the approved dose as described on the local label may be used.
- History of abdominal or tracheoesophageal fistula, GI perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment
- History of intestinal obstruction and/or clinical signs or symptoms of GI obstruction, including subocclusive or occlusive syndrome related to the underlying disease, or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding prior to initiation of study treatment
- Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure
- Serious, non-healing, or dehiscing wound, active ulcer, or untreated bone fracture

- Grade ≥2 proteinuria, as demonstrated by ≥2+ protein on dipstick urinalysis and ≥1.0 g of protein in a 24-hour urine collection
  - All patients with ≥2+ protein on dipstick urinalysis at screening must undergo a 24-hour urine collection (or an alternative method such as protein:creatinine ratio, per local guidance) for protein and must demonstrate <1 g of protein in 24 hours.
  - Patients with <2+ protein on dipstick urinalysis are eligible for the study.
- History of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including but not limited to peptic ulcer disease, diverticulitis, or colitis
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to initiation of study treatment; or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 60 days prior to initiation of study treatment; or anticipation of need for major surgical procedure, other than potentially curative liver resection, during the course of the study; or non-recovery from side effects of any such procedure
  - Complete healing from minor surgery (e.g., simple excision, tooth extraction) must have occurred at least 7 days before enrollment.
- Chronic daily treatment with a non-steroidal anti-inflammatory drug (NSAID)
  - The occasional use of NSAIDs for the symptomatic relief of medical conditions such as headache or fever is allowed.
- Serious infection requiring oral or IV antibiotics and/or hospitalization within 4 weeks prior to screening, 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 participant safety
- Any serious medical condition or abnormality in clinical laboratory tests that precludes an individual's safe participation in and completion of the study
- History of malignancy within 5 years prior to screening, with the exception of the cancer under investigation in this study and 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
  - Patients with localized prostate cancer (defined as Stage ≤pT2c, Gleason score ≤7, and prostate-specific antigen (PSA) at prostate cancer diagnosis ≤20 ng/mL) treated with curative intent and without PSA recurrence are eligible.
  - Patients with pre-existing low-risk prostate cancer (defined as Stage cT1/T2a, Gleason score ≤6, and PSA ≤10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible.

- Patients with malignancies associated with a negligible risk of metastasis or death (e.g., risk of metastasis or death $<5\%$ at 5 years) are eligible provided they meet all of the following criteria:

  Malignancy treated with expected curative intent (e.g., adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent)

  No evidence of recurrence or metastasis by follow-up imaging and any disease-specific tumor markers

- 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 (see Appendix 8 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
  - [redacted]
  - [redacted]
  - [redacted]
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study
  - Female participants of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Prior treatment with an anti-TIGIT agent
- [redacted]
  - [redacted]
- Prior treatment with an anti–LAG-3 agent

- History of myocarditis (regardless of etiology)
- Left ventricular ejection fraction (LVEF) < 50% assessed by either transthoracic echocardiogram (TTE) or multiple-gated acquisition (MUGA) scan (TTE preferred test) within 6 months prior to initiation of study treatment
- Cardiac enzymes: Troponin T (TnT) or troponin I (TnI) > [redacted] ULN
  - Patients with TnT or TnI levels [redacted] need to undergo a cardiac evaluation and may be considered for treatment if there are no clinically significant findings.
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins.
- Known sensitivity to Chinese hamster ovary cell products or recombinant human antibodies.
- [redacted]
  - [redacted]
- Prior allogeneic stem cell or solid organ transplantation
- Active tuberculosis

4.2 METHOD OF TREATMENT ASSIGNMENT

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

Participants who do not receive at least one dose of each drug for their assigned treatment regimen will not be included in the efficacy analyses. Additional participants may be enrolled to reach the target number of treated participants planned for analysis.

4.3 STUDY TREATMENT

Details on the therapeutic agents for each treatment arm are provided in the respective appendix for that treatment arm, as outlined in Table 4. In this protocol, "study treatment" refers to the combination of treatments assigned to participants as part of this study (e.g., atezolizumab and bevacizumab).

4.3.1 Investigational Medicinal Product Handling and Accountability

The IMPs for this study are atezolizumab, bevacizumab, tiragolumab, and tobemstomig (see Appendix 15). All IMPs required for completion of this study will be provided by the Sponsor where required by local practices. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received and ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. 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. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor (if supplied by 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 a drug accountability log.

Refer to the pharmacy manual and/or the applicable Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.2 Post-Trial Access to Study Treatment

Currently, the Sponsor does not have any plans to provide study treatments or interventions to participants who have completed the study. The Sponsor may evaluate whether to continue providing study treatments in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

4.4 CONCOMITANT THERAPY AND PROHIBITED FOOD

Details on concomitant therapy, prohibited food, and additional restrictions for each treatment arm are provided in the respective appendix for that treatment arm, as outlined in Table 4.

4.5 STUDY ASSESSMENTS

A schedule of activities to be performed during the study is provided for each treatment arm (see Table A12-5, Table A13-6, and Table A14-5). All activities must be performed and documented for each participant. Participants will be closely monitored for safety and tolerability throughout the study. Participants 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

Written informed consent for participation in the study must be documented before performing any study-related procedures (including screening evaluations) and may be obtained more than 28 days before initiation of study treatment. Informed Consent Forms for enrolled participants and for patients who are not subsequently enrolled will be maintained at the study site.

Screening evaluations are to be performed within 28 days prior to initiation of study treatment (Day 1). All screening assessments and procedures are outlined in Appendix 11. All screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before enrollment.

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for two re-screening opportunities (for a total of three screenings per individual) at the investigator's discretion. Individuals must re-sign the consent form prior to re-screening. The investigator will maintain a record of reasons for screen failure.

Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 (within 7 days prior to Day 1 for laboratory tests) may be used; such tests do not need to be repeated for screening or re-screening (see the schedules of activities for each arm in Table A12-5, Table A13-6, and Table A14-5).

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the participant within a

specified time prior to initiation of study treatment will be recorded (as outlined for each arm in Appendix 12, Appendix 13, and Appendix 14). At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded. Demographic data will include age, sex, and self-reported race or ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, GI, genitourinary, and neurologic systems. The physical examination should also include an evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions electronic Case Report Form (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.

During visits when a participant will undergo a tumor assessment, the physical examination should include an evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

Height will be recorded at screening. Weight will be recorded at screening and at specified timepoints during the study.

4.5.4 Vital Signs

At screening, vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic BP while the participant is in a seated position, as well as pulse oximetry and temperature.

Vital signs should be measured at other specified timepoints as outlined in the schedule of activities for each arm in Table A12-5, Table A13-6, and Table A14-5.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits, new or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.5 Electrocardiograms

An ECG is required at screening (see Appendix 11) and as outlined in the schedule of activities for each arm (see Table A12-5, Table A13-6, and Table A14-5). ECGs for each participant should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. It is recommended that participants be resting in a supine position for at least 10 minutes prior to ECG recording.

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

4.5.6 Transthoracic Echocardiograms

Measurement of LVEF by TTE or MUGA will be performed at screening for each arm following a standard procedure.

The complete, resting TTE measurements should be performed by the same operator whenever possible, following the most recent echocardiography society guidelines. Paper copies of reports will be kept as part of the participant's permanent study file at the site.

4.5.7 Esophagogastroduodenoscopy

An EGD is required at screening for all participants. All sizes of varices (small to large) must be assessed and treated per local standard of care prior to enrollment (e.g., band ligation therapy and/or administration of β-blockers). Participants who have undergone an EGD within 6 months prior to initiation of study treatment do not need to repeat the procedure.

4.5.8 Tumor Response and Imaging

Participants will be assessed for both pathologic and radiologic response to treatment.

4.5.8.1 Assessment of Pathologic Response

Participants will undergo pathologic tumor assessments at the time of surgery based on the resected tumor mass. Pathologic response in the resection specimen will be determined by local and central pathologic review as specified in **Table 5**.

Table 5 Pathological Response Categories

Pathological Response Category	% Viable Tumor Cells
Pathological complete response (pCR)	0%
Major pathological response (MPR or near pCR)	≤10%
Partial pathological response (pPR)	>10 to ≤50%
Pathological non-response (pNR)	>50%

4.5.8.2 Imaging

Participants will undergo radiographic tumor assessments at baseline and following completion of neoadjuvant treatment prior to surgery (restaging). Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1) and modified HCC RECIST (see Appendix 2) at the restaging scan. Confirmation of response by later imaging assessments is not required.

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

Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or magnetic resonance imaging (MRI) scans (with IV contrast) 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 (i.e., in participants with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast, if feasible) of the abdomen and pelvis should be performed. If a CT scan with contrast is not contraindicated, it is mandatory to obtain a multiphase imaging 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 participants (MRI scan must be performed if CT scan is contraindicated). Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

If clinical activity is demonstrated in an experimental arm, the Sponsor may request that tumor assessment scans for that arm be submitted for evaluation by an independent review facility.

If a CT scan for tumor assessment 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 measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Except for baseline, head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1) and HCC mRECIST (see Appendix 2). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

4.5.8.3 Post-Surgery Disease Recurrence Assessments

After surgery, during long-term follow-up, disease status will be assessed radiographically [redacted] until disease recurrence or for up to [redacted] years after completion/discontinuation of neoadjuvant therapy, whichever occurs first. The first disease status assessment will occur [redacted] weeks after surgery for participants who complete treatment (neoadjuvant treatment and surgery). For participants who do not undergo surgery, disease assessments will begin [redacted] after the final dose of neoadjuvant treatment. At the investigator's discretion, disease status assessments may be repeated at any time if recurrence is suspected.

Diagnosis of intrahepatic HCC recurrence will be based on non-invasive criteria and/or biopsy-proven pathologic confirmation of recurrence as defined by the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines 2018 (see Appendix 5). 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 according to RECIST v1.1.

All radiographic assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

4.5.9 Classification of Surgical Complications

Surgical Complications will be scored according to Clavien-Dindo classification (see Appendix 6). Complication rates for every grade will be reported and scored for participants that underwent central lymph node dissection, as outlined in the schedule of activities for each arm (see Table A12-5, Table A13-6, and Table A14-5).

4.5.10 Laboratory, Biomarker, and Other Biological Samples

Laboratory tests must be performed within 72 hours prior to dosing during the treatment period. If screening laboratory assessments were performed within 72 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

For information about the timing of laboratory assessments, please refer to the schedule of activities for screening (Appendix 11) or the appropriate treatment arm (Table A12-5, Table A13-6, and Table A14-5).

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (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)
- Cardiac enzymes: TnT and TnI
- α-fetoprotein testing (serum)
- C-reactive protein
- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- Tuberculin purified protein derivative (PPD) skin test or tuberculosis (TB) blood test
  - Participants will undergo a tuberculin PPD skin test or a TB blood test within 3 months prior to initiation of study treatment. A chest X-ray will be performed for participants who have a positive tuberculin PPD skin test.
- Pregnancy test
  - All women of childbearing potential will have a serum pregnancy test at screening. Urine or serum pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
  - A woman is considered to be of childbearing potential if she is 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
  - If urinary protein is ≥2+ on dipstick, then a 24-hour urine collection is required to check the total urinary protein. If there is an explanation for the positive dipstick result (e.g., menses), it should be recorded, and there is no need to perform further laboratory assessments.

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

- Serum sample for analysis of autoantibodies: anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody
- Serum samples for PK analysis through use of validated assays (see Appendix 12, Appendix 13, and Appendix 14)
- Serum samples for immunogenicity analysis through use of validated assays (see Appendix 12, Appendix 13, and Appendix 14)
- [redacted]
- [redacted]



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

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- [redacted]
- [redacted]

When a participant withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the participant 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, [redacted], will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of [redacted], data derived from these analyses will generally not be provided to study investigators or participants 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.

4.5.11 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Participants 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. 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 site's 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 4.5.11) will not be applicable at that site.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and 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 4.5.10 for details on use of samples after participant withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 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, lipids).
The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of biomarker assays, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. 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 assays and establish the performance characteristics of these assays

4.5.12.2 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 4.5.12) will not be applicable at that site.

4.5.12.3 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 CIT or diseases:

- [redacted]

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, whole metagenomic sequencing and comprehensive analysis of the microbiome, or other genomic analysis methods. Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and 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.

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).

4.5.12.4 Confidentiality

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

Participant 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 participant, 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 participants 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.

4.5.12.5 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 participant the objectives, methods, and potential hazards of participation in the RBR. Participants 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 participant's agreement to provide optional RBR samples. Participants who decline to participate will not provide a separate signature.

The investigator should document whether or not the participant has given consent to participate and (if applicable) the date 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.

4.5.12.6 Withdrawal from the Research Biosample Repository

Participants 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 participant. 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 participant 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 participant'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 participant 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 participant number to the following email address:

global.rcr-withdrawal@roche.com

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

4.5.12.7 Monitoring and Oversight

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, PARTICIPANT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Participants must permanently discontinue study treatment if any of the following criteria are met:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual participant's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the participant's safety if he or she continues study treatment
- Investigator or Sponsor determines it is in the best interest of the participant
- Use of another non–protocol-specified anti-cancer therapy
- Pregnancy
- Confirmed disease progression or dissemination prior to surgery. Participants who discontinue study treatment early because of unacceptable toxicity should continue to be followed for both resolution of toxicity and disease recurrence as outlined in the schedule of activities for each arm (see Table A12-5, Table A13-6, and Table A14-5).

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Regardless of whether they complete the neoadjuvant treatment period or discontinue study drug prematurely, participants who proceed to surgery will return to the clinic for a neoadjuvant treatment completion/discontinuation visit [redacted] weeks after surgery. Participants who do not proceed to surgery will return to the clinic for a neoadjuvant treatment completion/discontinuation visit ≤[redacted] days after the final dose of study treatment. The visit at which response assessment shows progressive disease or loss of clinical benefit may be used as the treatment discontinuation visit.

After neoadjuvant treatment completion or discontinuation, information on survival follow-up and initiation of new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, participant medical records, and/or clinic visits approximately [redacted] until disease recurrence or for up to [redacted] years after completion/discontinuation of neoadjuvant therapy, whichever occurs first (unless the participant withdraws consent or the Sponsor terminates the study). Participants who complete the neoadjuvant treatment period will have their first survival follow-up visit [redacted] months after surgery [redacted] Participants who discontinue study drug prematurely will have their first survival follow-up visit [redacted] months after the final dose of study treatment. If a participant requests to be withdrawn from follow-up, this request must be documented

in the source documents and signed by the investigator. If the participant withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all participants discontinue treatment and pass the safety follow-up window, as well as approximately [redacted] of participants discontinued from the study, the Sponsor may conclude the arm (the remaining approximately [redacted] of participants will be discontinued from the study).

See the schedule of activities (see Appendix 12, Appendix 13, and Appendix 14) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment.

4.6.2 Participant Discontinuation from Study

Participants 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 participant from the study at any time.

Reasons for participant discontinuation from the study may include but are not limited to the following:

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

Every effort should be made to obtain information on participants who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Participants who withdraw from the study will not be replaced.

If a participant 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 participants.
- Participant 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 participants have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

A safety plan for each treatment arm, including a summary of risks and management guidelines for participants who experience specific adverse events, is provided in the respective appendix for that treatment arm, as outlined in Appendix 12, Appendix 13, and Appendix 14 (see Appendix 10 for the management guidelines for risks associated with atezolizumab and tiragolumab).

With the exception of viral hepatitis infection (see Section 4.1.2), participants with active infection are excluded from study participation (see Section 1.3 and Appendix 10 for additional details related to SARS-CoV-2 infection). 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).

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. 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 participant 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 participant'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 participant 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)

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 each treatment arm are listed in the respective appendix for that treatment arm, as outlined in Appendix 12, Appendix 13, and Appendix 14.

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 participant contact. All adverse events, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF.

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

After initiation of study treatment, all adverse events will be reported until [redacted] days after the final dose of study treatment or [redacted] Serious adverse events and adverse events of special interest, as well as treatment-related non-serious adverse events that lead to surgery delay, will continue to be reported until [redacted] days after the final dose of study treatment or [redacted]

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 participant 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 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 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 participants 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.



Table 7 ASTCT CRS Consensus Grading Scale

Grade	Symptom(s)
1	• Fever [a], with or without constitutional symptoms • No hypotension • No hypoxia
2	• Fever [a] combined with at least one of the following: – Hypotension not requiring vasopressors – Hypoxia requiring low-flow oxygen [b] by nasal cannula or blow-by
3	• Fever [a] combined with at least one of the following: – Hypotension requiring one vasopressor, with or without vasopressin – Hypoxia requiring high-flow oxygen [b] by nasal cannula, face mask, non-rebreather mask, or Venturi mask
4	• Fever [a] combined with at least one of the following: – Hypotension requiring multiple vasopressors (excluding vasopressin) – Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)
5	• Death due to CRS for which the cause is not the principal factor leading to this outcome

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome.

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the participant, 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 participant 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 participant'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 participants 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 and Cytokine Release Syndrome

There may be significant overlap in signs and symptoms of infusion-related reactions (IRRs) and CRS. While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies, such as delayed hypersensitivity reactions, sepsis or infections, hemophagocytic lymphohistiocytosis, tumor lysis syndrome, early-disease progression, or other manifestations of systemic inflammation.

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 on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction" or "cytokine release syndrome"). Avoid ambiguous terms such as "systemic reaction." Cases of late-onset CRS should be reported as "cytokine release syndrome" on the Adverse

Event eCRF. Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF or Cytokine Release Syndrome eCRF, as appropriate.

If a participant experiences both a local and systemic reaction to a single administration 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 or Cytokine Release Syndrome eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 10.

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 participant 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 participant 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).

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 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 participant has not experienced an adverse event.
- Hospitalization due solely to 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 participant requirement for outpatient care outside of normal outpatient clinic operating hours.

5.3.5.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively 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

- Intentional overdose: intentional 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.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse
  - In cases where drug is to be self-administered by the participant, drug misuse could involve the drug being administered to someone other than the participant.

Note: 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, 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, bevacizumab, tiragolumab, and tobemstomig, 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.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with atezolizumab, bevacizumab, tiragolumab, and tobemstomig, 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.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the participant: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

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.

5.4 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 (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see arm-specific appendices for details on pregnancy reporting requirements for each treatment arm)

For serious adverse events and adverse events of special interest, 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 Medical Monitors and 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.

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, 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, serious adverse events and adverse events of special interest will be reported until [redacted] after the final dose of study treatment [redacted] 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

The reporting requirements for pregnancies are presented in the arm-specific appendices (see Appendix 12, Appendix 13, and Appendix 14).

5.5 FOLLOW-UP OF PARTICIPANTS 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, or the event is assessed as stable by the investigator, or the participant is lost to follow-up, or the participant 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 participant's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Section 5.4.3.

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, electronic mail, 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 [redacted] after the final dose of study treatment [redacted], all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

After the end of the reporting period for non-serious adverse events (defined as [redacted] days after the final dose of study treatment), all treatment-related non-serious adverse events that lead to surgery delay will continue to be reported until [redacted] days after the final dose of study treatment.

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 has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authority (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

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 using the following reference documents:

- Atezolizumab Investigator's Brochure
- Bevacizumab Investigator's Brochure
- Tiragolumab Investigator's Brochure
- Tobemstomig (RO7247669) 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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The final study analysis will be based on participant data collected through study discontinuation. If not otherwise specified, efficacy analyses will be based on the efficacy-evaluable population, defined as all participants who receive at least one dose of each drug for their assigned treatment regimen, and safety analyses will be based on the safety-evaluable population, defined as all participants who receive any amount of study treatment.

The analysis results will be summarized by the treatment regimen that participants actually received. Data will be described and summarized as warranted by sample size. Continuous variables will be summarized through use of means, standard deviations, medians, and ranges. Categorical variables will be summarized through use of counts and percentages. Listings will be used in place of tables in the event of small sample sizes.

6.1 DETERMINATION OF SAMPLE SIZE

This study is not designed to make explicit power and type I error considerations for a hypothesis test. Instead, this study is designed to obtain preliminary safety, efficacy, and PK data on immunotherapy-based treatment combinations when administered to patients with HCC as neoadjuvant therapy.

Approximately 90−150 participants will be randomly allocated to the experimental arms during the study. Please see Table 4 for further details.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment will be summarized by region, country, and investigator by treatment arm. Participant disposition will be summarized by treatment arm within each stage. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

For safety-evaluable participants, study drug administration data will be tabulated or listed by treatment arm, and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose and dose intensity for each study drug. The reasons for discontinuation of study treatment will also be tabulated.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, weight, malignancy duration, metastatic disease site, and baseline ECOG Performance Status) will be summarized overall and by treatment arm.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is MPR rate (as described in Table 2). MPR rate is defined as the proportion of participants who have achieved MPR and will be estimated for each treatment cohort in the efficacy-evaluable population. MPR is defined as $\leq$10% residual viable tumor in the tumor bed at the time of surgical resection in the primary tumor, as assessed by the central pathology laboratory. Participants who do not proceed to surgery are considered as non-responders for MPR. MPR will be calculated for each arm along with 95% Clopper-Pearson CIs.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are relapse-free survival (RFS), EFS, OS, ORR, proportion of participants with a pCR, proportion of participants downstaged to within Milan criteria (for participants beyond criteria at randomization), and R0 resection rate, as defined in Table 2.

RFS is defined as the time from surgery to the first documented recurrence of disease (intrahepatic or extrahepatic) according to EASL and/or RECIST v1.1, or death from any cause. For participants who do not have documented recurrence of disease or death, RFS will be censored at the day of the last tumor assessment.

EFS is defined as the time from randomization to any of the following events (whichever occurs first): Disease progression that precludes surgery, as assessed by the investigator according RECIST v1.1; local or distant disease recurrence as measured by EASL and/or RECIST v1.1; or death from any cause. Participants who have not

experienced such events will be censored at the time of their last post-surgical tumor assessment.

OS is defined as the time from randomization to death from any cause. Participants who are still alive at the time of OS analysis will be censored at the last date they were known to be alive.

OS rate is defined as the proportion of patients who have not experienced death from any cause. Participants who are still alive at the time of OS analysis will be censored at the last date they were known to be alive.

The Kaplan-Meier method will be used to estimate the median for RFS, EFS, and OS, with 95% CIs constructed through use of the Brookmeyer and Crowley method. The OS rate at specific timepoints will also be estimated using the Kaplan-Meier method, with 95% CIs calculated on the basis of Greenwood's estimate for the variance.

The ORR will be assessed after completion of neoadjuvant treatment and is defined as the proportion of participants with a radiographic complete response or partial response prior to surgery, as determined by the investigator according to RECIST v1.1 and HCC mRECIST (Appendix 1 and Appendix 2). Responses will be assessed and determined by the investigator in accordance with RECIST v1.1 and HCC mRECIST, but confirmation by subsequent imaging assessments is not required. Participants with missing or no response assessments will be classified as non-responders. Note that ORR will be determined using unconfirmed pre-operative radiologic responses. ORR will be calculated for each arm, along with 95% Clopper-Pearson CIs.

The pCR rate is defined as the proportion of participants who have achieved pCR. pCR is defined as the absence of any viable tumor cells in both the primary tumor and all sampled lymph nodes at the time of surgical resection. pCR rate will be analyzed using the same statistical methodology as MPR rate for each treatment cohort for the efficacy-evaluable population.

The proportion of participants downstaged to within Milan criteria is defined as the number of participants who were beyond Milan criteria at enrollment and stage as within Milan criteria (single tumor $\leq$5 cm or 2 to 3 nodules all $\leq$3 cm) during the study. The proportion will be calculated for each arm, along with 95% Clopper-Pearson CIs.

R0 resection rate is defined as the proportion of participants who achieved complete resection (R0 resection, confirmed by pathology). The denominator of the proportion will be based on the efficacy-evaluable population. R0 resection rate will be calculated for each arm, along with 95% Clopper-Pearson CIs.

[redacted]

[redacted]

6.5 SAFETY ANALYSES

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

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs and ECGs, and exposure to study drugs. Exposure to combination treatment and length of safety follow-up will be summarized by treatment arm.

Treatment-emergent adverse events occurring after initiation of treatment will be summarized. For each participant, the maximum reported severity of each adverse event will be used in the summaries by severity grade. All treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of study treatment, Grade ≥ 3 adverse events, deaths, and causes of death will be listed and summarized by mapped term, appropriate thesaurus level, and NCI CTCAE severity grade.

Relevant laboratory, vital sign (pulse rate, respiratory rate, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

To assess the impact of neoadjuvant treatment on surgical feasibility, the proportion of participants with delayed or canceled surgery due to treatment-related adverse events will be evaluated in totality.

All adverse events, serious adverse events, and drug-related adverse events resulting in surgical delays and post-surgical complications will be collected. Specific data will be collected to assess the impact of neoadjuvant treatment on surgical complexity, outcomes, and complications, including:

- Preoperative attrition (percent not resected)
- Treatment-related adverse events leading to delayed or cancelled surgery
- Length of surgical delay

- Time from end of neoadjuvant treatment to surgery
- Duration of surgery
- Length of hospital stay
- Type of liver resection (anatomical or nonanatomical; based on Brisbane criteria)
- Quality of liver resection (R0, R1, or R2)
- Width of resection margin
- Surgical approach (minimally invasive vs. open)
- Extent of surgery (minor [$<$3 Couinaud segments] vs. major resection [$\geq$3 Couinaud segments] according to Brisbane criteria)
- Intraoperative blood loss
- Requirement for intraoperative blood or platelet transfusion
- Postoperative 30- and 90-day mortality

Post-operative surgical complication rates will be calculated according to the Clavien-Dindo surgical classification (see Appendix 6; clinically relevant complications are defined as Clavien-Dindo Grade $\geq$IIIa). Complication rates for every grade will be reported and scored for participants that underwent liver resection, as outlined in the schedule of activities for each arm (see Table A12-5, Table A13-6, and Table A14-5). Post-operative mortality is defined as death within 90 days after surgery or prior to discharge.

Surgical complications will be scored according to Clavien-Dindo classification (Appendix 6). Complication rates for every grade will be reported and scored for patients that underwent liver resection, as outlined in the schedule of activities for each arm (see Table A12-5, Table A13-6, and Table A14-5).

6.6 PHARMACOKINETIC ANALYSES

Sparse samples will be collected for potential PK analyses of atezolizumab (participants who receive at least one dose of atezolizumab) and specified drugs given in combination, with or without atezolizumab (participants who receive at least one dose of the drug). Serum or plasma concentrations of the various study drugs may be reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by treatment arm and by cycle and day when appropriate and as data allow. Individual and median serum or plasma concentrations of the various study drugs may be plotted by treatment arm and by cycle and day when appropriate and as data allow. PK data for combination drugs may be compared with available historical data from internal and published previous studies. Atezolizumab or other study drug 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 concentration–time curve.

[redacted]

6.9 INTERIM ANALYSES

[redacted]

A posterior probability may be used to guide further enrollment in a treatment arm after completing safety evaluation and the preliminary phase, based on an interim analysis of clinical activity in the experimental arm compared with a predefined MPR threshold. All data from the safety evaluation will be incorporated with the preliminary phase data at the time of interim analysis.

The predefined MPR threshold will be based on emerging internal and external data for in-class immune-modulating investigational and other compounds for the participant population. The Sponsor may make a decision to expand enrollment in an arm on the basis of the totality of available data including but not limited to RFS, EFS, and potentially early OS data. Safety and biomarker data (available at the time of making this decision) will also be taken into consideration from the perspective of an adequate benefit–risk assessment.

The interim analyses will be performed and interpreted by Sponsor study team personnel.

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 will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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.

7.2 ELECTRONIC CASE REPORT FORMS

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. 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. 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 participant data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc 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 participant 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, participant-reported outcomes, 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, participant 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 IMPs, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 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 Clinical Study Report has been completed 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 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. Food and Drug Administration 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 Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Forms (and ancillary sample Informed Consent Forms such as a Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, they will be provided in a certified translation into 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 participant the objectives, methods, and potential risks associated with each optional procedure. Participants 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 participant'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 participant or the participant's legally authorized representative before his or her participation in the study. The case history or clinical records for each participant 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 subject 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 participant is participating in the study, the participant 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 participant 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 participant or the participant's legally authorized representative. All signed and dated Consent Forms must remain in each participant'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 participant 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 participant 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 participant, 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 participant 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 9.6).

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 participant enrolled in the study through assignment of a unique participant identification number. This means that participant names are not included in data sets that are transmitted to any Sponsor location.

Participant 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 participant, unless permitted or required by law.

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

Given the complexity and exploratory nature of [redacted], data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

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 9.5).

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 (i.e., LPLV, 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 participant 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 participant 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 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' 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.

9.4 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. 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, [redacted] and PK analyses), as specified in Section 4.5.10. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate participant safety throughout the study. An SOC will provide external expert opinions on the safety data collected during the study.

9.5 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). In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulations, and will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of 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 participants 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 participants 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.

9.6 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 participants or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

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

TUMOR MEASURABILITY

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

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 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) because 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 locoregional 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, because 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 participant 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 participant at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For participants 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 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 participant 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 because the same lesion may appear to have a different size using a new modality.

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

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized 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 participants have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention because 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 because 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 because 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 schedules 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.

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 participant'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 A1-1 provides a summary of the overall response status calculation at each response assessment timepoint for participants who have measurable disease at baseline.

Table A1-1 Criteria for Overall Response at a Single Timepoint: Participants with Target Lesions (with or without Non-Target Lesions)

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

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

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the participant 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 participant 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 participant will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Participants with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as having "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 participants is to be determined by evaluation of target and non-target lesions as shown in Table A1-1.

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

REFERENCES

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

Appendix 2
Hepatocellular Carcinoma–Specific Modified RECIST (HCC mRECIST)

IMAGE ACQUISITION FOR HCC-SPECIFIC MODIFIED RECIST

Optimization of image acquisition protocols and consistency in the use of the same protocol throughout follow-up examinations are key for proper application of hepatocellular carcinoma (HCC)-specific modified Response Evaluation Criteria in Solid Tumors ([RECIST], HCC mRECIST; Lencioni et al. 2010).

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

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

ASSESSMENT OF TUMOR LESIONS

TARGET LESIONS

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

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

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

- HCC lesions previously treated with locoregional or systemic treatments may or may not be considered as suitable to be selected as target lesions for HCC mRECIST: If the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is at least 1 cm in longest diameter, then it can be selected as a target lesion. In contrast, if the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion for HCC mRECIST.

Table A2-1 Target Lesion Selection Criteria

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

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

Defining Treatment Response and Tumor Progression:

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

Table A2-2 Target Lesion Response Definition

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

HCC = hepatocellular carcinoma; mRECIST = modified Response Evaluation Criteria in Solid Tumors; PD = progressive disease; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

NON-TARGET LESIONS

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

- Portal vein thrombosis. Malignant portal vein thrombosis should be considered a non-measurable lesion due to the difficulty in performing consistent measurements of the malignant thrombus during the course of the treatment. Measurements of the extent of the malignant thrombus may be impaired by the possible presence of a bland component of the thrombosis.
- Porta hepatic lymph node. Lymph nodes detected at the portal hepatitis can be considered as malignant if the lymph node short axis is at least 20 mm. Evidence of reactive lymph nodes at the porta hepatic, in fact, is a common finding in patients with cirrhosis regardless of the presence of an HCC. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor.

- Pleural effusion and ascites. The original RECIST publication specifies that cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed).
- The emergence or the increase in ascites is a common event during the course of treatment in a cirrhotic patient, which may be due to worsening of the underlying chronic liver disease and be unrelated to cancer progression. Other effusions, such as pleural effusion, may also be unrelated to cancer progression and be caused by the liver insufficiency. Thus, the HCC mRECIST emphasizes that cytopathologic confirmation of the neoplastic nature of any effusion (particularly ascites) that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. It has to be underlined that peritoneal carcinomatosis is a very rare event in HCC.

Table A2-3 Non-Target Lesion Response Definition

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

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

NEW LESIONS

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

OVERALL VISIT RESPONSE

Overall visit response is obtained in a similar fashion as for RECIST v1.1 by combining the response assessment for target lesions, non-target lesions, and new lesions.

Table A2-4 Summary Table

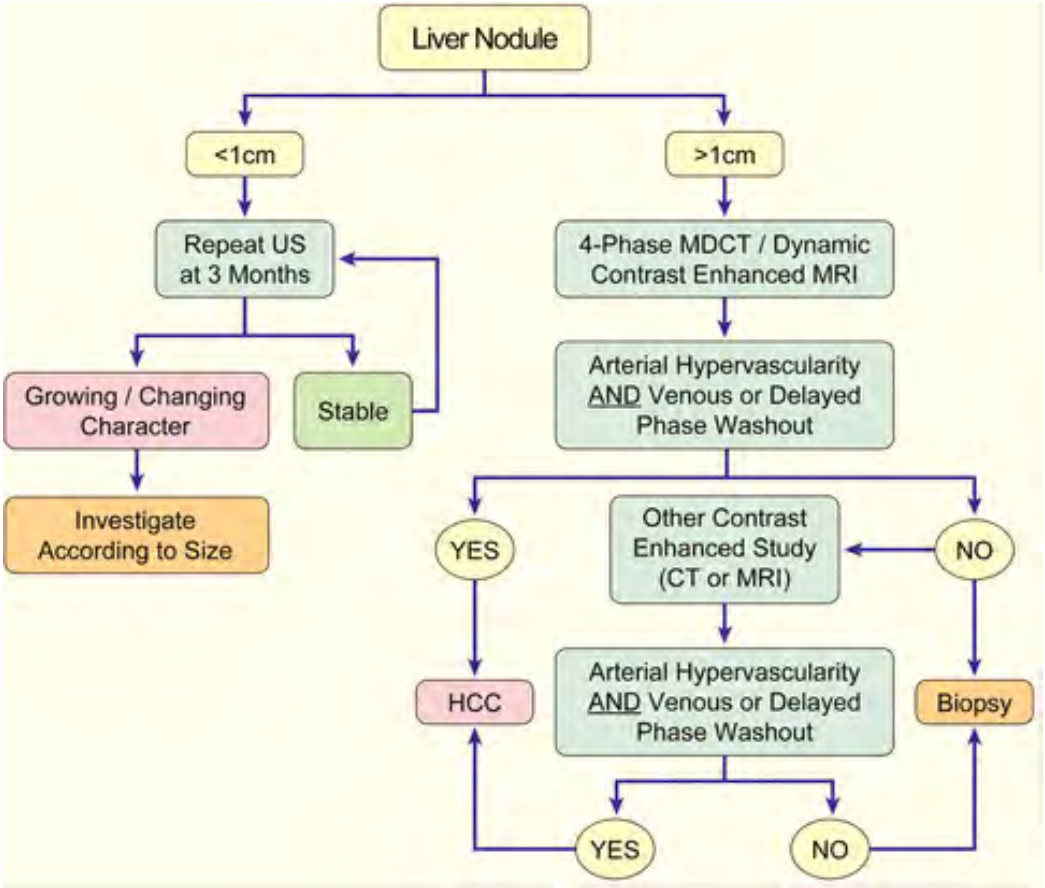
Target Lesions		
Response Category	RECIST v1.1	HCC-Specific mRECIST
Complete response	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial response	≥ 30% decrease in sum of the longest diameters of target lesions compared with baseline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

HCC = hepatocellular carcinoma; mRECIST = modified Response Evaluation Criteria in Solid Tumors; PD = progressive disease; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

REFERENCES

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

Appendix 3
Association for the Study of Liver Diseases Criteria: Algorithm for Investigation of Small Nodules Found at Screening in Patients at Risk for HCC



CT = computed tomography; HCC = hepatocellular carcinoma; MDCT = multi-detector CT scan; MRI = magnetic resonance imaging; US = ultrasound.

REFERENCE

Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53:1020–2.

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

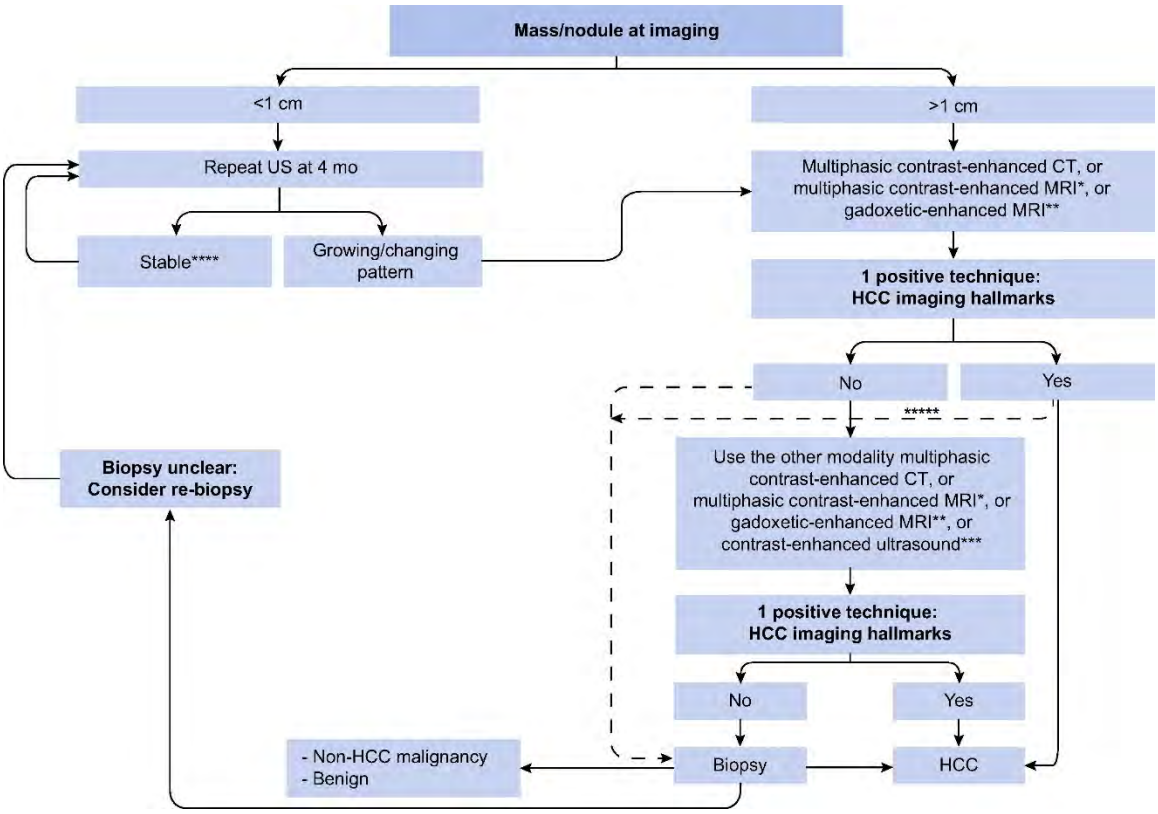
Points	Class
5–6	A
7–9	B
10–15	C

REFERENCES

Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG, editor. The liver and portal hypertension. 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
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 programs.

REFERENCE

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

Appendix 6
Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for Grade I complications Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic, or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)[a] requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge,[b] the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

IC = intermediate care; ICU = intensive care unit.

[a] Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.

[b] For examples of complication grades, see Table 2 in Dindo et al. (2004).

REFERENCE

Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240:205–13.

Appendix 7
ECOG Performance Status Scale

Grade	Description
0	Fully active; able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours.
3	Capable of only limited self-care; confined to a bed or chair > 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG = Eastern Cooperative Oncology Group.

Appendix 8
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias for whom 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, tiragolumab, or tobemstomig 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 regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies



Appendix 9
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 medications are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: electrocardiogram monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, 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 administration, the following procedures should be performed:

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

Appendix 10
Risks Associated with Atezolizumab and/or Tiragolumab, and/or Tobemstomig and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab, and/or Tobemstomig

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the adverse event management guidelines described in this appendix, including those for continuing, withholding, resuming, and discontinuing atezolizumab, as outlined below, are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for $>$21 days, the patient will be discontinued from tobemstomig.

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.

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.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in subsequent subsections.

- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- The investigator should consider the benefit–risk balance for a given patient prior to further administration of atezolizumab. [redacted]

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. Coronavirus disease 2019 (COVID-19) evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table A10-1.

Table A10-1 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. – Consider resuming on radiographic evidence of improvement.
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 the 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 the Medical Monitor. [c, d] • 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.

Table A10-1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

BAL = bronchoscopic alveolar lavage.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

[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.

[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; liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table A10-2.

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 A10-2 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 the Medical Monitor. [c]
AST or ALT increases to $>10\times$ ULN or total bilirubin increases to $>3\times$ ULN	• Permanently discontinue atezolizumab and contact the 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 ≥ 1 month.

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

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for >21 days, the patient will be discontinued from tobemstomig.

[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 A10-3.

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 A10-3 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, initiate empiric IV corticosteroids 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 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]

GI = gastrointestinal.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

[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 A10-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
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 the Medical Monitor. [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact the 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.

GI = gastrointestinal.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

[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 A10-4.

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. TSH and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table A10-4 Management Guidelines for Endocrine Events

Event	Management
Hypothyroidism, Grade 1	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Hypothyroidism, Grade 2	• 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.
Hypothyroidism, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer patient to endocrinologist. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism. [c]

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for >21 days, the patient will be discontinued from tobemstomig.

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A10-4 Management Guidelines for Endocrine Events (cont.)

Hyperthyroidism, Grade 1	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for Grade 2 hyperthyroidism. • Consider patient referral to endocrinologist.
Hyperthyroidism, Grade 2	• Consider withholding atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Hyperthyroidism, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer patient to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A10-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
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.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for >21 days, the patient will be discontinued from tobemstomig.

[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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A10-4 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.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

[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 A10-5.

Table A10-5 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.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

[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

In high-risk patients (including those with abnormal baseline cardiac troponin levels, when available), transthoracic echocardiogram (TTE) monitoring should be considered, as clinically indicated, and based on local clinical practice. Management guidelines for cardiac events are provided in Table A10-6.

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., troponin, 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 immune-mediated 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, a TTE for evaluation of left ventricular ejection fraction and global longitudinal strain, 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 A10-6.

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 immune-mediated 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 (e.g., metastatic disease), cancer treatment (e.g., chest radiotherapy), cardiac injury (e.g., injury due to myocardial infarction or iatrogenesis), 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, TTE, 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 A10-6. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table A10-6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2–4 **or** Immune-mediated pericardial disorders, Grades 2–4	• Permanently discontinue atezolizumab and the contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider anti-arrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1 g/day IV methylprednisolone for 3–5 days and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 24 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.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

INFUSION-RELATED REACTIONS AND CYTOKINE RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, 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 A10-7.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-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 A10-7 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. • 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 A10-7 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. • 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 the 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. • 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 A10-7 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.

Notes: 1) The management guidelines have been adapted from the NCCN guidelines for the management of CAR T-cell–related toxicities (Version 2.2019). 2) Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: if tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

[a] Grading system for these management guidelines is based on ASTCT Consensus Grading Scale for CRS (Lee et al. 2019) (see Section 5.3.3, Table 7). NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive antipyretic, 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 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. 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).

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 A10-8.

Table A10-8 Management Guidelines for Pancreatic Events, Including Pancreatitis

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

GI = gastrointestinal; ULN = upper limit of normal.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

[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 A10-8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact the 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.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: if tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

[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 A10-9.

Table A10-9 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 patient is 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]

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for >21 days, the patient will be discontinued from tobemstomig.

[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 A10-9 Management Guidelines for Dermatologic Events (cont.)

Event	Management
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact the 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.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for >21 days, the patient will be discontinued from tobemstomig.

[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. Myasthenia may be associated with myositis (see section on immune-mediated myositis) and patients should be managed accordingly. Management guidelines for neurologic disorders are provided in Table A10-10, with specific guidelines for myelitis provided in Table A10-11.

Table A10-10 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: – Initial observation, OR initiate prednisone 1–2 mg/kg/day (if progressing from mild). Initiate treatment with gabapentin, pregabalin, or duloxetine, for pain. – 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]

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for >21 days, the patient will be discontinued from tobemstomig.

[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 A10-10 Management Guidelines for Neurologic Disorders (cont.)

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 and proceed as per Guillain-Barré syndrome management.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact the Medical Monitor. • 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. • Consider IVIG or plasmapheresis in patients with rapid progression with development of bulbar and/or respiratory symptoms. • In life-threatening cases, consider IV methylprednisolone 1 g/day for 3–5 days and consider other immunosuppressive agent.

IVIG = intravenous immunoglobulin.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

[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 A10-11 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 neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Investigate etiology and refer patient to 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. • Initiate non-opioid treatment (e.g., pregabalin, gabapentin, duloxetine) for pain. • Hospitalize patient. – Initiate treatment with corticosteroids equivalent to 1 g/day IV methylprednisolone. – If event does not improve or there is worsening of symptoms within 3 days, consider IVIG or plasmapheresis and manage as per institutional guidelines. • Refer patient to neurologist.

IVIG = intravenous immunoglobulin.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

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 listed in Table A10-12.

Table A10-12 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 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.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

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 A10-13.

Table A10-13 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function closely, including creatinine and urine protein, 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 the Medical Monitor. [c]
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.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

[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/creatine phosphokinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients may initially present with low grade nondescript symptoms including mild pain and weakness; thus, there should be a low threshold for suspicion of myositis. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis (see section on immune-mediated myocarditis) and myasthenia gravis (bulbar symptoms such as dysphagia, dysphonia, and dyspnea; see section on neurologic disorders).

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A10-14.

Table A10-14 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]

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for >21 days, the patient will be discontinued from tobemstomig.

[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 A10-14 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 3	• 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. • 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. • Consider IVIG or plasmapheresis. • If event does not improve within 24–48 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.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact the 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. • Consider IVIG or plasmapheresis. • If event does not improve within 24–48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Table A10-14 Management Guidelines for Immune-Mediated Myositis (cont.)

IVIG = intravenous immunoglobulin.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

[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

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

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 $<100\times10^9$/L ($<$100,000/μL)
  - ANC $<1.0\times10^9$/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 $\geq$2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected HLH should be treated according to the guidelines in Table A10-15.

Table A10-15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis

Event	Management
Suspected HLH	• 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 respond to treatment within 24 hours, contact the Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = hemophagocytic lymphohistiocytosis.

Note: Because of the expected pharmacologic activity of tiragolumab and tobemstomig, the guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab and tobemstomig with one exception: If tobemstomig is withheld for > 21 days, the patient will be discontinued from tobemstomig.

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Appendix 11
Schedule of Activities for Screening

Table A11-1 Schedule of Activities for Screening

Assessment/Procedure	Protocol Section	Screening
Participant information		Days –28 to –1
Informed consent	Section 4.5.1	x
Demographics	Section 4.5.2	x
Medical history and baseline conditions		x
Clinical assessments		Days –28 to –1 (unless otherwise indicated)
Vital signs	Section 4.5.4	x
Weight	Section 4.5.3	x
Height		x
Complete physical examination		x
ECOG Performance Status	Appendix 7	x
ECG	Section 4.5.5	x
TTE or MUGA scan	Section 4.5.6	x
Baseline tumor assessments	Section 4.5.8.2	x
Concomitant medications	Section 4.5.2	x
Adverse events	Section 5.3.1	x
EGD	Section 4.5.7	x
Local laboratory assessments		Within 72 hours prior to Day 1
Hematology	Section 4.5.10	x
Chemistry panel		x
Cardiac enzymes (TnT or TnI)		x
α-fetoprotein		x
Coagulation (INR, aPTT)		x
TSH, free T3 (or total T3), and free T4		x
Viral serology [a]		x
TB test		x
C-reactive protein		x
Pregnancy test (serum)		x
Urinalysis		x
Central laboratory assessments		Days –28 to –1
Serum autoantibody sample		x
Tumor biopsy		x

Table A11-1 Schedule of Activities for Screening (cont.)

[redacted] ECOG = Eastern Cooperative Oncology Group; EGD = esophagogastroduodenoscopy; [redacted] MUGA = multiple-gated acquisition (scan); TB = tuberculosis; TnI = troponin I; TnT = troponin T; TTE = transthoracic echocardiogram; VCA = viral capsid antigen.

[a] [redacted]

Appendix 12
Study Details Specific to Atezo + Bev Arm

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A12–1 BACKGROUND ON ATEZO + BEV ARM

A12–1.1 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 cluster of differentiation [CD] 80), 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 fragment crystallizable (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 (CIT).

Atezolizumab is approved for the treatment of urothelial carcinoma (UC), non-small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma (HCC), melanoma, and alveolar soft part sarcoma.

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

A12–1.2 BACKGROUND ON BEVACIZUMAB

Bevacizumab is a recombinant humanized monoclonal antibody that recognizes all isoforms of vascular endothelial growth factor (VEGF). It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor microenvironment. Additional anti-tumor activity may be on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).

Bevacizumab is approved for the first-line and second-line treatment of metastatic colorectal cancer, first-line treatment of advanced NSCLC, metastatic breast cancer, advanced renal cell carcinoma (RCC), ovarian cancer, fallopian tube, peritoneum, cervical, and HCC, and treatment of recurrent glioblastoma. Bevacizumab is currently being tested in combination with atezolizumab in Phase I–III clinical trials. Bevacizumab has been generally well tolerated, and adverse events have been manageable.

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

A12–2 RATIONALE FOR ATEZO + BEV ARM

A12–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

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

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with advanced malignancies in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active as monotherapy for many patients. To date, targeting the PD-L1 pathway with single-agent atezolizumab has shown minimal activity in the treatment of patients with locally advanced or unresectable HCC.

A12–2.2 THE VEGF PATHWAY

VEGF-A is a pro-angiogenic molecule produced by endothelium, tumors, and tumor-associated macrophages. In addition to promoting tumor angiogenesis, there is increasing evidence that the VEGF pathway also plays an important role in cancer immune evasion by exerting and maintaining an immunosuppressive tumor microenvironment through several mechanisms.

VEGF-A inhibits the maturation of dendritic cells (DCs), promotes the expression of inhibitory immune checkpoint molecules on intratumoral $CD8^+$ T cells, and induces Fas ligand (FasL) expression on endothelial cells, which acquired the ability to kill effector $CD8^+$ T cells but not T-regulatory cells (Gabrilovich et al. 1996; Huang et al. 2007; Motz et al. 2014; Voron et al. 2015). Experiments with activated endothelial cells also suggest that VEGF may reduce lymphocyte adhesion to vessel walls in the tumor microenvironment, thus contributing to decreased immune cell recruitment to the tumor site (Bouzin et al. 2007). In addition, VEGF recruits macrophages into the tumor microenvironment that have a M2 polarization state, which is typically involved in wound healing. These M2 tumor–associated macrophages ultimately help establish and maintain an immunosuppressive microenvironment (Chen and Mellman 2013).

Targeting the VEGF pathway with agents such as bevacizumab has been clinically validated with demonstrated anti-tumor activity in patients with several advanced malignancies. However, when administered as a single agent in patients with HCC, bevacizumab has only demonstrated minimal activity (Siegel et al. 2008; Boige et al. 2012).

A12–2.3 COMBINATION TREATMENT WITH ANTI–PD-L1 AND ANTI-VEGF AGENTS

Durable clinical benefit is limited to a minority of patients treated with single-agent PD-1/PD-L1 inhibitors. Therapies targeting the mechanisms of resistance to anti–PD-1/PD-L1 therapies are needed to improve outcomes in patients with solid-tumor cancers. A strong scientific rationale and emerging clinical data suggest that combined PD-L1 and VEGF inhibition may be clinically beneficial in a number of tumor types.

Anti-VEGF agents promote the normalization of tumor vasculature, thereby increasing access of therapeutic agents (Jain 2001). In addition, bevacizumab can restore and/or maintain the antigen-presentation capacity of DCs, leading to enhanced T-cell infiltration in tumors (Oelkrug and Ramage 2014; Wallin et al. 2016). Administration of anti–VEGF-A has been shown to attenuate tumor endothelial FasL expression and produce a significant increase in the influx of tumor-rejecting $CD8^+$ T cells, leading to tumor growth suppression (Motz et al. 2014). Anti-VEGF therapies can also reduce the

frequency of myeloid-derived suppressor cells, decrease production of suppressive cytokines, and lower expression of inhibitory checkpoints on $CD8^+$ T cells in tumors (Roland et al. 2009; Voron et al. 2015).

The immunomodulatory effects of bevacizumab are anticipated to increase $CD8^+$ T-cell recruitment and relieve intratumoral immunosuppression, thereby boosting the effects of immunotherapy. Indeed, clinical data have demonstrated a beneficial effect of anti-angiogenesis and immunomodulation within the context of atezolizumab treatment. The activity of combination treatment with atezolizumab and bevacizumab has been demonstrated in multiple, large, randomized Phase III clinical studies in patients with NSCLC, RCC, and HCC.

In chemotherapy-naive patients with Stage IV NSCLC, results from Study GO29436 (IMpower150) have shown that atezolizumab plus bevacizumab and chemotherapy results in significantly longer overall survival (OS) compared with bevacizumab and chemotherapy alone (Socinski et al. 2018). For patients with inoperable, locally advanced, or metastatic RCC, results from Study WO29637 (IMmotion151) demonstrated improved progression-free survival (PFS) after treatment with the combination of atezolizumab and bevacizumab compared with sunitinib in a treatment-naive patient population (Rini et al. 2019). Most recently, results from Study YO40245 (IMbrave150) have demonstrated a statistically significant and clinically meaningful improvement in PFS and OS in patients with unresectable locally advanced or metastatic HCC treated with atezolizumab plus bevacizumab compared with sorafenib (Finn et al. 2020) (see Section A12–2.4 for more details on clinical studies evaluating the combination of atezolizumab with bevacizumab in HCC).

A12–2.4 CLINICAL STUDIES OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB IN HEPATOCELLULAR CARCINOMA

The efficacy and safety of atezolizumab in combination with bevacizumab as a treatment for patients with unresectable, locally advanced, or metastatic HCC is currently being investigated in two studies (GO30140 and YO40245 [IMbrave150]).

A12–2.4.1 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. Arm A was designed to evaluate the combination of atezolizumab plus bevacizumab in 104 participants with locally advanced or metastatic HCC who had not received prior systemic therapy. Arm F was added to the study at a later date to compare combination treatment with atezolizumab plus bevacizumab to atezolizumab alone. A total of 119 participants with locally advanced or metastatic HCC were randomized in a 1:1 ratio to receive atezolizumab plus bevacizumab or

atezolizumab monotherapy. Results for Arms A and F have been recently presented (Lee et al. 2019).

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 based on Independent Review Facility (IRF) assessment per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) was 35.6% (37 of 104 participants). Among the 37 responders, 12 participants (11.5%) achieved a complete response, and the remaining 25 participants (24.0%) achieved a partial response. Median duration of response was not reached at the time of this analysis. Moreover, Arm F met its primary efficacy endpoint by demonstrating a statistically significant and clinically meaningful improvement in PFS for the combination compared with atezolizumab monotherapy (stratified hazard ratio [HR] = 0.55 ; 95% CI: 0.40 to 0.74]; p = 0.0108; median PFS, 5.6 vs. 3.4 months, respectively).

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.

A12–2.4.2 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 (Finn et al. 2020). The study enrolled 501 participants randomized in a 2:1 ratio. The co-primary efficacy endpoints were OS and IRF-assessed PFS by RECIST v1.1.

As of the clinical cutoff date of 29 August 2019, the primary analysis demonstrated statistically significant and clinically meaningful improvements for atezolizumab plus bevacizumab compared with sorafenib for the co-primary endpoints. The risk of death was reduced by 42% for the atezolizumab plus bevacizumab arm compared with the sorafenib arm (stratified HR = 0.58; 95% CI: 0.42 to 0.79; p = 0.0006; median OS, not estimable vs. 13.24 months). IRF-assessed PFS per RECIST v1.1 also demonstrated a statistically significant and clinically meaningful improvement favoring combination treatment (stratified HR = 0.59; 95% CI: 0.47 to 0.76; p < 0.0001; median PFS, 6.83 vs. 4.27 months).

Overall, the atezolizumab plus bevacizumab combination in HCC was generally well tolerated with manageable toxicities, and the safety profile was consistent with the known risks of the individual study treatments and with the underlying disease.

Refer to the Atezolizumab Investigator's Brochure and Bevacizumab Investigator's Brochure for additional details on all ongoing and planned clinical studies.

A12–2.5 BENEFIT–RISK ASSESSMENT

The combination of atezolizumab with bevacizumab showed clinically meaningful improvement in PFS and OS relative to sorafenib in patients with locally advanced or metastatic HCC who have not received prior systemic therapy (Finn et al. 2020). No new safety signals were identified with this combination. These results demonstrated proof of concept for the activity of this treatment combination in this patient population and support a favorable benefit–risk assessment.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please see Section 1.3.

A12–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + BEV ARM

A12–3.1 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.

A12–3.2 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 an approved dosage for bevacizumab.

A12–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + BEV ARM

A12–4.1 TREATMENT IN ATEZO + BEV ARM

A12–4.1.1 Formulation and Packaging

A12–4.1.1.1 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 of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A12–4.1.1.2 Bevacizumab

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

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

A12–4.1.2 Dosage, Administration, and Compliance

Participants in the atezolizumab plus bevacizumab (Atezo + Bev) arm will receive up to three cycles of treatment as outlined in Table A12-1 until surgery or unacceptable toxicity, whichever occurs first. It is recommended that treatment be initiated no later than 7 calendar days after randomization. However, the first dose of study treatment should not occur within 3 days after a core biopsy or other surgical procedure.

Table A12-1 Treatment Regimen for Atezo + Bev Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg by IV infusion on Day 1 • Bevacizumab 15 mg/kg by IV infusion on Day 1 [a]

Atezo + Bev = atezolizumab plus bevacizumab.

[a] On Day 1 of each cycle, bevacizumab will be administered at least 5 minutes after completion of the atezolizumab infusion.

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

Medication errors 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. No safety data related to overdosing of atezolizumab or bevacizumab are available to date.

A12–4.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 9. Atezolizumab infusions will be administered per the instructions outlined in Table A12-2.

Table A12-2 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, pulse oximetry, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (± 15) minutes. • If clinically indicated, vital signs should be recorded every 15 (± 5) minutes during the infusion and 30 (± 10) minutes after the infusion. • Participants 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 participant experienced an IRR with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an IRR, or 60 (± 15) minutes if the participant experienced an IRR with the previous infusion. • If the participant experienced an IRR with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (± 10) minutes after the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 10.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A12–5.1.4. Atezolizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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.

A12–4.1.2.2 Bevacizumab

Bevacizumab will be administered by IV infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle. On Day 1 of each cycle, bevacizumab will be administered at least 5 minutes after completion of the atezolizumab infusion.

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 9. Bevacizumab infusions will be administered per the instructions outlined in Table A12-3.

Table A12-3 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, pulse oximetry, and temperature) should be measured within 60 minutes prior to the infusion. • Bevacizumab should be infused over 90 (±15) minutes. • Vital signs should be recorded at the end of infusion and 2 (±1) hours after the infusion. • Participants 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 participant experienced an IRR with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Bevacizumab should be infused over 60 (±10) minutes if the previous 90-minute infusion was tolerated without an IRR, or 90 (±15) minutes if the participant experienced an IRR with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (±5) minutes thereafter. • Vital signs should be recorded within 30 minutes after completion of the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of IRRs for bevacizumab are provided in Section A12–5.1.4.

No dose modification for bevacizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A12–5.1.4. Bevacizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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.

A12–4.2 CONCOMITANT THERAPY FOR ATEZO + BEV ARM

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

A12–4.2.1 Permitted Therapy for Atezo + Bev Arm

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

- Oral contraceptives with a failure rate of < 1% per year
- Hormone-replacement therapy
- Prophylactic use of low-dose anticoagulation, unfractionated heparin, or low-molecular-weight heparin (LMWH)
  - Adherence to the label-recommended dose for prophylactic use of anticoagulants is required.
  - The preferred choice for anticoagulation treatment should be LMWH as per American Society of Clinical Oncology (ASCO) guidelines (Key et al. 2020).
- Low-dose aspirin (< 325 mg/day)
  - Co-administration of proton pump inhibitors is strongly recommended to reduce potential gastrointestinal (GI) damage.
- Vaccinations (such as influenza, COVID-19)
  - Live, attenuated vaccines are not permitted (see Section A12–4.3.3).
- 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. Other use of corticosteroids may be at the investigator's discretion. The Medical Monitor is available to advise as needed.

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

A12–4.2.2 Cautionary Therapy for Atezo + Bev Arm

A12–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF 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 (see Appendix 10 for details).

A12–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A12–4.3.3) may be used during the study at the discretion of the investigator.

A12–4.2.2.3 Bisphosphonates

Osteonecrosis of the jaw has been reported in patients receiving bevacizumab, mainly in combination with bisphosphonates. Thus, caution must be exercised in using bevacizumab in participants receiving concomitant bisphosphonates.

A12–4.2.3 Prohibited Therapy for Atezo + Bev Arm

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

- Concomitant therapy intended for the treatment of cancer (including but not limited to chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment.
- Concomitant use of herbal therapies or traditional Chinese medicine with anti-cancer activity included in the label
- Investigational therapy within 28 days prior to initiation of study treatment and during study treatment
- Live, attenuated vaccines (e.g., FluMist®) within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the final dose of atezolizumab
- Systemic immunostimulatory agents (including but not limited to interferons and interleukin-2) 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 anticoagulants, thrombolytic therapy at therapeutic doses, or anti-platelet therapy
  - Local label-recommended doses for prophylactic use of anticoagulants or thrombolytic therapies are allowed.
  - Low-dose aspirin (< 325 mg/day) is permitted. Co-administration of proton pump inhibitors is strongly recommended to reduce potential GI damage.
  - If a participant experiences a venous thromboembolism event while still receiving study drug treatment, it may still be possible for the participant to remain on study medication despite anticoagulation treatment (see Section 4.1.2).
- Use of warfarin or Coumadin-like products (includes for prophylactic use)
  - Prophylactic use of low-dose anticoagulation, unfractionated heparin, or LMWH is permitted. Adherence to the label-recommended dose for prophylactic use of anticoagulants is required. The preferred choice for anticoagulation treatment should be LMWH as per ASCO guidelines (Key et al. 2020).
- Concomitant chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) while receiving study drugs, with the exception of chronic low-dose aspirin (< 325 mg/day)
  - However, for the symptomatic relief of medical conditions (e.g., headache, fever) intermittent or short-term intake of oral NSAIDs is allowed, when co-administered with proton pump inhibitors to reduce potential GI damage.

A12–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + BEV ARM

Contraception requirements for women and men in the Atezo + Bev arm are outlined below:

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:
  - Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the final dose of atezolizumab and for 6 months after the final dose of bevacizumab.
  - 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). 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 participant. 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 participant. 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, information about the reliability of abstinence will be described in the local Informed Consent Form.

A12–5 ASSESSMENT OF SAFETY FOR ATEZO + BEV ARM

A12–5.1 SAFETY PLAN FOR ATEZO + BEV ARM

The safety plan for participants 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 A12–5.1.1, A12–5.1.2, and A12–5.1.3). Guidelines for management of participants who experience specific adverse events are provided in Section A12–5.1.4.

Measures will be taken to ensure the safety of subjects participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of participants during the study. Special caution will be taken by performing a planned safety evaluation phase for participants randomized to this arm (see Section 3.1.3).

Administration of study treatment 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. Adverse events will be reported as described in Sections 5.2–5.6.

A12–5.1.1 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, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 10 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A12–5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: GI perforations, hemorrhage, arterial thromboembolic events, fistulae, wound-healing complications, hypertension, venous thromboembolism, proteinuria, congestive heart failure, and posterior reversible encephalopathy syndrome (PRES). Refer to Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for bevacizumab.

A12–5.1.3 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.

A12–5.1.4 Management of Participants Who Experience Specific Adverse Events in Atezo + Bev Arm

A12–5.1.4.1 Dose Modifications

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

A12–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in participants 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 participant will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for participants to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the participant is likely to derive clinical benefit. The decision to re-challenge participants 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.

Bevacizumab treatment may be temporarily suspended in participants experiencing toxicity considered to be related to study treatment. If bevacizumab is withheld for > 42 days, the participant will be discontinued from bevacizumab. Bevacizumab can be resumed after being withheld for > 42 days if the participant is likely to derive clinical benefit. The decision to re-challenge participants with bevacizumab should be based on investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

If atezolizumab or bevacizumab is withheld or discontinued, the other study drug can be continued if the participant is likely to derive clinical benefit, as determined by the investigator per medical judgment.

See Section A12–4.2.2 for information on dose interruptions for reasons other than toxicity.

A12–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for management of participants who experience specific adverse events are provided in Table A12-4. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Table A12-4 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev Arm

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reaction	
General guidance	• Guidelines for management of IRRs and CRS for atezolizumab are provided in Appendix 10. • For anaphylaxis precautions, see Appendix 9. • For severe hypersensitivity reactions, permanently discontinue atezolizumab and bevacizumab.
IRR to bevacizumab, Grade 1	• Continue bevacizumab. • Systemic intervention is not indicated.
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 participant'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.
Hemophagocytic lymphohistiocytosis	• Follow guidelines for atezolizumab in Appendix 10. • Withhold all treatment. The Medical Monitor is available to advise as needed.

Atezo + Bev = atezolizumab plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] 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.

[c] 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.

[d] Institutional protocols acceptable.

Table A12-4 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev Arm

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 for complete obstruction. • If surgery is necessary, participant may restart bevacizumab after full recovery from surgery and at the investigator's discretion.

Atezo + Bev = atezolizumab plus bevacizumab; GI = gastrointestinal.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] 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.

[c] 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.

[d] Institutional protocols acceptable.

Table A12-4 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev Arm

Event	Action to Be Taken
Hypertension	
General guidance	• Treat with anti-hypertensive medication as needed.
Hypertension, Grade 1	• Continue atezolizumab and bevacizumab. • Consider increased blood pressure 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 blood pressure $< 160/90$ mmHg.
Hypertension, Grade 4	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.

Atezo + Bev = atezolizumab plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] 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.

[c] 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.

[d] Institutional protocols acceptable.

Table A12-4 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev Arm

Event	Action to Be Taken
Hemorrhage	
Hemorrhage, Grade 3 or 4 (excluding cerebral hemorrhage)	• Continue atezolizumab. • Permanently discontinue bevacizumab.
Cerebral hemorrhage, any grade	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Grade ≥ 2 hemoptysis (≥ 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.

Atezo + Bev = atezolizumab plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] 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.

[c] 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.

[d] Institutional protocols acceptable.

Table A12-4 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev Arm

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 Grade > 2 hemorrhagic events while in the study. – The patient must be on stable dose of heparin, low-molecular-weight heparin, or have an in-range INR (usually 2 to 3) on a stable dose of warfarin prior to restarting bevacizumab. • If thromboemboli worsen or 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.

Atezo + Bev = atezolizumab plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] 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.

[c] 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.

[d] Institutional protocols acceptable.

Table A12-4 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev Arm

Event	Action to Be Taken
Proteinuria [d]	
Proteinuria, Grade 1 (1+ by dipstick; urinary protein < 1.0 g/24 hr)	• Continue atezolizumab and bevacizumab.
Proteinuria, Grade 2 (2+ and 3+ by dipstick; urinary protein 1.0–3.4 g/24 hr)	• Continue atezolizumab. • For 2+ dipstick: Continue bevacizumab and collect 24-hour urine protein prior to subsequent bevacizumab administration. • For 3+ dipstick: Obtain 24-hour urine prior to administering bevacizumab. • Withhold bevacizumab for urinary protein ≥ 2 g/24 hr. • If bevacizumab is withheld and urine protein improves to < 2 g/24 hr within 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab.
Proteinuria, Grade 3 (4+ by dipstick; urinary protein ≥ 3.5 g/24 hr) 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 hr within 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.

Atezo + Bev = atezolizumab plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] 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.

[c] 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.

[d] Institutional protocols acceptable.

Table A12-4 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev Arm

Event	Action to Be Taken
Fistula	
Tracheoesophageal fistula, any grade	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a]
Fistula (non-tracheoesophageal), Grade 4	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a]
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.

Atezo + Bev = atezolizumab plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] 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.

[c] 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.

[d] Institutional protocols acceptable.

Table A12-4 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev Arm

Event	Action to Be Taken
Posterior reversible encephalopathy syndrome or reversible posterior leukoencephalopathy syndrome	
PRES/RPLS, any grade confirmed by MRI	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a]
Hepatic events	
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 $5\times$ ULN at baseline and increases to $>8\times$ ULN to $\leq 10\times$ ULN	• Monitor LFTs more frequently until return to baseline values or Grade 1 or better. • Withhold atezolizumab for up to 12 weeks after event onset. [b] • Continue bevacizumab. • 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. [c] • If event does not resolve to baseline or to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. The Medical Monitor is available to advise as needed. [a]

Atezo + Bev = atezolizumab plus bevacizumab; LFT = liver function test; MRI = magnetic resonance imaging; PRES = posterior reversible encephalopathy syndrome; RPLS = reversible posterior leukoencephalopathy syndrome; ULN = upper limit normal.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] 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.

[c] 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.

[d] Institutional protocols acceptable.

Table A12-4 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev Arm

Event	Action to Be Taken
Hepatic events (cont.)	
AST or ALT increases to > 10 × ULN or total bilirubin increases to > 3 × ULN	• Permanently discontinue atezolizumab. The Medical Monitor is available to advise as needed. [a] • Withhold bevacizumab. • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to baseline, taper corticosteroids over ≥ 1 month. • If event resolves to Grade 1 within 42 days resume bevacizumab at the discretion of investigator. If not, permanently discontinue bevacizumab. [a]

Atezo + Bev = atezolizumab plus bevacizumab; GI = gastrointestinal; ULN = upper limit of normal.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] 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.

[c] 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.

[d] Institutional protocols acceptable.

Table A12-4 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev Arm

Event	Action to Be Taken
Endocrine disorders	
Hypothyroidism, all grades	• Follow guidelines for atezolizumab in Appendix 10. • Continue bevacizumab.
Hyperthyroidism, Grade 1	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Follow guidelines for atezolizumab in Appendix 10. • Continue bevacizumab. **TSH < 0.1 mU/L:** • Follow guidelines for atezolizumab in Appendix 10. • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Hyperthyroidism, Grade 2	• Follow guidelines for atezolizumab in Appendix 10. • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Hyperthyroidism, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 10. • Bevacizumab may continue at the discretion of the investigator per medical judgment.

Atezo + Bev = atezolizumab plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] 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.

[c] 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.

[d] Institutional protocols acceptable.

Table A12-4 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev Arm

Event	Action to Be Taken
Neurologic disorder	
Immune-mediated meningoencephalitis, all grades	• Follow guidelines for atezolizumab in Appendix 10. • Withhold bevacizumab. • If patient stabilizes within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab.
Dermatologic events	
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 10. • Withhold bevacizumab. • If event resolves to Grade 1 or better, resume bevacizumab. • Permanently discontinue bevacizumab if withheld for > 42 days or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed.

Atezo + Bev = atezolizumab plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] 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.

[c] 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.

[d] Institutional protocols acceptable.

Table A12-4 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev Arm

Event	Action to Be Taken
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 10. • Continue bevacizumab.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 10. • Withhold bevacizumab. • If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]

Atezo + Bev = atezolizumab plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] 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.

[c] 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.

[d] Institutional protocols acceptable.

Table A12-4 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev Arm

Event	Action to Be Taken
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 within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]
Grade 4	• Withhold atezolizumab and bevacizumab. • If event improves and atezolizumab should be continued, resume atezolizumab. If not, permanently discontinue atezolizumab. The Medical Monitor is available to advise as needed. • If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]

Atezo + Bev = atezolizumab plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] 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.

[c] 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.

[d] Institutional protocols acceptable.

A12–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + BEV ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

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 the Atezo + Bev arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either 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.
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

A12–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + BEV ARM

A12–5.3.1 Pregnancies in Female Participants

Female participants of childbearing potential will be instructed 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 participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant 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.

A12–5.3.2 Pregnancies in Female Partners of Male Participants

Male participants 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. 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. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant 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 when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male participant 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.

A12–5.3.3 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.

A12–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female participant exposed to study treatment or the female partner of a male participant 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).

A12–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR NEOADJUVANT ATEZO + BEV ARM

Table A12-5 Schedule of Activities for Neoadjuvant Atezo + Bev Arm

Assessment/ Procedure	Protocol Section	Screening (see Appendix 11)	Neoadjuvant Treatment Cycles (21-Day Cycles) [a]		Pre-Surgery (restaging)	Surgery (liver resection)	Post-Surgery	[redacted]	
			Cycle 1	Cycle 2 & 3					
		D −28 to D −1	Day 1 (≤7 days after randomization)	Day 1 (±3 days)	≥2 weeks after Cycle 3	4–6 weeks after Cycle 3	≥2 weeks after surgery		
IMP Administration									
Atezolizumab administration	A12–4.2.2		x	x					
Bevacizumab administration			x	x					
Clinical or Surgical Assessments and Procedures									
Weight	4.5.3		x	x	x		x	x	
Complete physical examination								x	
Limited physical examination			x	x	x		x		
Vital signs	4.5.4		x	x	x		x	x	

Table A12-5 Schedule of Activities for [redacted] (cont.)

Assessment/ Procedure	Protocol Section	Screening (see Appendix 11)	Neoadjuvant Treatment Cycles (21-Day Cycles) [a]		Pre-Surgery (restaging)	Surgery (liver resection)	Post-Surgery	[redacted]	
			Cycle 1	Cycle 2 & 3					
		D −28 to D −1	Day 1 (≤7 days after randomization)	Day 1 (±3 days)	≥2 weeks after Cycle 3	4–6 weeks after Cycle 3	≥2 weeks after surgery		
12-Lead ECG	4.5.5		Perform as clinically indicated					x	
ECOG Performance Status	Appendix 7		x	x	x		x	x	
Surgical delay assessment					x				
Liver resection/HCC curative surgery	3.1.2					x			
Tumor response assessments	4.5.8				x				
Disease recurrence assessments	4.5.8				x			x	x
Concomitant medications	A12–4.3		x	x	x		x	x	
Adverse events	5.3.1, 5.5.1, and 5.6		x	x	x		x	x	x

Table A12-5 Schedule of Activities for [redacted] (cont.)

Assessment/ Procedure	Protocol Section	Screening (see Appendix 11)	Neoadjuvant Treatment Cycles (21-Day Cycles) [a]		Pre-Surgery (restaging)	Surgery (liver resection)	Post-Surgery	[redacted]	
			Cycle 1	Cycle 2 & 3					
		D −28 to D −1	Day 1 (≤7 days after randomization)	Day 1 (±3 days)	≥2 weeks after Cycle 3	4–6 weeks after Cycle 3	≥2 weeks after surgery		
Clavien-Dindo assessment	4.5.9, and Appendix 6							x	
Survival follow-up and anti-cancer treatment	4.6.1								x
Local Laboratory Assessments									
Hematology	4.5.10		x	x	x		x	x	
Chemistry			x	x	x		x	x	
α-fetoprotein				x	x			x	
Coagulation (INR and aPTT)			x	x	x				
Thyroid function testing			x	x [d]	x		x	x	
C-reactive protein			x	x	x		x	x	
Serum autoantibody sample			Perform if a participant experiences a suspected immune-mediated adverse event.						

Table A12-5 Schedule of Activities for [redacted] (cont.)

Assessment/ Procedure	Protocol Section	Screening (see Appendix 11)	Neoadjuvant Treatment Cycles (21-Day Cycles) [a]		Pre-Surgery (restaging)	Surgery (liver resection)	Post-Surgery	[redacted]	
			Cycle 1	Cycle 2 & 3					
		D −28 to D −1	Day 1 (≤7 days after randomization)	Day 1 (±3 days)	≥2 weeks after Cycle 3	4–6 weeks after Cycle 3	≥2 weeks after surgery		
Pregnancy test [e]	4.5.10		x	x	x		x		
Urinalysis			Perform as clinically indicated.						
Viral serology [f]				x					
Cardiac enzymes (TnT or TnI)			Perform as clinically indicated.						
Central Laboratory Assessments									
Serum PK samples	4.5.10		See Table A12-6.						
Serum ADA samples			See Table A12-6.						
Plasma, serum, and blood for PBMC samples for biomarkers			See Table A12-6.						
Resected tissue						x			
Blood sample for WGS/WES analysis (at participating sites)	4.5.11		See Table A12-6.						

Table A12-5 Schedule of Activities for [redacted] (cont.)

ADA = anti-drug antibody; App. = Appendix; Atezo + Bev = atezolizumab plus bevacizumab; D = day; Discont. = discontinuation; ECOG = Eastern Cooperative Oncology Group; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IMP = investigational medicinal product; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; WES = whole exome sequencing; WGS = whole genome sequencing.

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

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

[b] Regardless of whether they complete the neoadjuvant treatment period or discontinue study drug prematurely, participants who proceed to surgery will return to the clinic for a neoadjuvant treatment completion/discontinuation visit [redacted] weeks after surgery. Participants who do not proceed to surgery will return to the clinic for a neoadjuvant treatment completion/discontinuation visit not more than 30 days after the final dose of study treatment.

[c] After neoadjuvant treatment completion or discontinuation, information on survival follow-up and initiation of new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, participant medical records, and/or clinic visits approximately [redacted] until disease recurrence or for up to [redacted] years after completion/discontinuation of neoadjuvant therapy, whichever occurs first (unless the participant withdraws consent or the Sponsor terminates the study). Participants who complete the neoadjuvant treatment period will have their first survival follow-up visit [redacted] months after surgery [redacted] Participants who discontinue study drug prematurely will have their first survival follow-up visit [redacted] months after the final dose of study treatment. If a participant requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If a participant withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all participants discontinued treatment and passed the safety follow-up window, as well as approximately [redacted] of participants discontinued from the study, the Sponsor may conclude the arm (the remaining approximately [redacted] of participants will be discontinued from the study).

[d] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 3. It will not be collected on Day 1 of Cycle 2.

Table A12-5 Schedule of Activities for [redacted] (cont.)

[e] All women of childbearing potential will have urine or serum pregnancy tests performed at specified visits during treatment and 6 months after the final dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[f] Participants with a positive HBsAg or HBcAb test at screening will undergo quantitative HBsAg and HBV DNA testing on Day 1 of Cycles 2 and 3 and at treatment discontinuation. Quantitative HBsAg will be tested by central laboratory. Participants with a positive HCV antibody test at screening will undergo quantitative HCV RNA testing on Day 1 of Cycles 2 and 3 and at treatment discontinuation.

Table A12-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Neoadjuvant Atezo + Bev Arm

Visit	Time	Sample Types
[redacted]	[redacted]	• WGS/WES (blood) [a] • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Bevacizumab PK (serum) • Biomarkers (plasma, serum, and blood for PBMC)
		• Atezolizumab PK (serum)
		• Bevacizumab PK (serum)
		• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, and blood for PBMC)
		• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Bevacizumab PK (serum) • Biomarkers (plasma, serum, and blood for PBMC)
		• Bevacizumab PK (serum)
		• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, and blood for PBMC)
		• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
		• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
		• Biomarkers (plasma, serum)

Table A12-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Neoadjuvant Atezo + Bev Arm (cont.)

ADA = anti-drug antibody; Atezo + Bev = atezolizumab plus bevacizumab; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; WES = whole exome sequencing; WGS = whole genome sequencing.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

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

[b] PK, ADA, and biomarker samples collections prior to surgery should be collected preferably the same day of surgery, or within 24 hours prior to surgery.

[c] [redacted]

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Appendix 13
Study Details Specific to Atezo + Bev + Tira Arm

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A13–1 BACKGROUND ON ATEZO + BEV + TIRA ARM

A13–1.1 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 cluster of differentiation [CD] 80), 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 fragment crystallizable (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 (CIT).

Atezolizumab is approved for the treatment of urothelial carcinoma (UC), non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer (TNBC), hepatocellular carcinoma (HCC), melanoma, and alveolar soft part sarcoma.

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

A13–1.2 BACKGROUND ON BEVACIZUMAB

Bevacizumab is a recombinant humanized monoclonal antibody that recognizes all isoforms of vascular endothelial growth factor (VEGF). It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor microenvironment. Additional anti-tumor activity may be on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).

Bevacizumab is approved for the first-line and second-line treatment of metastatic colorectal cancer, first-line treatment of advanced NSCLC, metastatic breast cancer, advanced renal cell carcinoma (RCC), ovarian cancer, fallopian tube, peritoneum, cervical, and HCC, and treatment of recurrent glioblastoma. Bevacizumab is currently being tested in combination with atezolizumab in Phase I–III clinical trials. Bevacizumab has been generally well tolerated and adverse events have been manageable.

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

A13–1.3 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/kappa monoclonal antibody that binds T-cell immunoreceptor with Ig and ITIM domains (TIGIT) and prevents its interaction with CD155 (also known as poliovirus receptor [PVR]). Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of tumor-specific T-cell responses, which may result in improved meaningful anti-tumor activity when tiragolumab is used in combination with other CITs and administered with chemotherapy. The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in patients with cancer.

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

A13–2 RATIONALE FOR ATEZO + BEV + TIRA ARM

A13–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

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

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with advanced malignancies in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active as monotherapy for many patients. To date, targeting the PD-L1 pathway with single-agent atezolizumab has shown minimal activity in the treatment of patients with locally advanced or unresectable HCC.

A13–2.2 THE VEGF PATHWAY

VEGF-A is a pro-angiogenic molecule produced by endothelium, tumors, and tumor-associated macrophages. In addition to promoting tumor angiogenesis, there is increasing evidence that the VEGF pathway also plays an important role in cancer immune evasion by exerting and maintaining an immunosuppressive tumor microenvironment through several mechanisms.

VEGF-A inhibits the maturation of dendritic cells (DCs), promotes the expression of inhibitory immune checkpoint molecules on intratumoral $CD8^+$ T cells, and induces Fas ligand (FasL) expression on endothelial cells, which acquired the ability to kill effector CD8 + T cells but not T-regulatory cells (Gabrilovich et al. 1996; Huang et al. 2007; Motz et al. 2014; Voron et al. 2015). Experiments with activated endothelial cells also suggest that VEGF may reduce lymphocyte adhesion to vessel walls in the tumor microenvironment, thus contributing to decreased immune cell recruitment to the tumor site (Bouzin et al. 2007). In addition, VEGF recruits macrophages into the tumor microenvironment that have a M2 polarization state, which is typically involved in wound healing. These M2 tumor-associated macrophages ultimately help establish and maintain an immunosuppressive microenvironment (Chen and Mellman 2013).

Targeting the VEGF pathway with agents such as bevacizumab has been clinically validated with demonstrated anti-tumor activity in patients with several advanced malignancies. However, when administered as a single agent in patients with HCC, bevacizumab has only demonstrated minimal activity (Siegel et al. 2008; Boige et al. 2012).

A13–2.3 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin superfamily. TIGIT is expressed on the surface of activated T-cell and natural killer (NK)–cell subsets and interacts with high affinity with CD155 (also known as PVR) (Yu et al. 2009). Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses in nonclinical models of autoimmune and viral infections, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; Johnston et al. 2014). TIGIT expression is elevated in the tumor microenvironment in many human tumors, is concordantly expressed with other immune checkpoint receptors such as PD-1 on the surface of T cells, and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014; Manieri et al. 2017). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017).

TIGIT is expressed in a wide variety of human tumors, including most solid tumors, such as NSCLC, breast cancer, HCC, and melanoma, and hematologic tumors, such as multiple myeloma and non-Hodgkin lymphoma. Fluorescence-activated cell sorting analysis of T cells isolated from fresh tumor samples revealed that TIGIT and PD-1 are also co-expressed on tumor-infiltrating T cells (Johnston et al. 2014; Yadav et al. 2016; Yang 2016; Guillerey at al. 2018; Duan et al. 2019; Liu et al. 2019). TIGIT expression was 30%–80% and 50%–80% on tumor-infiltrating $CD4^+$ and $CD8^+$ T cells, respectively (Johnston et al. 2014).

Therefore, TIGIT is a potential target for therapeutic intervention, aimed at restoring the immune response against the tumor. Agents that inhibit TIGIT's interaction with PVR may inhibit an important source of tumor-associated immune suppression and therefore may enhance the activity of other immune-based therapies. Nonclinical studies using blocking antibodies in genetically deficient mice have revealed a key role for TIGIT in regulating T-cell responses in cancer. Together, these data support the hypothesis that anti-TIGIT may reactivate anti-tumor immunity and provide clinical benefits to patients with cancer.

A13–2.4 COMBINATION TREATMENT WITH ANTI–PD-L1, ANTI-VEGF, AND ANTI-TIGIT AGENTS

Durable clinical benefit is limited to a minority of patients treated with single-agent PD-1/PD-L1 inhibitors. Therapies targeting the mechanisms of resistance to anti–PD-1/PD-L1 therapies are needed to improve outcomes in patients with solid-tumor cancers. A strong scientific rationale and emerging clinical data suggest that combined PD-L1, VEGF, and TIGIT inhibition may be clinically beneficial in a number of tumor types.

Anti-VEGF agents promote the normalization of tumor vasculature, thereby increasing access of therapeutic agents (Jain 2001). In addition, bevacizumab can restore and/or maintain the antigen-presentation capacity of DCs, leading to enhanced T-cell infiltration in tumors (Oelkrug and Ramage 2014; Wallin et al. 2016). Administration of anti–VEGF-A has been shown to attenuate tumor endothelial FasL expression and produce a significant increase in the influx of tumor-rejecting $CD8^+$ T cells, leading to tumor growth suppression (Motz et al. 2014). Anti-VEGF therapies can also reduce the frequency of myeloid-derived suppressor cells, decrease production of suppressive cytokines, and lower expression of inhibitory checkpoints on $CD8^+$ T cells in tumors (Roland et al. 2009; Voron et al. 2015).

The immunomodulatory effects of bevacizumab are anticipated to increase $CD8^+$ T-cell recruitment and relieve intratumoral immunosuppression, thereby boosting the effects of immunotherapy. Indeed, clinical data have demonstrated a beneficial effect of anti-angiogenesis and immunomodulation within the context of atezolizumab treatment. The activity of combination treatment with atezolizumab and bevacizumab has been demonstrated in multiple, large, randomized Phase III clinical studies in patients with NSCLC, RCC, and HCC.

In chemotherapy-naive patients with Stage IV NSCLC, results from Study GO29436 (IMpower150) have shown that atezolizumab plus bevacizumab and chemotherapy results in significantly longer overall survival (OS) compared with bevacizumab and chemotherapy alone (Socinski et al. 2018). For patients with inoperable, locally advanced, or metastatic RCC, results from Study WO29637 (IMmotion151) demonstrated improved progression-free survival (PFS) after treatment with the combination of atezolizumab and bevacizumab compared with sunitinib in a treatment-naive patient population (Rini et al. 2019). Most recently, results from Study YO40245 (IMbrave150) have demonstrated a statistically significant and clinically meaningful improvement in PFS and OS in patients with unresectable locally advanced or metastatic HCC treated with atezolizumab plus bevacizumab compared with sorafenib (Finn et al. 2020) (see Section A13–2.5 for more details on clinical studies evaluating the combination of atezolizumab with bevacizumab in HCC).

Resistance to PD-1/PD-L1 blockade may result in the expression of multiple co-inhibitory receptors on the surface of effector T cells. Nonclinical tumor models have shown that TIGIT selectively suppresses the effector function of chronically stimulated $CD8^+$ T cells, and that inhibiting both TIGIT and PD-1/PD-L1 results in superior efficacy compared with single-agent treatments (Johnston et al. 2014). Higher levels of $PD\text{-}1^+$, $TIGIT^+$, $CD8^+$ T cells have been reported in patients with advanced HCC and are associated with poor clinical outcomes, including accelerated disease progression and death (Liu et al. 2019). Hence, targeting TIGIT and PD-L1 with tiragolumab and atezolizumab, respectively, may

enhance the efficacy of PD-1/PD-L1 blockade across different cancer types, including HCC (see Section A13–2.6 for a description of clinical studies of tiragolumab combined with atezolizumab).

Based on the above-described data, it is hypothesized that combination treatment with atezolizumab, bevacizumab, and tiragolumab may augment the anti-tumor immune response, resulting in an improved and more durable clinical benefit in patients with HCC.

A13–2.5 CLINICAL STUDIES OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB IN HEPATOCELLULAR CARCINOMA

The efficacy and safety of atezolizumab in combination with bevacizumab as a treatment for patients with unresectable, locally advanced, or metastatic HCC is currently being investigated in two studies (GO30140 and YO40245 [IMbrave150]).

A13–2.5.1 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. 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 added to the study at a later date to compare combination treatment with atezolizumab plus bevacizumab to atezolizumab alone. A total of 119 patients with locally advanced or metastatic HCC were randomized in a 1:1 ratio to receive atezolizumab plus bevacizumab or atezolizumab monotherapy. Results for Arms A and F have been recently presented (Lee et al. 2019).

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, Version 1.1 (RECIST v1.1) was 35.6% (37 of 104 patients). Among the 37 responders, 12 patients (11.5%) achieved a complete response and the remaining 25 patients (24.0%) achieved a partial response. Median duration of response was not reached at the time of this analysis. Moreover, Arm F met its primary efficacy endpoint by demonstrating a statistically significant and clinically meaningful improvement in PFS for the combination compared with atezolizumab monotherapy (stratified hazard ratio [HR] = 0.55; 95% CI: 0.40 to 0.74; p = 0.0108; median PFS, 5.6 vs. 3.4 months, respectively).

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.

A13–2.5.2 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 (Finn et al. 2020). The study enrolled 501 patients randomized in a 2:1 ratio. The co-primary efficacy endpoints were OS and IRF-assessed PFS by RECIST v1.1.

As of the clinical cutoff date of 29 August 2019, the primary analysis demonstrated statistically significant and clinically meaningful improvements for atezolizumab plus bevacizumab compared with sorafenib for the co-primary endpoints. The risk of death was reduced by 42% for the atezolizumab plus bevacizumab arm compared with the sorafenib arm (stratified HR = 0.58; 95% CI: 0.42 to 0.79; p = 0.0006; median OS, not estimable vs. 13.24 months). IRF-assessed PFS per RECIST v1.1 also demonstrated a statistically significant and clinically meaningful improvement favoring combination treatment (stratified HR = 0.59; 95% CI: 0.47 to 0.76; p < 0.0001; median PFS, 6.83 vs. 4.27 months).

Overall, the atezolizumab plus bevacizumab combination in HCC was generally well tolerated with manageable toxicities and the safety profile was consistent with the known risks of the individual study treatments and with the underlying disease.

Refer to the Atezolizumab Investigator's Brochure and Bevacizumab Investigator's Brochure for additional details on all ongoing and planned clinical studies.

A13–2.6 CLINICAL STUDIES OF TIRAGOLUMAB

Tiragolumab is currently under investigation in two ongoing clinical studies in patients with solid tumors (Studies GO30103 and GO40290), with data available in advanced HCC (Study GO42216; NCT148034).

A13–2.6.1 Study GO30103

Study GO30103 is a first-in-human, Phase I, open-label, dose-escalation, and dose-expansion study of tiragolumab as a single agent and in combination with atezolizumab in patients with locally advanced, recurrent, or metastatic incurable tumors, including UC, RCC, NSCLC, head and neck squamous cell carcinoma, esophageal cancer, CRC, gastric cancer, cholangiocarcinoma, and TNBC.

Appendix 13: Study Details Specific to Atezo + Bev + Tira Arm

As of 1 October 2021, a total of [redacted] participants have been enrolled, of which [redacted] participants were enrolled in the Phase Ia portion of the study across tiragolumab dose levels from 2 mg to 1200 mg every 3 weeks (Q3W), and [redacted] participants were enrolled in the Phase Ib portion of the study across tiragolumab dose levels from 2 mg to 1200 mg Q3W in combination with atezolizumab 1200 mg Q3W. In addition, [redacted] of [redacted] participants enrolled in Phase Ia crossed over to the Phase Ib portion of the study. Of the enrolled [redacted] participants (intent-to-treat [ITT] population) in the Phase Ib portion of the study (excluding the [redacted] crossover participants from the Phase Ia portion of the study), [redacted] participants received any study treatment, and [redacted] participants received both tiragolumab and atezolizumab. [redacted] participant enrolled in the 30-mg tiragolumab-plus-atezolizumab dose group did not receive any study treatment, and [redacted] participant in the 600-mg tiragolumab-plus-atezolizumab dose group only received tiragolumab treatment.

Overall, from the Phase Ia portion of Study GO30103, the Eastern Cooperative Oncology Group (ECOG) Performance Status at screening for the ITT population was either 0 ([redacted]% of participants) or 1 ([redacted]% of participants). The most common primary tumor types (≥[redacted]% of participants) were lung cancer ([redacted]%), colon cancer ([redacted]%), and head and neck cancers ([redacted]%).

From the Phase Ib portion, the ECOG performance status at screening for the ITT population was either 0 ([redacted]% of participants) or 1 ([redacted]% of participants). The most common primary tumor types (≥ 10% of participants) were NSCLC ([redacted]%) and esophageal and breast cancers ([redacted]% each). Squamous cell carcinoma ([redacted]%) and adenocarcinoma ([redacted]%) were the two most common histopathologic subtypes.

For the [redacted] crossover participants (ITT population), the ECOG performance status at screening was either 0 ([redacted]% of participants) or 1 ([redacted]% of participants); the most common primary tumor types were NSCLC ([redacted]%), colon cancer ([redacted]%), and rectum cancer ([redacted]%).

No maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), or clear dose-related trends in the incidence or severity of adverse events have been determined for tiragolumab as a single agent or in combination with atezolizumab. A fatal case of hepatic toxicity culminating in fulminant liver failure occurred in [redacted] with metastatic head and neck cancer receiving single-agent tiragolumab at the highest dose cleared for enrollment (1200 mg) (see the Tiragolumab Investigator's Brochure for details). No other fatal cases of fulminant liver failure have been observed.

Overall, tiragolumab as a single agent or in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile is observed to be consistent across different solid tumor indications.

A13–2.6.2 Study GO40290

Study GO40290 is a Phase II, randomized, blinded, placebo-controlled study of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated locally advanced unresectable or metastatic PD-L1–positive (defined as tumor proportion score [TPS] ≥ 1%) NSCLC.

In the Phase II GO40290 study (CITYSCAPE), the data analysis (clinical cutoff date of 16 August 2021) showed that the combination of tiragolumab plus atezolizumab improved ORR and PFS compared with placebo plus atezolizumab in the ITT population. Objective response rate for tiragolumab plus atezolizumab was 38.8% (95% CI: 26.4% to 51.2%) compared with placebo plus atezolizumab which was 20.6% (95% CI: 10.2% to 30.9%). This was associated with a 38% relative risk reduction in disease worsening or death (median investigator-assessed PFS for tiragolumab plus atezolizumab was 5.6 months [95% CI: 4.2 to 10.4 months] compared with placebo plus atezolizumab, which was 3.9 months [95% CI: 2.7 to 4.5 months], with a HR of 0.62 [95% CI: 0.42 to 0.91]). At the time of the clinical cutoff date of 16 August 2021, a total of 12 participants (8.9%) were still receiving study treatment in the ITT population.

The investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group over the placebo plus atezolizumab group in PD-L1 high expression (TPS ≥ 50%) (unstratified HR = 0.29; 95% CI: 0.15 to 0.53; median PFS 16.6 vs. 4.1 months, respectively). Regarding OS, in the PD-L1 high expression group, fewer deaths had occurred in the tiragolumab plus atezolizumab arm (27.6%) compared with the placebo plus atezolizumab arm (72.4%). The median OS for the tiragolumab plus atezolizumab was not yet reached (95% CI: 30.3 to not estimable) compared with the placebo plus atezolizumab arm of 12.8 months (95% CI: 4.7 to 24.2 months), with an unstratified HR of 0.23 (95% CI: 0.10 to 0.53). In the PD-L1 low subgroup, the median OS was similar between the tiragolumab plus atezolizumab arm (13.3 months; 95% CI: 8.0 to 20.7 months) and the placebo plus atezolizumab arm (14.5 months; 95% CI: 8.3 to 25.6 months]), with an unstratified HR of 1.16 (95% CI: 0.70 to 1.94).

To date, most adverse events have been Grade 1 or 2. Serious adverse events, Grade 3–5 adverse events, adverse events leading to discontinuation, and adverse events leading to death have been balanced between the two treatment arms. Serious and high-grade treatment-related adverse events have also been balanced between the two treatment arms. Immune-mediated adverse events have been balanced between the two treatment arms, with the exception of a higher frequency of infusion-related reaction (IRR), arthralgia, pruritis, and rash reported in the atezolizumab plus tiragolumab arm.

[redacted]

Overall, tiragolumab in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile seems to be consistent as reported across different solid tumor indications.

Refer to the Tiragolumab Investigator's Brochure for additional details on all ongoing and planned clinical studies.

A13–2.7 BENEFIT–RISK ASSESSMENT

Nonclinical and early clinical data suggest that neoadjuvant use of immunotherapy may be more effective than adjuvant treatment (Topalian et al. 2020). As the nature of recurrence with HCC is believed to originate from occult micrometastases that persist after resection, neoadjuvant treatment may reduce the burden of disease prior to resection to improve clinical outcomes.

The combination of atezolizumab with bevacizumab showed clinically meaningful and statistically significant improvement in PFS and OS relative to sorafenib in patients with locally advanced or metastatic HCC who have not received prior systemic therapy (Finn et al. 2020). In addition to the promising anti-tumor activity, these results demonstrated proof of concept for the activity of this treatment combination in this patient population and support a favorable benefit–risk assessment.

TIGIT is an inhibitory immunoreceptor that can also limit the effector function of tumor-associated lymphocytes. Unlike other inhibitory co-receptors, TIGIT is often coordinately expressed with PD-1 on tumor-infiltrating T cells in multiple tumors, including HCC. In nonclinical models, combined blockade of TIGIT and PD-L1/PD-1 has shown superior efficacy compared with blockade of either pathway alone (Johnston et al. 2014).

Taking into account the potentially synergistic mechanisms of action of tiragolumab and atezolizumab, as well as the preliminary efficacy and manageable safety profiles of the above-described combinations, treatment with atezolizumab, bevacizumab, and tiragolumab (Atezo + Bev + Tira) appears to have therapeutic potential in solid tumors such as HCC. Because of the potential for overlapping toxicities (see Section A13–5.1.4 for details), [redacted] in the Atezo + Bev + Tira arm must complete a safety evaluation before additional participants can be enrolled in that arm (see Section 3.1.3 for details).

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please see Section 1.3.

A13–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + BEV + TIRA ARM

A13–3.1 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.

A13–3.2 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 an approved dosage for bevacizumab.

A13–3.3 RATIONALE FOR TIRAGOLUMAB DOSE AND SCHEDULE



A13–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + BEV + TIRA ARM

A13–4.1 TREATMENT IN ATEZO + BEV + TIRA ARM

A13–4.1.1 Formulation and Packaging

A13–4.1.1.1 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 of atezolizumab, refer to the pharmacy manual and the Atezolizumab Investigator's Brochure.

A13–4.1.1.2 Bevacizumab

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

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

A13–4.1.1.3 Tiragolumab

The tiragolumab drug product will be supplied by the Sponsor in single-use, 15-mL glass vials. The vial contains 10 mL of tiragolumab. The approximate concentration of tiragolumab antibody in each vial is 60 mg/mL.

For information on the formulation of tiragolumab, refer to the pharmacy manual and the Tiragolumab Investigator's Brochure.

A13–4.1.2 Dosage, Administration, and Compliance

Participants in the Atezo + Bev + Tira arm will receive up to three cycles of treatment as outlined in Table A13-1 until surgery or unacceptable toxicity, whichever occurs first. It is recommended that treatment be initiated no later than 7 calendar days after randomization; however, the first dose of study treatment should not occur within 3 days after a core biopsy or other surgical procedure.

Table A13-1 Treatment Regimen for Atezo + Bev + Tira Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg by IV infusion on Day 1 • Bevacizumab 15 mg/kg by IV infusion on Day 1 [a] • Tiragolumab 600 mg by IV infusion on Day 1 [b]

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab;
IRR = infusion-related reaction.

[a] On Day 1 of each cycle, bevacizumab will be administered at least 5 minutes after completion of the atezolizumab infusion.

[b] On Day 1 of Cycle 1, tiragolumab will be administered at least [redacted] minutes after completion of the bevacizumab infusion. The interval between subsequent infusions will be at least [redacted] minutes if the previous bevacizumab infusion was given without premedication and tolerated without an IRR or [redacted] minutes if the participant experienced an IRR with the previous bevacizumab infusion.

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

Medication errors 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.
No safety data related to overdosing of atezolizumab, bevacizumab, or tiragolumab are available to date.

A13–4.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 9. Atezolizumab infusions will be administered per the instructions outlined in Table A13-2.

Table A13-2 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, pulse oximetry, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (± 15) minutes. • If clinically indicated, vital signs should be recorded every 15 (± 5) minutes during the infusion and 30 (± 10) minutes after the infusion. • Participants 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 participant experienced an IRR with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an IRR, or 60 (± 15) minutes if the participant experienced an IRR with the previous infusion. • If the participant experienced an IRR with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (± 10) minutes after the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of IRRs for atezolizumab are provided in Appendix 10.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A13–5.1.5. Atezolizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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.

A13–4.1.2.2 Bevacizumab

Bevacizumab will be administered by IV infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle. On Day 1 of each cycle, bevacizumab will be administered at least 5 minutes after completion of the atezolizumab infusion.

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 9. Bevacizumab infusions will be administered per the instructions outlined in Table A13-3.

Table A13-3 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, pulse oximetry, and temperature) should be measured within 60 minutes prior to the infusion. • Bevacizumab should be infused over 90 (±15) minutes. • Vital signs should be recorded at the end of infusion and 2 (±1) hours after the infusion. • Participants 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 participant experienced an IRR with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Bevacizumab should be infused over 60 (±10) minutes if the previous 90-minute infusion was tolerated without an IRR, or 90 (±15) minutes if the participant experienced an IRR with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (±10) minutes thereafter. • Vital signs should be recorded within 30 minutes after completion of the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of IRRs for bevacizumab are provided in Section A13–5.1.5.

No dose modification for bevacizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A13–5.1.5. Bevacizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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.

A13–4.1.2.3 Tiragolumab

Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle with a post-infusion observation period as described in Table A13-4.

On Day 1 of Cycle 1, tiragolumab will be administered at least [redacted] minutes after completion of the bevacizumab infusion. The interval between subsequent infusions will be at least [redacted] minutes if the previous bevacizumab infusion was given without premedication and tolerated without an IRR or at least [redacted] minutes if the participant experienced an IRR with the previous bevacizumab infusion.

Administration of tiragolumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 9. Tiragolumab infusions will be administered per the instructions outlined in Table A13-4.

Table A13-4 Administration of First and Subsequent Tiragolumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the tiragolumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be recorded within [redacted] minutes prior to the infusion. • Tiragolumab should be infused over [redacted] minutes. • Vital signs should be recorded every [redacted] minutes during the infusion and at [redacted] minutes after the infusion. • After the infusion of tiragolumab, the participant begins a [redacted]-minute observation period. • Participants will be informed about the possibility of delayed post-infusion symptoms and will be instructed to contact their study physician if they develop such symptoms.	• If the participant experienced an IRR with any previous infusion, [redacted] may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within [redacted] minutes prior to the infusion. • Tiragolumab should be infused over [redacted] minutes if the previous infusion was tolerated without an IRR, or [redacted] minutes if the participant experienced an IRR with the previous infusion. • Participants should be observed for [redacted] minutes after completion of the tiragolumab infusion if the previous infusion was tolerated without an IRR, or [redacted] minutes after completion of the tiragolumab infusion if the participant experienced an IRR with the previous infusion. • If the participant experienced an IRR with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at [redacted] minutes after the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of IRRs for tiragolumab are provided in Appendix 10.

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A13–5.1.5. Tiragolumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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.

A13–4.2 CONCOMITANT THERAPY FOR ATEZO + BEV + TIRA ARM

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

A13–4.2.1 Permitted Therapy for Atezo + Bev + Tira Arm

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

- [redacted]

[redacted]

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

A13–4.2.2 Cautionary Therapy for Atezo + Bev + Tira Arm

A13–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and/or tiragolumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF 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 and/or tiragolumab therapy (see Appendix 10 for details).

A13–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A13–4.2.3) may be used during the study at the discretion of the investigator.

A13–4.2.2.3 Bisphosphonates

Osteonecrosis of the jaw has been reported in patients receiving bevacizumab, mainly in combination with bisphosphonates. Thus, caution must be exercised in using bevacizumab in participants receiving concomitant bisphosphonates.

A13–4.2.3 Prohibited Therapy for Atezo + Bev + Tira Arm

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

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Current use of full-dose anticoagulants, thrombolytic therapy at therapeutic doses, or anti-platelet therapy
  - Local-label recommended doses for prophylactic use of anticoagulants or thrombolytic therapies are allowed.
  - Low-dose aspirin (< 325 mg/day) is permitted. Co-administration of proton pump inhibitors is strongly recommended to reduce potential GI damage.
  - If a participant experiences a venous thromboembolism event while still receiving study drug treatment, it may still be possible for the participant to remain on study medication despite anticoagulation treatment (see Section 4.1.2).
- Use of warfarin or Coumadin-like products (includes for prophylactic use)
  - Prophylactic use of low-dose anticoagulation, unfractionated heparin, or LMWH is permitted. Adherence to the label-recommended dose for prophylactic use of anticoagulants is required. The preferred choice for anticoagulation treatment should be LMWH as per ASCO guidelines (Key et al. 2020).

- Concomitant chronic use of non-steroidal anti-inflammatory drug (NSAIDs) while receiving study drugs, with the exception of chronic low-dose aspirin (< 325 mg/day)
  - However, for the symptomatic relief of medical conditions (e.g., headache, fever) intermittent or short-term intake of oral NSAIDs is allowed, when co-administered with proton pump inhibitors to reduce potential GI damage.

A13–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + BEV + TIRA ARM

Contraception requirements for women and men in the Atezo + Bev + Tira arm are outlined below:

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:
  - Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the final dose of atezolizumab, for 6 months after the final dose of bevacizumab, and for 90 days after the final dose of tiragolumab.
  - 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). 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 participant. 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 and for 90 days after the final dose of tiragolumab 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 participant. 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, information about the reliability of abstinence will be described in the local Informed Consent Form.

A13–5 ASSESSMENT OF SAFETY FOR ATEZO + BEV + TIRA ARM

A13–5.1 SAFETY PLAN FOR ATEZO + BEV + TIRA ARM

The safety plan for participants in this study is based on clinical experience with atezolizumab, bevacizumab, and tiragolumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A13–5.1.1, A13–5.1.2, A13–5.1.3, and A13–5.1.4). Guidelines for management of participants who experience specific adverse events are provided in Section A13–5.1.5.

Measures will be taken to ensure the safety of participants participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of participants during the study. Because of the potential for overlapping toxicities for atezolizumab, bevacizumab, and tiragolumab, special caution will be taken by performing a planned safety evaluation phase for participants randomized to this arm (see Section 3.1.3).

Administration of study treatment 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. Adverse events will be reported as described in Sections 5.2–5.6.

A13–5.1.1 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, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to HLH. Refer to Appendix 10 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A13–5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: GI perforations, hemorrhage, arterial thromboembolic events, fistulae, wound-healing complications, hypertension, venous thromboembolism, proteinuria, congestive heart failure, and posterior reversible encephalopathy syndrome (PRES). Refer to Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for bevacizumab.

A13–5.1.3 Risks Associated with Tiragolumab

[redacted] While clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events).

Refer to Appendix 10 of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks for tiragolumab.

A13–5.1.3.1 Infusion-Related Reactions

Because tiragolumab is a therapeutic monoclonal antibody and targets immune cells, IRRs associated with hypersensitivity reactions and/or target-mediated cytokine release may occur. Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. IRRs have been reported in patients treated with tiragolumab, with or without atezolizumab. The majority of events were mild to moderate and manageable.

To minimize the risk and sequelae of IRRs, the initial dose of tiragolumab will be administered over [redacted] minutes followed by a [redacted]-minute observation period. Subsequent infusions and observation times may be shortened if the preceding infusion was well tolerated. All infusions of tiragolumab will be administered in an appropriate medical setting.

See Section A13–4.1.2 for detailed guidance on administration of tiragolumab in this study. See Appendix 9 for guidance on anaphylaxis precautions and Appendix 10 for guidance on the management of IRRs.

[redacted]

A13–5.1.3.2 Immune-Mediated Adverse Events

Nonclinical models have suggested a role of TIGIT signaling interruption in autoimmunity. In a knockout model (TIGIT–/–), loss of TIGIT signaling resulted in hyperproliferative T-cell responses and exacerbation of experimental autoimmune encephalitis (EAE). TIGIT–/– and wild-type B6 mice were immunized with suboptimal doses of myelin oligodendrocyte glycoprotein peptide to induce EAE. In contrast to the wild-type B6 mice, the majority of the TIGIT–/– mice developed severe EAE (Joller et al. 2011).

Clinical experience with therapeutics intended to enhance anti-tumor T-cell responses has demonstrated that development of autoimmune inflammatory conditions is a general risk and may therefore be considered a potential risk of tiragolumab. Such immune-mediated adverse events have been described for virtually all organ systems and include but are not limited to colitis, pneumonitis, endocrinopathies, ocular toxicity, pancreatic toxicity, neurologic toxicity, cardiac toxicity, nephritis, myositis, and severe cutaneous adverse reactions.

Patients with a history of autoimmune disease will be excluded from this study. See Section 4.1.2 for details.

In this study, specified immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A13–5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

Management guidelines for individual suspected immune-mediated adverse events are provided in Appendix 10.

A13–5.1.3.3 Lymphopenia

[redacted]

[redacted] Participants with a lymphocyte count $< 0.5 \times 10^9$/L (500/μL) will be excluded from the study (see Section 4.1.1), and CBCs will be monitored regularly during the study (see Section A13–6).

Embryofetal Toxicity

Embryofetal toxicity is a potential risk with tiragolumab. Administration of tiragolumab is expected to have adverse effects on pregnancy based on the expression of TIGIT on decidual NK and $CD8^+$ T cells (Powell et al. 2017; van der Zwan et al. 2018; Vento-Tormo et al. 2018), and the expected role of these cells in the recognition and response to foreign fetal, placental, and viral antigens at the maternal-fetal interface as well as maintenance of maternal-fetal tolerance. No reproductive or teratogenicity studies in animals have been conducted with tiragolumab. There are no clinical studies of tiragolumab in pregnant women. Tiragolumab should not be administered to pregnant women.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of embryofetal toxicity.

A13–5.1.4 Risks Associated with Combination Use of Atezolizumab, Bevacizumab, and Tiragolumab

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab, bevacizumab, and tiragolumab: IRRs and immune-mediated toxicities (including HLH and MAS).

A13–5.1.5 Management of Participants Who Experience Specific Adverse Events in Atezo + Bev + Tira Arm

A13–5.1.5.1 Dose Modifications

There will be no dose modifications for atezolizumab, bevacizumab, and tiragolumab in this study.

A13–5.1.5.2 Treatment Interruption for Toxicities

Atezolizumab and/or tiragolumab treatment may be temporarily suspended in participants experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over [redacted] to the equivalent of [redacted] before atezolizumab and tiragolumab can be resumed. [redacted]



See Section A13–4.1.2 for information on dose interruptions for reasons other than toxicity.

A13–5.1.5.3 Management Guidelines for Adverse Events

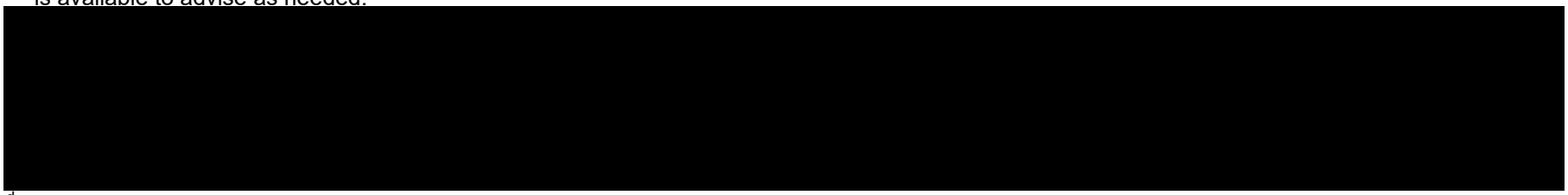
Guidelines for management of participants who experience specific adverse events are provided in Table A13-5. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Table A13-5 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev + Tira Arm

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reaction	
General guidance	• Guidelines for management of IRRs and CRS for atezolizumab and tiragolumab are provided in Appendix 10. • For anaphylaxis precautions, see Appendix 9. • For severe hypersensitivity reactions, permanently discontinue atezolizumab, bevacizumab, and tiragolumab.
IRR to bevacizumab, Grade 1	• Continue bevacizumab. • Systemic intervention is not indicated.
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.

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction.

[a] Resumption of treatment 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] Institutional protocols acceptable.

Table A13-5 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev + Tira Arm (cont.)

Event	Action to Be Taken
[redacted]	[redacted]
Gastrointestinal toxicity	
[redacted]	
[redacted]	
[redacted]	

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab; CRS = cytokine release syndrome; GI = gastrointestinal; IRR = infusion-related reaction.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[redacted]

[d] Institutional protocols acceptable.

Table A13-5 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev + Tira Arm (cont.)

Event	Action to Be Taken
Hypertension	
General guidance	• [redacted]
[redacted]	•
	•
[redacted]	•
	•
	•
[redacted]	•
	•
	•
[redacted]	•
	•

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[redacted]

[d] Institutional protocols acceptable.

Table A13-5 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev + Tira Arm (cont.)

Event	Action to Be Taken
Hemorrhage	
[redacted]	[redacted]

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[redacted]

[d] Institutional protocols acceptable.

Table A13-5 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev + Tira Arm (cont.)

Event	Action to Be Take
Thromboembolic events	
[redacted]	[redacted]

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[redacted]

[d] Institutional protocols acceptable.

Table A13-5 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev + Tira Arm (cont.)

Event	Action to Be Taken
Proteinuria [d]	
[redacted]	

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[redacted]

[d] Institutional protocols acceptable.

Table A13-5 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev + Tira Arm (cont.)

Event	• Action to Be Taken
Fistula	
[redacted]	[redacted]
Wound dehiscence	
[redacted]	

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[redacted]

[d] Institutional protocols acceptable.

Table A13-5 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev + Tira Arm (cont.)

Event	Action to Be Taken
Congestive heart failure	
[redacted]	• [redacted]
Posterior reversible encephalopathy syndrome or reversible posterior leukoencephalopathy syndrome	
[redacted]	• [redacted]

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab; MRI = magnetic resonance imaging; PRES = posterior reversible encephalopathy syndrome; RPLS = reversible posterior leukoencephalopathy syndrome.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[redacted]

Institutional protocols acceptable.

Table A13-5 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev + Tira Arm (cont.)

Event	Action to Be Taken
Hepatic events	
[redacted]	• [redacted]

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab; LFT = liver function test; ULN = upper limit of normal.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[redacted]

[d] Institutional protocols acceptable.

Table A13-5 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev + Tira Arm (cont.)

Event	Action to Be Take
Hepatic events (cont.)	
[redacted]	• [redacted]

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab; GI = gastrointestinal; ULN = upper limit of normal.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[redacted]

[d] Institutional protocols acceptable.

Table A13-5 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev + Tira Arm (cont.)

Event	Action to Be Taken
Endocrine disorders	
[redacted]	[redacted]

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[redacted]

[d] Institutional protocols acceptable.

Table A13-5 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev + Tira Arm (cont.)

Event	Action to Be Taken
Neurologic disorder	
[redacted]	• [redacted]
Dermatologic events	
[redacted]	• [redacted]

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[redacted]

[d] Institutional protocols acceptable.

Table A13-5 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev + Tira Arm (cont.)

Event	Action to Be Take
Atezolizumab and tiragolumab-related toxicities not described above	
[redacted]	• [redacted]
[redacted]	• [redacted]

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[redacted]

[d] Institutional protocols acceptable.

Table A13-5 Guidelines for Management of Participants Who Experience Adverse Events in Atezo + Bev + Tira Arm (cont.)

Event	Action to Be Taken
Bevacizumab-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab, bevacizumab, and tiragolumab.
Grade 3	• Continue atezolizumab and tiragolumab. Withhold bevacizumab. • If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]
Grade 4	• Withhold atezolizumab, bevacizumab, and tiragolumab. • If event improves and Medical Monitor agrees that atezolizumab and tiragolumab should be continued, resume atezolizumab and tiragolumab. If not, permanently discontinue atezolizumab and tiragolumab. • If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]

Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[redacted]

[d] Institutional protocols acceptable.

A13–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + BEV + TIRA ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

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 the Atezo + Bev + Tira arm are as follows:

- [redacted]
- [redacted]
  - [redacted]
- [redacted]

- [redacted]
- [redacted]

A13–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + BEV + TIRA ARM

A13–5.3.1 Pregnancies in Female Participants

Female participants of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab, 6 months after the final dose of bevacizumab, or 90 days after the final dose of tiragolumab. 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 participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant 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.

A13–5.3.2 Pregnancies in Female Partners of Male Participants

Male participants 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 or 90 days after the final dose of tiragolumab. 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. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant 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 when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male participant 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.

A13–5.3.3 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.

A13–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female participant exposed to study treatment or the female partner of a male participant 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).

A13–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR NEOADJUVANT ATEZO + BEV + TIRA ARM

Table A13-6 Schedule of Activities for Neoadjuvant Atezo + Bev + Tira Arm

Assessment/ Procedure	Protocol Section	Screening (see Appendix 11)	Neoadjuvant Treatment Cycles (21-Day Cycles) [a]		Pre-Surgery (restaging)	Surgery (Liver resection)	Post-Surgery	[redacted]	
			Cycle 1	Cycles 2 & 3					
		D –28 to D –1	Day 1 (≤7 days after randomization)	Day 1 (±3 days)	≥2 weeks after Cycle 3	4–6 weeks after Cycle 3	≥2 weeks after surgery		
IMP Administration									
Atezolizumab administration	A13–4.1.2		x	x					
Bevacizumab administration			x	x					
Tiragolumab administration			x	x					
Clinical or Surgical Assessments and Procedures									
Weight	4.5.3		x	x	x		x	x	
Complete physical examination								x	
Limited physical examination			x	x	x		x		
Vital signs	4.5.4		x	x	x		x	x	
12-Lead ECG	4.5.5		Perform as clinically indicated.					x	

Table A13-6 Schedule of Activities for Neoadjuvant Atezo + Bev + Tira Arm (cont.)

Assessment/ Procedure	Protocol Section	Screening (see Appendix 11)	Neoadjuvant Treatment Cycles (21-Day Cycles) [a]		Pre-Surgery (restaging)	Surgery (Liver resection)	Post-Surgery	[redacted]	
			Cycle 1	Cycles 2 & 3					
		D −28 to D −1	Day 1 (≤7 days after randomization)	Day 1 (±3 days)	≥2 weeks after Cycle 3	4–6 weeks after Cycle 3	≥2 weeks after surgery		
ECOG Performance Status	Appendix 7		x	x	x		x	x	
Surgical delay assessment					x				
Liver resection/HCC curative surgery	3.1.2					x			
Tumor response assessments	4.5.8				x				
Disease recurrence assessments	4.5.8				x			x	x
Concomitant medications	A13–4.2		x	x	x		x	x	
Adverse events	5.3.1, 5.5.1, and 5.6		x	x	x		x	x	x

Table A13-6 Schedule of Activities for Neoadjuvant Atezo + Bev + Tira Arm (cont.)

Assessment/ Procedure	Protocol Section	Screening (see Appendix 11)	Neoadjuvant Treatment Cycles (21-Day Cycles) [a]		Pre-Surgery (restaging)	Surgery (Liver resection)	Post-Surgery	[redacted]	
			Cycle 1	Cycles 2 & 3					
		D −28 to D −1	Day 1 (≤7 days after randomization)	Day 1 (±3 days)	≥2 weeks after Cycle 3	4–6 weeks after Cycle 3	≥2 weeks after surgery		
Clavien-Dindo assessment	4.5.9 and Appendix 6							x	
Survival follow-up and anti-cancer treatment	4.6.1								x
Local Laboratory Assessments									
Hematology	4.5.10		x	x	x		x	x	
Chemistry			x	x	x		x	x	
α-fetoprotein				x	x			x	
Coagulation (INR and aPTT)			x	x	x				
Thyroid function testing			x	x [d]	x		x	x	
C-reactive protein			x	x	x		x	x	
Serum autoantibody sample			Perform if a participant experiences a suspected immune-mediated adverse event.						
Pregnancy test [e]			x	x	x		x	x	x [e]
Urinalysis			Perform as clinically indicated.					x	
Viral serology [f]	4.5.10			x				x	

Table A13-6 Schedule of Activities for Neoadjuvant Atezo + Bev + Tira Arm (cont.)

Assessment/ Procedure	Protocol Section	Screening (see Appendix 11)	Neoadjuvant Treatment Cycles (21-Day Cycles) [a]		Pre-Surgery (restaging)	Surgery (Liver resection)	Post-Surgery	[redacted]
			Cycle 1	Cycles 2 & 3				
		D −28 to D −1	Day 1 (≤7 days after randomization)	Day 1 (±3 days)	≥2 weeks after Cycle 3	4–6 weeks after Cycle 3	≥2 weeks after surgery	
Cardiac enzymes (TnT or TnI)			Perform as clinically indicated.					
Central Laboratory Assessments								
[redacted]								

ADA = anti-drug antibody; Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab; Discont. = discontinuation; ECOG = Eastern Cooperative Oncology Group; [redacted] HCC = hepatocellular carcinoma [redacted] IMP = investigational medicinal product; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; WES = whole exome sequencing; WGS = whole genome sequencing.

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

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

[b] Regardless of whether they complete the neoadjuvant treatment period or discontinue study drug prematurely, participants who proceed to surgery will return to the clinic for a neoadjuvant treatment completion/discontinuation visit [redacted] weeks after surgery. Participants who do not

Table A13-6 Schedule of Activities for Neoadjuvant Atezo+Bev+Tira Arm (cont.)

proceed to surgery will return to the clinic for a neoadjuvant treatment completion/discontinuation visit not more than 30 days after the final dose of study treatment.

[c] After neoadjuvant treatment completion or discontinuation, information on survival follow-up and initiation of new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, participant medical records, and/or clinic visits approximately [redacted] until disease recurrence or for up to [redacted] years after completion/discontinuation of neoadjuvant therapy, whichever occurs first (unless the participant withdraws consent or the Sponsor terminates the study). Participants who complete the neoadjuvant treatment period will have their first survival follow-up visit [redacted] months after surgery [redacted] Participants who discontinue study drug prematurely will have their first survival follow-up visit [redacted] months after the final dose of study treatment. If a participant requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If a participant withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all participants discontinued treatment and passed the safety follow-up window, as well as approximately [redacted] of participants discontinued from the study, the Sponsor may conclude the arm (the remaining approximately [redacted] of participants will be discontinued from the study).

[d] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 3. It will not be collected on Day 1 of Cycle 2.

[e] All women of childbearing potential will have urine or serum pregnancy tests performed at specified visits during treatment, and 6 months after the final dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[f] [redacted]

Table A13-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Neoadjuvant Atezo + Bev + Tira Arm

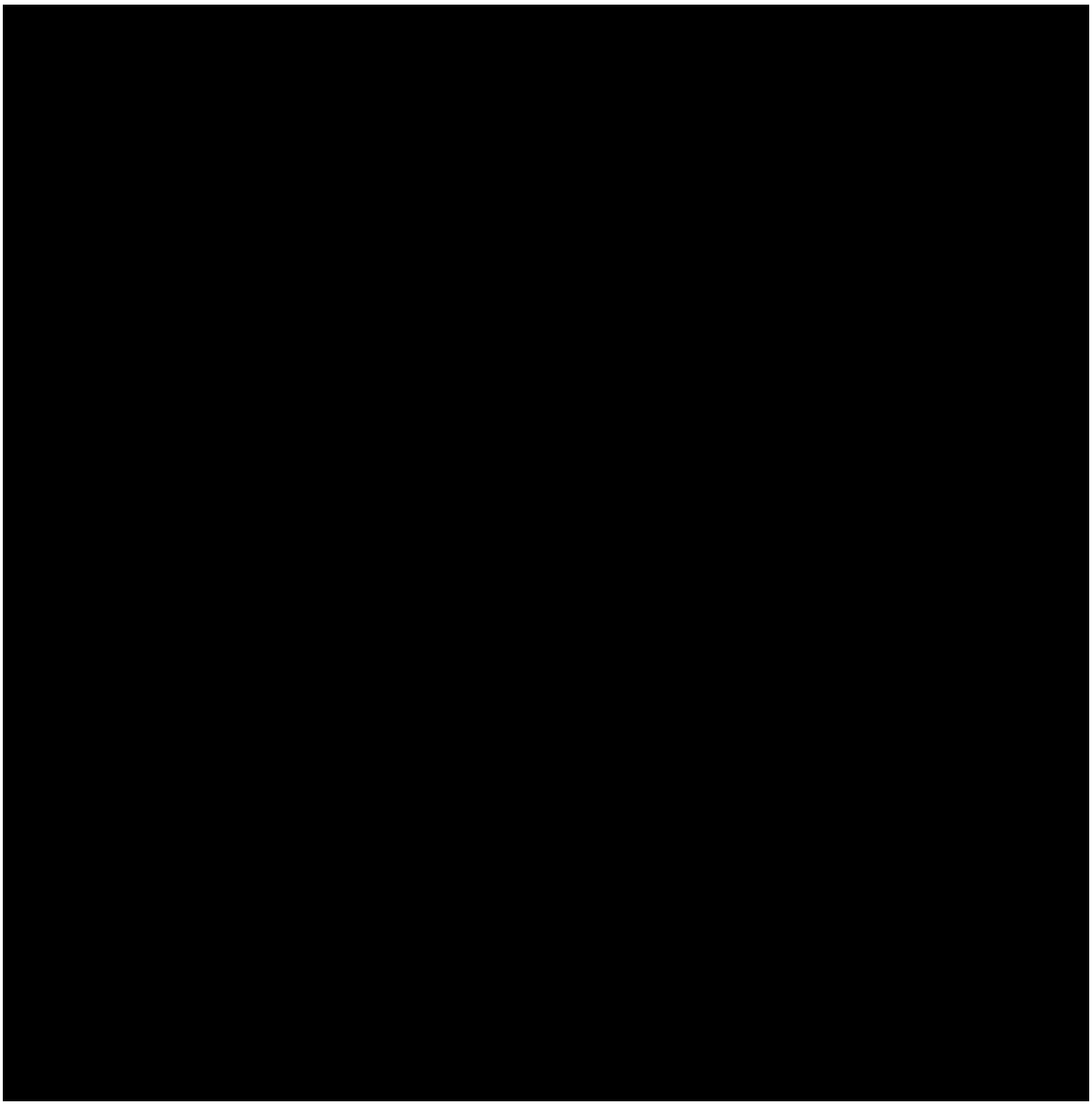


Table A13-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Bev + Tira Arm (cont.)



ADA = anti-drug antibody; Atezo + Bev + Tira = atezolizumab plus bevacizumab plus tiragolumab; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; WES = whole exome sequencing; WGS = whole genome sequencing.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

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

[b] PK, ADA, and biomarker samples collections prior to surgery should be collected preferably the same day of surgery, or within 24 hours prior to surgery.

[c] After neoadjuvant treatment completion or discontinuation, information on survival follow-up and initiation of new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, participant medical records, and/or clinic visits approximately [redacted] until disease recurrence or for up to [redacted] years after completion/discontinuation of neoadjuvant therapy, whichever occurs first (unless the participant withdraws consent or the Sponsor terminates the study).

A13–7 REFERENCES

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Appendix 14
Study Details Specific to Tobe+Bev Arm

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A14–1 BACKGROUND ON TOBE+BEV ARM

A14–1.1 BACKGROUND ON TOBEMSTOMIG

Tobemstomig is a novel, fragment crystallizable (Fc)-silent IgG1-based bispecific antibody (bsAb) in the 1+1 format that incorporates monovalent binding to two immune checkpoint proteins: PD-1 and LAG-3. Tobemstomig is designed to target dysfunctional tumor antigen-specific T lymphocytes (expressing PD-1 and LAG-3) to establish or re-establish an effective anti-tumor immune response in patients with cancer, which may result in improved therapeutic responses over currently available therapies. In addition, tobemstomig is engineered to prevent binding to Fc-gamma receptors, thus potentially avoiding tumor-associated macrophage resistance mechanisms, which have been observed with IgG4-based anti–PD-1 antibodies, such as pembrolizumab and nivolumab (Arlauckas et al. 2017). Clinical evaluation of tobemstomig is ongoing in a first-in-human, dose-finding study (NP41300) as a single-agent in patients with and without prior checkpoint inhibitor (CPI) exposure.

Refer to the Tobemstomig (RO7247669) Investigator's Brochure for additional information on the chemistry and pharmacology of tobemstomig, as well as details on nonclinical and clinical studies.

A14–1.2 BACKGROUND ON BEVACIZUMAB

Bevacizumab is a recombinant humanized monoclonal antibody that recognizes all isoforms of vascular endothelial growth factor (VEGF). It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor microenvironment. Additional anti-tumor activity may be on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).

Bevacizumab is approved for the first-line and second-line treatment of metastatic colorectal cancer, first-line treatment of advanced non–small cell lung cancer (NSCLC), metastatic breast cancer, advanced renal cell carcinoma (RCC), ovarian cancer, fallopian tube, peritoneum, cervical, and hepatocellular carcinoma (HCC) and treatment of recurrent glioblastoma. Bevacizumab is currently being tested in combination with atezolizumab in Phase I–III clinical trials. Bevacizumab has been generally well tolerated, and adverse events have been manageable.

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

A14–2 RATIONALE FOR TOBE+BEV ARM

A14–2.1 THE PD-1/PD-L1 PATHWAY

Encouraging clinical data in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-1/PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-1 is an inhibitory receptor that is expressed on activated and exhausted T cells, including tumor infiltrating $CD8^+$ T cells that recognize mutated tumor antigens (neo-antigens). Binding of PD-L1 to PD-1 inhibits T-cell proliferation, activation, cytokine production, and cytolytic activity, leading to a functionally inactivated and exhausted T-cell state (Butte et al. 2007; Yang et al. 2011). Therapeutic targeting of the PD-1/PD-L1 pathway to enhance anti-tumor T-cell responses has been clinically validated across multiple solid tumors, both as a single agent and in combination with chemotherapy and other targeted agents.

Cancer immunotherapy (CIT) agents, particularly immune CPIs, have made a significant impact on the treatment of patients with advanced malignancies in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active as monotherapy for many patients.

A14–2.2 THE LAG-3 PATHWAY

LAG-3 is an immune checkpoint protein involved in the regulation of anti-tumor immunity and chronic infection. LAG-3 is expressed on activated T cells, B cells, natural killer (NK) cells, a subset of tolerogenic plasmacytoid dendritic cells (DCs), and constitutively on T-regulatory cells (Huard et al. 1994). Structurally similar to CD4, LAG-3 is a member of the Ig superfamily and binds to major histocompatibility complex class II (MHC-II). The interaction of LAG-3 with MHC-II inhibits T-cell proliferation, activation, cytolytic function, and proinflammatory cytokine production (Goldberg and Drake 2011). The effect of LAG-3 expression on T-regulatory cells is controversial. An early report concluded that LAG-3 promotes T-regulatory cell–mediated immune suppression (Camisaschi et al. 2010). However, a more recent report from the same authors describes LAG-3 to limit T-regulatory cell–mediated immune suppression (Zhang et al. 2017).

Expression of LAG-3 has been reported across various tumor types, including breast cancer, ovarian cancer, NSCLC, melanoma, RCC, prostate cancer, and HCC and is associated with poor prognosis (Matsuzaki et al. 2010; Baitsch et al. 2011; Thommen et al. 2015; He et al. 2016; Norstrom et al. 2016). Clinical evaluation of

anti–LAG-3 agents, given as a single agent and in combination with other CPIs, is ongoing in several early-phase studies in patients with advanced solid tumors (Long et al. 2018). Preliminary data demonstrate that anti–LAG-3 therapy was well tolerated as a single agent and in combination with anti–PD-1 therapies, and the safety profiles were consistent with those of other CPIs (Ascierto et al. 2017; Hong et al. 2018; Stratton et al. 2018).

Emerging clinical data highlight a role for the LAG-3 pathway in the pathogenesis of HCC. The expression of LAG-3 is significantly elevated on tumor-infiltrating lymphocytes (TILs) of hepatitis B virus–infected patients with HCC compared with peripheral blood lymphocytes, and this is associated with a severe functional T-cell defect at the tumor site (Li et al. 2013). In patients with HCC who have not received prior systemic therapy for their disease, a similar elevation in LAG-3 expression on TILs was reported, and no relationship was identified between LAG-3 expression and any disease-related characteristics, including viral status (Yarchoan et al. 2017). LAG-3 expression has also recently been identified as a prognostic factor (in addition to vascular invasion, tumor size, and cirrhosis) for poor survival outcomes in patients with HCC (Guo et al. 2020).

Taken together, therapeutic targeting of LAG-3 may represent an attractive strategy for the treatment of patients with HCC.

A14–2.3 THE VEGF PATHWAY

VEGF-A is a pro-angiogenic molecule produced by endothelium, tumors, and tumor-associated macrophages. In addition to promoting tumor angiogenesis, there is increasing evidence that the VEGF pathway also plays an important role in cancer immune evasion by exerting and maintaining an immunosuppressive tumor microenvironment through several mechanisms.

VEGF-A inhibits the maturation of DCs, promotes the expression of inhibitory immune checkpoint molecules on intratumoral $CD8^+$ T-cells, and induces Fas ligand (FasL) expression on endothelial cells, which acquire the ability to kill effector $CD8^+$ T cells but not T-regulatory cells (Gabrilovich et al. 1996; Huang et al. 2007; Motz et al. 2014; Voron et al. 2015). Experiments with activated endothelial cells also suggest that VEGF may reduce lymphocyte adhesion to vessel walls in the tumor microenvironment, thus contributing to decreased immune cell recruitment to the tumor site (Bouzin et al. 2007). In addition, VEGF recruits macrophages into the tumor microenvironment that have a M2 polarization state, which is typically involved in wound healing.
These M2 tumor–associated macrophages ultimately help to establish and to maintain an immunosuppressive microenvironment (Chen and Mellman 2013).

Targeting the VEGF pathway with agents such as bevacizumab has been clinically validated with demonstrated anti-tumor activity in patients with several advanced malignancies. However, when administered as a single agent to patients with HCC, bevacizumab has demonstrated only minimal activity (Siegel et al. 2008; Boige et al. 2012).

A14–2.4 COMBINATION TREATMENT WITH AN ANTI–PD-1/LAG-3 BISPECIFIC ANTIBODY AND AN ANTI-VEGF AGENT

Durable clinical benefit is limited to a minority of patients treated with single-agent PD-1/PD-L1 inhibitors. Therapies targeting the mechanisms of resistance to anti–PD-1/PD-L1 therapies are needed to improve outcomes in patients with solid tumor cancers. A strong scientific rationale and emerging clinical data suggest that combined PD-1, LAG-3, and VEGF inhibition may be clinically beneficial in a number of tumor types.

Anti-VEGF agents promote the normalization of tumor vasculature, thereby increasing access of therapeutic agents (Jain 2001). In addition, bevacizumab can restore and/or maintain the antigen-presentation capacity of DCs, leading to enhanced T-cell infiltration in tumors (Oelkrug and Ramage 2014; Wallin et al. 2016). Administration of anti–VEGF-A has been shown to attenuate tumor endothelial FasL expression and produce a significant increase in the influx of tumor-rejecting $CD8^+$ T cells, leading to tumor growth suppression (Motz et al. 2014). Anti-VEGF therapies can also reduce the frequency of myeloid-derived suppressor cells and decrease production of suppressive cytokines (Roland et al. 2009). In addition, VEGF-A was shown to induce the expression of PD-1, and other inhibitory immune checkpoint proteins, including TIM-3 and LAG-3 on $CD8^+$ T cells, which could be reversed by VEGF inhibition (Voron et al. 2015).

The immunomodulatory effects of bevacizumab are anticipated to increase $CD8^+$ T-cell recruitment and relieve intratumoral immunosuppression, thereby boosting the effects of immunotherapy. Indeed, clinical data have demonstrated a beneficial effect of anti-angiogenesis and immunomodulation within the context of PD-1/PD-L1 pathway blockade. Early-phase studies have demonstrated that combination treatment of the anti–PD-1 therapies nivolumab and pembrolizumab with different anti-angiogenesis agents can elicit responses in patients with metastatic urothelial carcinoma, RCC, ovarian, and endometrial cancers (Apolo et al. 2017; Lee et al. 2017; Makker et al. 2017; Liu et al. 2019; Dudek et al. 2020). The activity of combination treatment with the anti–PD-L1 therapy atezolizumab and bevacizumab has also been demonstrated in multiple large randomized Phase III clinical studies in patients with NSCLC, RCC, and HCC (Socinski et al. 2018; Rini et al. 2019; Finn et al. 2020).

Resistance to PD-1/PD-L1 blockade may result in the expression of multiple co-inhibitory immune checkpoints on the surface of effector T cells. LAG-3 is frequently co-expressed with PD-1 on TILs, and dual blockade of PD-1 and LAG-3 has been shown to enhance $CD8^+$ T-cell effector function and potentiate anti-tumor immunity in nonclinical models. Blockade of these two receptors in mice with colon, fibrosarcoma, or ovarian tumors resulted in tumor remission in approximately 80% of animals compared with 10% to 40% with either as a single agent (Woo et al. 2012; Huang et al. 2015). Tumor-infiltrating lymphocytes from patients with ovarian cancer showed that antigen-specific $CD8^+$ T cells co-expressing PD-1 and LAG-3 exhibited greater impairment in their ability to respond to cognate antigen stimulation compared with $CD8^+$ T cells that expressed one checkpoint molecule (Matsuzaki et al. 2010). In patients with NSCLC, overexpression of LAG-3 on TILs was correlated with PD-1/PD-L1 expression and was linked to higher risk of recurrence and poor survival outcomes (He et al. 2017). In clinical samples from patients with untreated HCC, the majority showed co-staining for LAG-3 and PD-1 with higher expression among TILs compared with expression in background liver tissue (Yarchoan et al. 2017).

Based on the above-described data, it is hypothesized that simultaneous targeting of the PD-1 and LAG-3 pathways with the bsAb tobemstomig, in combination with the immunomodulatory effects of bevacizumab, may augment the anti-tumor immune response, resulting in an improved and more durable clinical benefit in patients with HCC.

A14–2.5 CLINICAL STUDIES OF ANTI–PD-1/PD-L1 AGENTS IN COMBINATION WITH BEVACIZUMAB

Proof of concept has been established for targeting the PD-1/PD-L1 pathway in combination with bevacizumab in patients with advanced solid tumors, including HCC, in Phase I–III clinical studies.

The efficacy and safety of nivolumab plus bevacizumab have been evaluated in a single-arm Phase II study in patients with relapsed ovarian cancer (Liu et al. 2019). The study enrolled 38 participants with platinum-sensitive and platinum-resistant disease. At the time of the primary analysis, an objective response rate (ORR) of 28.6% was observed for the combination, which represents an improvement over reports from single-agent studies in a similar pretreated patient population (nivolumab, 13.3%; bevacizumab, 15.9%–21%). The efficacy and safety of pembrolizumab plus bevacizumab have been evaluated in a single-arm Phase Ib/II study in patients with clear cell metastatic RCC (Dudek et al. 2020). The study enrolled 48 participants who had not received prior therapy for their disease in the Phase II portion. An ORR of 60.9% was observed for the combination, which compares with 33.6% and 10% for pembrolizumab and bevacizumab, respectively, as single agents in other studies.

In both studies, the combination regimens was well tolerated, and the adverse event profiles were aligned with the known risks for each of the individual agents. No new safety signals were identified (Liu et al. 2019; Dudek et al. 2020).

A14–2.5.1 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. Arm A was designed to evaluate the combination of atezolizumab plus bevacizumab in 104 patients with locally advanced or metastatic HCC who had not received prior systemic therapy. Arm F was added to the study at a later date to compare combination treatment with atezolizumab plus bevacizumab to atezolizumab alone. One-hundred and nineteen patients with locally advanced or metastatic HCC were randomized in a 1:1 ratio to receive atezolizumab plus bevacizumab or atezolizumab monotherapy. Results for Arm A and Arm F have been recently presented (Lee et al. 2019).

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 ORR based on an independent review facility's (IRF's) assessment per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) was 35.6% (37 of 104 participants) . Among the 37 responders, 12 participants (11.5%) achieved a complete response (CR) and the remaining 25 participants (24.0%) achieved a partial response (PR). Median duration of response was not reached at the time of this analysis. Moreover, Arm F met its primary efficacy endpoint by demonstrating a statistically significant and clinically meaningful improvement in progression-free survival (PFS) for the combination compared with atezolizumab monotherapy (stratified hazard ratio [HR]: 0.55; 95% CI: 0.40 to 0.74; $p = 0.0108$; median PFS: 5.6 vs. 3.4 months, respectively).

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.

A14–2.5.2 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 not received prior systemic treatment (Finn et al. 2020). The study enrolled 501 participants randomized in a 2:1 ratio. The co-primary efficacy endpoints were overall survival (OS) and IRF-assessed PFS by RECIST v1.1.

As of the clinical cutoff date of 29 August 2019, the primary analysis demonstrated statistically significant and clinically meaningful improvements for atezolizumab plus bevacizumab compared with sorafenib for the co-primary endpoints. The risk of death was reduced by 42% in the atezolizumab plus bevacizumab arm compared with the sorafenib arm (stratified HR: 0.58; 95% CI: 0.42 to 0.7; p = 0.0006; median OS: not estimable vs. 13.24 months). Independent review facility–assessed PFS per RECIST v1.1 also demonstrated a statistically significant and clinically meaningful improvement favoring combination treatment (stratified HR: 0.59; 95% CI: 0.47 to 0.76; p < 0.0001; median PFS: 6.83 vs. 4.27 months).

Overall, the atezolizumab plus bevacizumab combination in patients with HCC was generally well tolerated with manageable toxicities, and the safety profile was consistent with the known risks of the individual study treatments and with the underlying disease.

Refer to the Atezolizumab Investigator's Brochure and Bevacizumab Investigator's Brochure for additional details on all ongoing and planned clinical studies.

A14–2.6 CLINICAL STUDIES OF AGENTS TARGETING THE PD-1 AND LAG-3 PATHWAYS

Clinical data are available for early-phase studies in advanced solid tumors evaluating the safety, tolerability, and preliminary anti-tumor activity of agents that target both the PD-1 and LAG-3 pathways. Evidence of clinical activity has been reported in some of these studies. Overall, adverse events have been manageable to date, and the safety profiles appear similar to those of single-agent CPIs (Ascierto et al. 2017; Hong et al. 2018).

An ongoing Phase I/IIa study is evaluating the safety, tolerability, and clinical activity of combination treatment with the anti–PD-1 monoclonal antibody nivolumab and the anti–LAG-3 monoclonal antibody relatlimab in patients with advanced solid tumors. Preliminary data suggest that the combination of nivolumab and relatlimab has the potential for increased benefit compared with single-agent anti–PD-1. In a cohort of patients with advanced melanoma who were previously treated with anti–PD-1/PD-L1, the ORR was 11.5% (n = 61) with a disease control rate (DCR) of 49%. The combination was also shown to have an acceptable safety profile that is similar to the safety profile of nivolumab monotherapy (Ascierto et al. 2017).

An ongoing Phase I/II study is evaluating the safety, tolerability, and clinical activity of combination treatment with the anti–PD-1 monoclonal antibody spartalizumab and the anti–LAG-3 monoclonal antibody LAG525 in patients with advanced solid tumors. Preliminary anti-tumor activity was observed for the combination during the Phase I dose-escalation portion of the study, including durable responses in patients with triple-negative breast cancer (TNBC) (reported in 2 of 5 participants) and

mesothelioma (2 of 8 participants). Analyses of tumor biopsies from the TNBC cohort also showed a trend of conversion from an immune-cold to an immune-activated phenotype. Common adverse events (reported in ≥ 10% of participants) included fatigue (18%), diarrhea (15%), and nausea (12%). The incidence of Grade 3 and 4 adverse events was 8% for both the combination (n = 121) and monotherapy (n = 119) arms (Hong et al. 2018).

An ongoing, first-in-human, dose-escalation, and dose expansion Phase I study is evaluating the safety, tolerability, and clinical activity of the anti–PD-1/LAG-3 dual-affinity re-targeting protein (DART®) bsAb MGD013 in patients with advanced solid tumors and hematologic malignancies. During the dose-escalation phase of the study, the maximum tolerated dose (MTD) was not reached, and the safety profile was consistent with anti–PD-1 monotherapy. A cohort of patients with HCC was included during dose escalation, and no ORR was observed. During the dose-expansion phase, anti-tumor activity was observed in patients with TNBC (n = 23; ORR: 4.3%; DCR: 39.1%), CPI-naive NSCLC (n = 14; ORR: 14.3%; DCR: 64.3%), and epithelial ovarian cancer (n = 23; ORR: 8.7%; DCR: 52.2%). Expression of LAG-3 and an interferon (IFN)-γ gene signature at baseline was associated with objective responses (Luke et al. 2020). Clinical studies evaluating MGD013 as monotherapy and in combination with anti–HER-2 agents are ongoing.

Study NP41300

Study NP41300 is an ongoing, first-in-human, dose-escalation, and dose-expansion Phase I study to evaluate the safety, pharmacokinetics, and therapeutic activity of the anti–PD-1/LAG-3 bsAb tobemstomig as a single agent in patients with locally advanced and/or metastatic solid tumors. Part A of the study is designed to determine the MTD and/or recommended dose for expansion (RDE) of tobemstomig. Part B of the study is designed to evaluate the anti-tumor activity of tobemstomig at the MTD or RDE in tumor-specific expansion cohorts.

As of the clinical cutoff date of 1 March 2022, preliminary safety data were available for [redacted] patients with solid tumors receiving tobemstomig monotherapy every 2 weeks (Q2W) or Q3W in Part A1 and Part B. In Part A1, no dose limiting toxicities (DLTs) were observed, and the MTD was not reached. The maximum dose of [redacted] mg Q2W was determined as the recommended dose for tumor-specific expansion in Part B of the study.

[redacted]



Refer to the Tobemstomig (RO7247669) Investigator's Brochure for additional details on all ongoing and planned clinical studies.

A14–2.7 BENEFIT–RISK ASSESSMENT

Combination treatment with atezolizumab plus bevacizumab is an approved, first-line treatment regimen for patients with unresectable, locally advanced, or metastatic HCC (Tecentriq® U.S. Package Insert). However, there is no effective perioperative treatment available for patients with HCC. While the potential benefit of neoadjuvant therapy in improving HCC resectability and eliminating micrometastases has been recognized, the lack of effective systemic treatment has hindered the development of neoadjuvant therapy.

Despite limited clinical experience with tobemstomig, the clinical efficacy and safety profiles of anti–PD-1/PD-L1 monoclonal antibodies are well characterized and established. The co-stimulatory action of tobemstomig on PD-1 and LAG-3 receptors may result in enhanced and/or more durable responses than either therapeutic modality alone. However, there may be a risk of exaggerated immune cell activation, particularly given the LAG-3-mediated modulation of the immune response. Preliminary data from Study NP41300 and recent early phase studies of anti-LAG-3 antibodies have demonstrated that anti-LAG-3 therapy was generally well tolerated as monotherapy or in

combination with anti–PD-1 therapies and that it had a safety profile consistent with the safety profile of other CPIs (Ascierto et al. 2017; Hong et al. 2018; Stratton et al. 2018). Taking into account the potentially synergistic mechanisms of action of tobemstomig and bevacizumab, as well as the preliminary efficacy and manageable safety profiles of the above-described combinations, treatment with tobemstomig 600 mg Q3W and bevacizumab (Tobe+Bev) appears to have therapeutic potential in solid tumors such as HCC.

A14–3 RATIONALE FOR DOSE AND SCHEDULE FOR TOBE+BEV ARM

A14–3.1 RATIONALE FOR TOBEMSTOMIG DOSE AND SCHEDULE

[redacted]

A14–3.2 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 an approved dosage for bevacizumab.

A14–4 MATERIALS AND METHODS SPECIFIC TO TOBE+BEV ARM

A14–4.1 TREATMENT IN TOBE+BEV ARM

A14–4.1.1 Formulation and Packaging

A14–4.1.1.1 Tobemstomig

The tobemstomig drug product will be supplied by the Sponsor as 50-mg/mL concentrate for solution for infusion.

For information on the formulation of tobemstomig, refer to the pharmacy manual and the Tobemstomig (RO7247669) Investigator's Brochure.

A14–4.1.1.2 Bevacizumab

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

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

A14–4.1.2 Dosage, Administration, and Compliance

Participants in the Tobe+Bev arm will receive up to three cycles of treatment as outlined in Table A14-1 until surgery or unacceptable toxicity, whichever occurs first. It is recommended that treatment be initiated no later than 7 calendar days after randomization; however, the first dose of study treatment should not occur within 3 days after a core biopsy or other surgical procedure.

Table A14-1 Treatment Regimen for Tobe+Bev Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Tobemstomig 600 mg by IV infusion on Day 1 • Bevacizumab 15 mg/kg by IV infusion on Day 1 [a]

IRR=infusion-related reaction; Tobe+Bev=tobemstomig plus bevacizumab.

[a] On Day 1 of Cycle 1, bevacizumab will be administered at least 90 minutes after completion of the tobemstomig infusion. If the first infusion is tolerated without an IRR, bevacizumab will be administered at least 60 minutes after the tobemstomig infusion. If the second infusion is tolerated without an IRR, bevacizumab will be administered at least 30 minutes after all subsequent tobemstomig infusions. If the participant experienced an IRR with the previous infusion, bevacizumab will be administered 90 minutes after completion of the tobemstomig infustion.

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

Medication errors 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. No safety data related to overdosing of tobemstomig or bevacizumab are available to date.

A14–4.1.2.1 Tobemstomig

Tobemstomig will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle.

Administration of tobemstomig will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 9. Tobemstomig infusions will be administered per the instructions outlined in Table A14-2.

Table A14-2 Administration of First, Second, and Subsequent Tobemstomig Infusions

First and Second Infusion	Subsequent Infusions
• No premedication is permitted prior to the first tobemstomig infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) should be recorded within [redacted] minutes prior to the infusion. • For the first infusion, tobemstomig should be infused over [redacted] minutes. • For the second infusion, tobemstomig should be infused over [redacted] minutes if the first infusion was tolerated without an IRR. • If clinically indicated, vital signs should be recorded every [redacted] minutes during the infusion and [redacted] minutes after the infusion. • Participants 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 participant experienced an IRR with any previous infusion, [redacted] may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within [redacted] minutes prior to the infusion. • Tobemstomig should be infused over [redacted] minutes if the previous infusion was tolerated without an IRR. • If the participant experienced an IRR with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at [redacted] minutes after the infusion.

IRR=infusion-related reaction.



Guidelines for medical management of IRRs for tobemstomig are provided in Section A14–5.1.4.

No dose modification for tobemstomig is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A14–5.1.4. Tobemstomig treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment, 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.

A14–4.1.2.2 Bevacizumab

Bevacizumab will be administered by IV infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle. On Day 1 of Cycle 1, bevacizumab will be administered at least 90 minutes after completion of the tobemstomig infusion. If the first infusion is tolerated without an IRR, bevacizumab will be administered at least 60 minutes after the tobemstomig infusion. If the second infusion is tolerated without an IRR, bevacizumab will be administered at least 30 minutes after all subsequent tobemstomig infusions.

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 9. Bevacizumab infusions will be administered per the instructions outlined in Table A14-3.

Table A14-3 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, pulse oximetry, and temperature) should be measured within 60 minutes prior to the infusion. • Bevacizumab should be infused over 90 (±15) minutes. • Vital signs should be recorded at the end of infusion and 2 (±1) hours after the infusion. • After the infusion of bevacizumab, the participant begins a 120-minute observation period. • Participants 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 participant experienced an IRR with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Bevacizumab should be infused over 60 (±10) minutes if the previous 90-minute infusion was tolerated without an IRR, or 90 (±15) minutes if the participant experienced an IRR with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (±10) minutes thereafter. • Vital signs should be recorded within 30 minutes after completion of the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of IRRs for bevacizumab are provided in Section A14–5.1.4.

No dose modification for bevacizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A14–5.1.4. Bevacizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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.

A14–4.2 CONCOMITANT THERAPY FOR TOBE+BEV ARM

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

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

A14–4.2.1 Permitted Therapy for Tobe+Bev Arm

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

- Oral contraceptives with a failure rate of $<1\%$ per year
- Hormone-replacement therapy
- Prophylactic use of low-dose anticoagulation, unfractionated heparin, or low-molecular-weight heparin (LMWH)
  - Adherence to the label-recommended dose for prophylactic use of anticoagulants is required.
  - The preferred choice for anticoagulation treatment should be LMWH as per American Society of Clinical Oncology (ASCO) guidelines (Key et al. 2020).
- Low-dose aspirin (<325 mg/day)
  - Co-administration of proton pump inhibitors is strongly recommended to reduce potential gastrointestinal (GI) damage.
- Vaccinations (such as influenza, COVID-19)
  - Live, attenuated vaccines are not permitted (see Section A14–4.2.3).
- 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. Other use of corticosteroids may be at the investigator's discretion. The Medical Monitor is available to advise as needed.

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

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

A14–4.2.2 Cautionary Therapy for Tobe+Bev Arm

A14–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with tobemstomig. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF 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 tobemstomig therapy (see Appendix 10 for details).

A14–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A14–4.2.3) may be used during the study at the discretion of the investigator.

A14–4.2.2.3 Bisphosphonates

Osteonecrosis of the jaw has been reported in patients receiving bevacizumab, mainly in combination with bisphosphonates. Thus, caution must be exercised in using bevacizumab in participants receiving concomitant bisphosphonates.

A14–4.2.3 Prohibited Therapy for Tobe+Bev Arm

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

- [redacted]

- [redacted]

A14–4.3 CONTRACEPTION REQUIREMENTS FOR TOBE + BEV ARM

Contraception requirements for women and men in the Tobe + Bev arm are outlined below:

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, 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 during the treatment period and for 4 months after the final dose of tobemstomig and for 6 months after the final dose of bevacizumab. Women must refrain from donating eggs during this same period.
  - 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). 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 participant. 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 contraceptive methods, and agreement to refrain from donating sperm, as defined below:
  - With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for 4 months after the final dose of tobemstomig 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.
  - With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 4 months after the final dose of tobemstomig and for 6 months after the final dose of bevacizumab to avoid exposing the embryo.
  - 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 participant. 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, information about the reliability of abstinence will be described in the local Informed Consent Form.

A14–5 ASSESSMENT OF SAFETY FOR TOBE+BEV ARM

A14–5.1 SAFETY PLAN FOR TOBE+BEV ARM

The safety plan for participants in this study is based on clinical experience with tobemstomig and bevacizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A14–5.1.1, A14–5.1.2, and A14–5.1.3). Guidelines for management of participants who experience specific adverse events are provided in Section A14–5.1.4.

Measures will be taken to ensure the safety of participants participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of participants during the study. Special caution will be taken by performing a planned safety evaluation phase for participants randomized to this arm (see Section 3.1.3).

Administration of study treatment 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. Adverse events will be reported as described in Sections 5.2–5.6.

A14–5.1.1 Risks Associated with Tobemstomig

Clinical evaluation of tobemstomig is ongoing, and not all risks are known. As an antagonist of PD-1 and LAG-3, tobemstomig is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Based on the mechanism of action of tobemstomig, the safety profile is anticipated to be similar to other CPIs. Potential risks associated with tobemstomig include the following: IRRs (including anaphylaxis), immunogenicity, and immune-mediated adverse events. Refer to Section 6 of the Tobemstomig (RO7247669) Investigator's Brochure for a detailed description of anticipated safety risks for tobemstomig.

A14–5.1.1.1 Infusion-Related Reactions and Anaphylaxis

Administration of therapeutic antibodies may cause IRRs, which may include symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea, and vomiting. Such reactions typically occur during or shortly after the infusion and are predominantly reported following the first infusion. The incidence and severity of IRRs typically decrease with subsequent infusions. Based on in vitro data, the risk of pro-inflammatory cytokine-mediated IRRs on first administration of tobemstomig as single agent is considered low.

See Section A14–4.1.2 detailed guidance on administration of tobemstomig in this study. See Appendix 9 for guidance on anaphylaxis precautions and Section A14–5.1.4 for guidance on the management of IRRs.

A14–5.1.1.2 Immunogenicity

Administration of therapeutic antibodies may cause the formation of anti-drug antibodies, which may negatively affect the safety of the therapeutic (e.g., allergic reactions, immune complex–mediated diseases).

A14–5.1.1.3 Immune-Mediated Adverse Events

The co-stimulatory action of tobemstomig, particularly given the LAG-3 modulation, might bear the risk of exaggerated immune cell activation that may result in the occurrence of enhanced, untoward, immune-mediated adverse events and increased cytokine release–mediated toxicities.

Toxicities from PD-1–blocking agents can involve any organ or tissue, although some immune-mediated adverse events occur much more frequently than others. The most frequently occurring immune-mediated adverse events affect skin, colon, endocrine organs, liver, and lungs. Others are very infrequent but may be very serious, even lethal, such as neurological disorders and myocarditis.

The limited data from recent early-phase studies showed generally that anti-LAG-3 therapy was well tolerated as a monotherapy or in combination with anti–PD-1 therapies and consistent with the safety profiles of other CPIs (Ascierto et al. 2017; Hong et al. 2018).

In this study, specified immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A14–5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

A14–5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: GI perforations, hemorrhage, arterial thromboembolic events, fistulae, wound-healing complications, hypertension, venous thromboembolism, proteinuria, congestive heart failure, and posterior reversible encephalopathy syndrome (PRES). Refer to Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for bevacizumab.

A14–5.1.3 Risks Associated with Combination Use of Tobemstomig and Bevacizumab

The risk of overlapping toxicities between tobemstomig 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 tobemstomig.

A14–5.1.4 Management of Participants Who Experience Specific Adverse Events in Tobe + Bev Arm

A14–5.1.4.1 Dose Modifications

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

A14–5.1.4.2 Treatment Interruption for Toxicities

Tobemstomig treatment may be temporarily suspended in participants experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before tobemstomig can be resumed. If tobemstomig is withheld for > 21 days, the participant will be discontinued from tobemstomig. However, the drug may be withheld for > 21 days to allow for participants to taper off corticosteroids prior to resuming treatment. Tobemstomig can be resumed after being

withheld for > 21 days if the participant is likely to derive clinical benefit. The decision to re-challenge participants with tobemstomig should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Bevacizumab treatment may be temporarily suspended in participants experiencing toxicity considered to be related to study treatment. If bevacizumab is withheld for > 42 days, the participant will be discontinued from bevacizumab. Bevacizumab can be resumed after being withheld for > 42 days if the participant is likely to derive clinical benefit. The decision to re-challenge participants with bevacizumab should be based on investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

If tobemstomig or bevacizumab is withheld or discontinued, the other study drug can be continued if the participant is likely to derive clinical benefit, as determined by the investigator per medical judgment.

See Section A14–4.1.2 for information on dose interruptions for reasons other than toxicity.

A14–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for management of participants who experience specific adverse events are provided in Table A14-4. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe + Bev Arm

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reaction	
General guidance	• For anaphylaxis precautions, see Appendix 9. • For severe hypersensitivity reactions, permanently discontinue tobemstomig and bevacizumab. • For suspected CRS, see Appendix 10 for guidance on supportive care.

CRS = cytokine release syndrome; IRR = infusion-related reaction; Tobe + Bev = tobemstomig plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., > 21 days 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.

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

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reaction (cont.)	
IRR to tobemstomig, Grade 1 or 2	• Slow infusion to ≤50% or interrupt infusion. • Give supportive treatment. Patients should be treated with acetaminophen/paracetamol and an antihistamine, such as diphenhydramine, if they have not been administered in the last 4 hours. IV fluids (e.g., normal saline) may be administered as clinically indicated. For bronchospasm, urticaria, or dyspnea, antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators may be administered per institutional practice. • Upon symptom resolution, infusion may resume (if interrupted) at 50% starting rate. The infusion must remain at the lower rate resulting in symptom resolution for the remainder of the infusion. • For Grade 2 IRRs, subsequent doses of tobemstomig should be administered with premedication, including acetaminophen/paracetamol and an antihistamine, such as diphenhydramine. • For Grade 2 wheezing or urticaria, patient must also be premedicated prior to subsequent doses (as described above). • If symptoms recur with the same or greater severity following the slower or interrupted infusion, the infusion must be stopped immediately. No further tobemstomig will be administered for the cycle. • For patients who experience a Grade 2 or higher IRR with tobemstomig, IgE and tryptase levels should be tested. In case of confirmed IgE-mediated hypersensitivity reaction, treatment should be permanently discontinued.

CRS=cytokine release syndrome; IRR=infusion-related reaction; Tobe+Bev=tobemstomig plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., >21 days 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.

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

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reaction (cont.)	
IRR to tobemstomig, Grade 3	• Discontinue infusion. No further tobemstomig will be administered for the cycle. • Give supportive treatment. Patients should be treated with acetaminophen/paracetamol and an antihistamine, such as diphenhydramine, if they have not been administered in the last 4 hours. IV fluids (e.g., normal saline) may be administered as clinically indicated. For bronchospasm, urticaria, or dyspnea, antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators may be administered per institutional practice. • Subsequent cycles of tobemstomig should be administered with premedication including acetaminophen/paracetamol, antihistamine, and corticosteroids. Subsequent infusions may be started at the original rate. The Medical Monitor is available to advise as needed. • If symptoms recur despite premedications with the same or greater severity at subsequent cycles, the infusion must be stopped immediately and patient permanently discontinued from study treatment. • Patients who experience Grade 3 wheezing, bronchospasm, or generalized urticaria at first occurrence must be discontinued from study treatment. • IgE and tryptase levels should be tested. In case of confirmed IgE-mediated hypersensitivity reaction, treatment should be permanently discontinued.

CRS = cytokine release syndrome; IRR = infusion-related reaction; Tobe+Bev = tobemstomig plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., > 21 days 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.

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

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reaction (cont.)	
IRR to tobemstomig, Grade 4	• Discontinue infusion immediately. • Give supportive treatment. • Permanently discontinue study treatment.
IRR to bevacizumab, Grade 1	• Continue bevacizumab. • Systemic intervention is not indicated.
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.
Hemophagocytic lymphohistiocytosis	• Follow guidelines for tobemstomig in Appendix 10. • Withhold all treatment. The Medical Monitor is available to advise as needed.

CRS=cytokine release syndrome; IRR=infusion-related reaction; Tobe+Bev=tobemstomig plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., >21 days 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.

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

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity	
GI perforation, any grade	• Withhold tobemstomig. • Permanently discontinue bevacizumab. • Initiate treatment per institutional guidelines. • If event improves, consider resuming tobemstomig. If not, permanently discontinue tobemstomig. [a]
Bowel obstruction, Grade 2	• Tobemstomig 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	• Tobemstomig may be continued at the discretion of the investigator. • Withhold bevacizumab for complete obstruction. • If surgery is necessary, patient may restart bevacizumab after full recovery from surgery and at the investigator's discretion.

GI = gastrointestinal; Tobe + Bev = tobemstomig plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., > 21 days 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.

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

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
Hypertension	
General guidance	• Treat with anti-hypertensive medication as needed.
Hypertension, Grade 1	• Continue tobemstomig and bevacizumab. • Consider increased blood pressure monitoring.
Hypertension, Grade 2	• Continue tobemstomig. • If asymptomatic, begin or modify baseline anti-hypertensive therapy and continue bevacizumab. • If symptomatic, start or adjust anti-hypertensive therapy.
Hypertension, Grade 3	• Continue tobemstomig. • Modify existing anti-hypertensive therapy (more than one drug or more intensive therapy than previously indicated). • Withhold bevacizumab until symptoms resolve and blood pressure is $<$160/90 mmHg.
Hypertension, Grade 4	• Tobemstomig may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.

Tobe+Bev=tobemstomig plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's assessment benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., $>$21 days after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of $\leq$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.

[c] If corticosteroids have been initiated, they must be tapered over $\geq$1 month to the equivalent of $\leq$10 mg/day oral prednisone before tobemstomig can be resumed.

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
Hemorrhage	
Hemorrhage, Grade 3 or 4 (excluding cerebral hemorrhage)	• Continue tobemstomig. • Permanently discontinue bevacizumab.
Cerebral hemorrhage, any grade	• Tobemstomig may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Grade ≥2 hemoptysis (≥2.5 mL of bright red blood per episode)	• Continue tobemstomig. • Permanently discontinue bevacizumab.
Bleeding in patients on full-dose anticoagulant therapy	• Continue tobemstomig. • Permanently discontinue bevacizumab.

Tobe+Bev=tobemstomig plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., >21 days 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.

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

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
Thromboembolic events	
Venous thromboembolic event, Grade 3	• Tobemstomig 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 Grade > 2 hemorrhagic events while in the study. – The patient must be on stable dose of heparin, low-molecular-weight heparin, or have an in-range INR (usually 2 to 3) on a stable dose of warfarin prior to restarting bevacizumab. • If thromboemboli worsen or recur upon resumption of study therapy, discontinue bevacizumab.
Venous thromboembolic event, Grade 4	• Tobemstomig may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.

Tobe+Bev = tobemstomig plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., > 21 days 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.

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

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
Thromboembolic events (cont.)	
Arterial thromboembolic event, any grade	• Tobemstomig may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Proteinuria [d]	
Proteinuria, Grade 1 (1+ by dipstick; urinary protein < 1.0 g/24 hr)	• Continue tobemstomig and bevacizumab.
Proteinuria, Grade 2 (2+ and 3 + by dipstick; urinary protein 1.0–3.4 g/24 hr)	• Continue tobemstomig. • For 2+ dipstick: Continue bevacizumab and collect 24-hour urine protein prior to subsequent bevacizumab administration. • For 3+ dipstick: Obtain 24-hour urine prior to administering bevacizumab. • Withhold bevacizumab for urinary protein ≥ 2 g/24 hr. • If bevacizumab is withheld and urine protein improves to < 2 g/24 hr within 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab.

Tobe + Bev = tobemstomig plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., > 21 days 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.

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

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
Proteinuria [d] (cont.)	
Proteinuria, Grade 3 (4+ by dipstick; urinary protein ≥3.5 g/24 hr) with no diagnosis of nephrotic syndrome	• Tobemstomig may be continued at the discretion of the investigator. • Withhold bevacizumab. • If urine protein improves to <2 g/24 hr within 42 days after event onset, resume bevacizumab.If not, permanently discontinue bevacizumab.
Nephrotic syndrome, Grade 3 or 4	• Tobemstomig may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Fistula	
Tracheoesophageal fistula, any grade	• Withhold tobemstomig. • Permanently discontinue bevacizumab. • If event improves, consider resuming tobemstomig. If not, permanently discontinue tobemstomig. [a]
Fistula (non-tracheoesophageal), Grade 4	• Withhold tobemstomig. • Permanently discontinue bevacizumab. • If event improves, consider resuming tobemstomig. If not, permanently discontinue tobemstomig. [a]

Tobe+Bev=tobemstomig plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., >21 days 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.

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

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
Wound dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	• Tobemstomig may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Congestive heart failure	
Congestive heart failure, Grade 3 or 4	• Tobemstomig may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Posterior reversible encephalopathy syndrome or reversible posterior leukoencephalopathy syndrome	
PRES/RPLS, any grade confirmed by MRI	• Withhold tobemstomig. • Permanently discontinue bevacizumab. • If event improves, consider resuming tobemstomig. If not, permanently discontinue tobemstomig. [a]

MRI = magnetic resonance imaging; PRES = posterior reversible encephalopathy syndrome; Tobe + Bev = tobemstomig plus bevacizumab; RPLS = reversible posterior leukoencephalopathy syndrome.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., > 21 days 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.

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

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
Hepatic events	
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 $5\times$ ULN at baseline and increases to $>8\times$ ULN to $\leq 10\times$ ULN	• Monitor LFTs more frequently until return to baseline values or Grade 1 or better. • Withhold tobemstomig for up to 21 days after event onset. [b] • Continue bevacizumab. • 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 tobemstomig. [c] • If event does not resolve to baseline or to Grade 1 or better while withholding tobemstomig, permanently discontinue tobemstomig. The Medical Monitor is available to advise as needed. [a]

LFT = liver-function test; Tobe + Bev = tobemstomig plus bevacizumab; ULN = upper limit of normal.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., >21 days 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.

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

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
Hepatic events (cont.)	
AST or ALT increases to $>10\times$ ULN or total bilirubin increases to $>3\times$ ULN	• Permanently discontinue tobemstomig. The Medical Monitor is available to advise as needed. [a] • Withhold bevacizumab. • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to baseline, taper corticosteroids over ≥ 1 month. • If event resolves to Grade 1 within 42 days, resume bevacizumab at the discretion of investigator. If not, permanently discontinue bevacizumab. [a]

GI = gastrointestinal; Tobe + Bev = tobemstomig plus bevacizumab; ULN = upper limit of normal.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., >21 days 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.

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

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
Endocrine disorders	
Hypothyroidism, all grades	• Follow guidelines for tobemstomig in Appendix 10. • Continue bevacizumab.
Hyperthyroidism, Grade 1	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Follow guidelines for tobemstomig in Appendix 10. • Continue bevacizumab. **TSH <0.1 mU/L:** • Follow guidelines for tobemstomig in Appendix 10. • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Hyperthyroidism, Grade 2	• Follow guidelines for tobemstomig in Appendix 10. • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Hyperthyroidism, Grade 3 or 4	• Follow guidelines for tobemstomig in Appendix 10. • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Neurologic disorder	
Immune-mediated meningoencephalitis, all grades	• Follow guidelines for tobemstomig in Appendix 10. • Withhold bevacizumab. • If patient stabilizes within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]

Tobe+Bev=tobemstomig plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., >21 days 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.

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

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
Dermatologic events	
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for tobemstomig in Appendix 10. • Withhold bevacizumab. • If event resolves to Grade 1 or better, resume bevacizumab. • Permanently discontinue bevacizumab if withheld for >42 days or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed.
Tobemstomig-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for tobemstomig in Appendix 10. • Continue bevacizumab.
Grade 3 or 4	• Follow guidelines for tobemstomig in Appendix 10. • Withhold bevacizumab. • If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]

Tobe+Bev=tobemstomig plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., >21 days 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.

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

[d] Institutional protocols acceptable.

Table A14-4 Guidelines for Management of Participants Who Experience Adverse Events in Tobe+Bev Arm (cont.)

Event	Action to Be Taken
Bevacizumab-related toxicities not described above	
Grade 1 or 2	• Continue tobemstomig and bevacizumab.
Grade 3	• Continue tobemstomig. Withhold bevacizumab. • If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]
Grade 4	• Withhold tobemstomig and bevacizumab. • If event improves, tobemstomig should be continued. If not, permanently discontinue tobemstomig. The Medical Monitor is available to advise as needed. • If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]

Tobe+Bev=tobemstomig plus bevacizumab.

[a] Resumption of treatment should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] Tobemstomig may be withheld for a longer period of time (i.e., >21 days 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.

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

[d] Institutional protocols acceptable.

A14–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR TOBE+BEV ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

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 the Tobe+Bev arm are as follows:

- [redacted]
- [redacted]
  - [redacted]

A14–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN TOBE+BEV ARM

A14–5.3.1 Pregnancies in Female Participants

Female participants 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 4 months after the final dose of tobemstomig 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 participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant 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.

A14–5.3.2 Pregnancies in Female Partners of Male Participants

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 4 months after the final dose of tobemstomig 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. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant 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 when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male participant 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.

A14–5.3.3 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.

A14–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female participant exposed to study treatment or the female partner of a male participant 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).

A14–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR NEOADJUVANT TOBE+BEV ARM

Table A14-5 Schedule of Activities for Neoadjuvant Tobe+Bev Arm

Assessment/ Procedure	Protocol Section	Screening (see Appendix 11)	Neoadjuvant Treatment Cycles (21-Day Cycles) [a]		Pre-Surgery (restaging)	Surgery (Liver Resection)	Post-Surgery	[redacted]	
			Cycle 1	Cycles 2 & 3					
		D −28 to D−1	Day 1 (≤7 days after randomization)	Day 1 (±3 days)	≥2 weeks after Cycle 3	4–6 weeks after Cycle 3	≥2 weeks after surgery		
IMP Administration									
Tobemstomig administration	A14–4.1.2		x	x					
Bevacizumab administration			x	x					
Clinical or Surgical Assessments and Procedures									
Weight	4.5.3		x	x	x		x	x	
Complete physical examination								x	
Limited physical examination			x	x	x		x		
Vital signs	4.5.4		x	x	x		x	x	
12-Lead ECG	4.5.5		Perform as clinically indicated.					x	
ECOG Performance Status	Appendix 7		x	x	x		x	x	
Surgical delay assessment					x				

Table A14-5 Schedule of Activities for Neoadjuvant Tobe+Bev Arm (cont.)

Assessment/ Procedure	Protocol Section	Screening (see Appendix 11)	Neoadjuvant Treatment Cycles (21-Day Cycles) [a]		Pre-Surgery (restaging)	Surgery (Liver Resection)	Post-Surgery	[redacted]	
			Cycle 1	Cycles 2 & 3					
		D −28 to D −1	Day 1 (≤7 days after randomization)	Day 1 (±3 days)	≥2 weeks after Cycle 3	4–6 weeks after Cycle 3	≥2 weeks after surgery		
Liver resection/HCC curative surgery	3.1.2					x			
Tumor response assessments	4.5.8				x				
Disease recurrence assessments	4.5.8				x			x	x
Concomitant medications	A14–4.2		x	x	x		x	x	
Adverse events	5.3.1, 5.5.1, and 5.6		x	x	x		x	x	x
Clavien-Dindo assessment	4.5.9 and Appendix 6							x	
Survival follow-up and anti-cancer treatment	4.6.1								x
Local Laboratory Assessments									
Hematology	4.5.10		x	x	x		x	x	
Chemistry			x	x	x		x	x	
α-fetoprotein				x	x			x	

Table A14-5 Schedule of Activities for Neoadjuvant Tobe+Bev Arm (cont.)

Assessment/ Procedure	Protocol Section	Screening (see Appendix 11)	Neoadjuvant Treatment Cycles (21-Day Cycles) [a]		Pre-Surgery (restaging)	Surgery (Liver Resection)	Post-Surgery	[redacted]	
			Cycle 1	Cycles 2 & 3					
		D −28 to D −1	Day 1 (≤7 days after randomization)	Day 1 (±3 days)	≥2 weeks after Cycle 3	4–6 weeks after Cycle 3	≥2 weeks after surgery		
Coagulation (INR and aPTT)			x	x	x				
Thyroid function testing			x	x [d]	x		x	x	
C-reactive protein			x	x	x		x	x	
Serum autoantibody sample			Perform if a participant experiences a suspected immune-mediated adverse event.						
Pregnancy test [e]			x	x	x		x	x	x [e]
Urinalysis			Perform as clinically indicated.					x	
Viral serology [f]	4.5.10			x				x	
Cardiac enzymes (TnT or TnI)			x	x	x		x	x	
Central Laboratory Assessments									
[redacted]									

Table A14-5 Schedule of Activities for Neoadjuvant Tobe+Bev Arm (cont.)

Assessment/ Procedure	Protocol Section	Screening (see Appendix 11)	Neoadjuvant Treatment Cycles (21-Day Cycles) [a]		Pre-Surgery (restaging)	Surgery (Liver Resection)	Post-Surgery	Neoadjuvant Treatment Completion/ Discont. [b]	Long-Term Follow-Up [c]
			Cycle 1	Cycles 2 & 3					
		D −28 to D −1	Day 1 (≤7 days after randomization)	Day 1 (±3 days)	≥2 weeks after Cycle 3	4–6 weeks after Cycle 3	≥2 weeks after surgery	6 weeks after surgery (±2 weeks)	For 2 years, every 4 months (±2 weeks)
[redacted]									

ADA=anti-drug antibody; App=Appendix; Atezo+Bev=atezolizumab plus bevacizumab; D=day; Discont.=discontinuation; ECOG=Eastern Cooperative Oncology Group; [redacted] HCC=hepatocellular carcinoma; [redacted] PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic; TnI=troponin I; TnT=troponin T; WES=whole exome sequencing; WGS=whole genome sequencing.

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

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

Table A14-5 Schedule of Activities for Neoadjuvant Tobe+Bev Arm (cont.)

[b] Regardless of whether they complete the neoadjuvant treatment period or discontinue study drug prematurely, participants who proceed to surgery will return to the clinic for a neoadjuvant treatment completion/discontinuation visit [redacted] weeks after surgery. [redacted]

[c] After neoadjuvant treatment completion or discontinuation, information on survival follow-up and initiation of new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, participant medical records, and/or clinic visits approximately [redacted] until disease recurrence or for up to [redacted] years after completion/discontinuation of neoadjuvant therapy, whichever occurs first (unless the participant withdraws consent or the Sponsor terminates the study). Participants who complete the neoadjuvant treatment period will have their first survival follow-up visit [redacted] months after surgery [redacted] Participants who discontinue study drug prematurely will have their first survival follow-up visit [redacted] months after the final dose of study treatment. If a participant requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If a participant withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all participants discontinued treatment and passed the safety follow-up window, as well as approximately [redacted] of participants discontinued from the study, the Sponsor may conclude the arm (the remaining approximately [redacted] of participants will be discontinued from the study).

[d] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 3. It will not be collected on Day 1 of Cycle 2.

Table A14-5 Schedule of Activities for Neoadjuvant Tobe+Bev Arm (cont.)

[e] All women of childbearing potential will have urine or serum pregnancy tests performed at specified visits during treatment and 6 months after the final dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[f] [redacted]

Table A14-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Neoadjuvant Tobe + Bev Arm

Visit	Time	Sample Type
[redacted]		

Table A14-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Neoadjuvant Tobe + Bev Arm (cont.)

Visit	Time	Sample Type
[redacted]		

ADA = anti-drug antibody; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; Tobe + Bev = tobemstomig plus bevacizumab; WES = whole exome sequencing; WGS = whole genome sequencing.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

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

[b] PK, ADA, and biomarker samples collections prior to surgery should be collected preferably the same day of surgery, or within 24 hours prior to surgery.

[c] After neoadjuvant treatment completion or discontinuation, information on survival follow-up and initiation of new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, participant medical records, and/or clinic visits approximately [redacted] until disease recurrence or for up to [redacted] years after completion/discontinuation of neoadjuvant therapy, whichever occurs first (unless the participant withdraws consent or the Sponsor terminates the study).

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Appendix 15
Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table A15-1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for the European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product) [a]	Authorized	No [b]
Bevacizumab (RO4876646)	IMP (test product) [a]	Authorized	No [c]
Tiragolumab (RO7092284)	IMP (test product)	Unauthorized	Not Applicable
Tobemstomig (RO7247669)	IMP (test product)	Unauthorized	Not Applicable

AxMP auxiliary medicinal product; EEA = European Economic Area; HCC = hepatocellular carcinoma; IMP = investigational medicinal product; PD-1 = programmed death−1.

[a] Atezolizumab and bevacizumab qualify as both test products and comparators.

[b] Atezolizumab in combination with bevacizumab is indicated for the treatment of patients with advanced or unresectable HCC who have not received prior systemic therapy but not as neoadjuvant immunotherapy combination in patients with resectable HCC.

[c] HCC is not an approved therapeutic indication of bevacizumab.

Table A15-2 Investigational and Non-Investigational Medicinal Product Designations for the United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in U.K.	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product) [a]	Authorized	No [b]
Bevacizumab (RO4876646)	IMP (test product) [a]	Authorized	No [c]
Tiragolumab (RO7092284)	IMP (test product)	Unauthorized	Not Applicable
Tobemstomig (RO7247669)	IMP (test product)	Unauthorized	Not Applicable

AxMP auxiliary medicinal product; EEA = European Economic Area; HCC = hepatocellular carcinoma; IMP = investigational medicinal product; NIMP = non-investigational medicinal product PD-1 = programmed death−1; U.K. = United Kingdom.

[a] Atezolizumab and bevacizumab qualify as both test products and comparators.

[b] Atezolizumab in combination with bevacizumab is indicated for the treatment of patients with advanced or unresectable HCC who have not received prior systemic therapy but not as neoadjuvant immunotherapy combination in patients with resectable HCC.

[c] HCC is not an approved therapeutic indication of bevacizumab.

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