PROTOCOL

TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH METASTATIC COLORECTAL CANCER (MORPHEUS-CRC)**
PROTOCOL NUMBER:	CO39612
VERSION NUMBER:	11
EUDRACT NUMBER:	2017-004566-99
IND NUMBER:	137508
NCT NUMBER:	NCT03555149
TEST PRODUCTS:	Atezolizumab (RO5541267), regorafenib, idasanutlin (RO5503781), AB928, LOAd703 (delolimogene mupadenorepvec)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann La- Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
22-Mar-2022 18:47:34	Company Signatory	[redacted]

CONFIDENTIAL

PROTOCOL HISTORY

Protocol	
Version	Date Final
11	See electronic date stamp on title page.
10	30 August 2021
9	16 February 2021
8	16 January 2021
7	22 March 2020
6 (France, Switzerland, United Kingdom)	10 January 2020
5 (United States, Australia, South Korea)	12 November 2019
4 (France)	29 October 2019
3	10 July 2019
2	16 October 2018
1	15 March 2018

PROTOCOL AMENDMENT, VERSION 11:
RATIONALE

Protocol CO39612 has been amended primarily to update risks and management guidelines for atezolizumab to align with the latest Atezolizumab Investigator's Brochure (Version 18). Changes to the protocol, along with a rationale for each change, are summarized below:

- The information on the atezolizumab, Imprime PGG, and bevacizumab arm, has been removed because enrollment and patient follow-up have been completed for this arm (Sections 1.3, 3.1.1, 3.1.1.1, 4.1.2, 4.2, 4.3.1, and 5.7, Appendices 8 and 15).
- The Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST) appendix (former Appendix 2) has been removed as the Sponsor no longer plans to perform these analyses (Sections 2, 3.1.3, 4.5.6, and 6.4.3; Section 3.3.3 has been deleted and subsequent sections have been renumbered).
- Text has been added to clarify that, if tumor assessment scans for an experimental arm are submitted for evaluation by an Independent Review Facility, scans for the corresponding control arm will also be submitted (Section 3.1.3).
- The inclusion criterion “Tumor accessible for biopsy” has been removed from Section 4.1.1.2 (Inclusion Criteria for Stage 1 and Stage 2), as it is redundant with existing criteria in Section 4.1.1.1 (Inclusion Criteria for Stage 1) and Section 4.1.1.3 (Inclusion Criteria for Stage 2).
- It has been clarified that during visits when a patient will undergo a tumor assessment, the physical examination should include an evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly (Section 4.5.4; Section 6 in Appendix 14).
- Text has been updated to align with current Roche protocol template language on genomic testing of blood and tissue samples for exploratory biomarker research (Section 4.5.7; and new Section 4.5.9 has been added and subsequent sections have been renumbered).
- The procedures for reporting infusion-related reactions (IRRs) have been modified to include reporting of cytokine release syndrome (CRS), as there may be significant overlap in signs and symptoms of IRRs and CRS (Section 5.3.5.1).
- The backup Medical Monitor for this study has changed and new contact information has been added (Section 5.4.1).
- Text has been revised to note that 95% confidence intervals will be calculated using normal approximation of the binomial distribution (Sections 6.4.1 and 6.4.2).
- The responsibilities of the investigator and the role of the Medical Monitor in determining patient eligibility have been clarified (Sections 3.1.3, 4.1.1.1, and 4.5.7; Appendices 4 and 6; Section 1.1.2 in Appendix 7; Sections 4.1.2 and 5.1.4.1–5.1.4.3 in Appendix 11; Sections 4.1.2 and 5.1.4.1–5.1.4.3 in Appendix 12; Sections 4.1.2 and 5.1.5.1–5.1.5.3 in Appendix 13; Sections 4.1.2, 5.1.4.2, and 5.1.4.3 in Appendix 14; Appendix 15).

- The medical term “primary biliary cirrhosis” has been replaced by the term “primary biliary cholangitis” to align with the updated preferred term in Medical Dictionary for Regulatory Activities (Appendix 4).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator’s Brochure, Version 18 (Appendix 6; Section 5.1.4.3 in Appendices 11 and 12; Section 5.1.5.3 in Appendix 13).
- To provide additional flexibility for patients and study sites, it has been clarified that the 96-hour window for laboratory testing is prior to dosing during the treatment period. An additional footnote has been added to note assessments that may be performed within 24 hours prior to dosing during the treatment period. (Appendices 7, 11–14).
- Guidance on concomitant administration of coronavirus disease 2019 vaccines has been added (Section 4.2.1 in Appendices 11–14).
- Immunosuppressive medications have been removed from the prohibited therapy section (Section 4.2.3 in Appendices 11–14) and added to the cautionary therapy section to align with management guidelines that permit use of immunosuppressive medications for the treatment of corticosteroid-refractory immune-mediated adverse events (Section 4.2.2 in Appendices 11–14).
- Safety and adverse event management guidelines have been updated to include CRS (Section 5.1.4.3 in Appendices 11 and 12; Section 5.1.5.3 in Appendix 13).
- It has been clarified that urinalysis may be performed up to 72 hours prior to Day 1 of each cycle, as results must be available prior to treatment administration (Section 6 in Appendices 12 and 13).
- The frequency of urinalysis assessments has been adjusted to as clinically indicated for the Atezo+LOAd703 Arm (Section 6 in Appendix 14).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH METASTATIC COLORECTAL CANCER (MORPHEUS-CRC)**
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MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	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 Covance.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH METASTATIC COLORECTAL CANCER (MORPHEUS-CRC)**
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PHASE:	Ib/II
INDICATION:	Colorectal cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of immunotherapy-based treatment combinations in patients with metastatic colorectal cancer (mCRC). Specific objectives and corresponding endpoints for the study are outlined below for Stage 1 (see Table 1) and Stage 2 (see Table 2).

Table 1 Objectives and Corresponding Endpoints for Stage 1

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• ORR, defined as the proportion of patients with a complete response or partial response on two consecutive occasions ≥4 weeks apart during Stage 1, as determined by the investigator according to RECIST v1.1

ORR = objective response rate; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.
Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1.

Table 1 Objectives and Corresponding Endpoints for Stage 1 (cont.)

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• PFS after randomization,[a] defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • OS after randomization,[a] defined as the time from randomization to death from any cause • OS at specific timepoints (e.g., 6 months) • DOR, defined as the time from the first occurrence of a documented objective response during Stage 1 to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • DCR, defined as the proportion of patients with stable disease for ≥ 12 weeks or a complete or partial response, as determined by the investigator according to RECIST v1.1
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 1	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	• Plasma or serum concentration of each drug (as appropriate) at specified timepoints
• To evaluate potential relationships between drug exposure during Stage 1 and the efficacy and safety of immunotherapy-based treatment combinations	• Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints
Exploratory Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline

ADA = anti-drug antibody; DCR = disease control rate; DOR = duration of response; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1.

[a] For the mandatory serial-biopsy arms, PFS and OS will be determined from the time of treatment initiation (rather than time of randomization).

Table 1 Objectives and Corresponding Endpoints for Stage 1 (cont.)

Exploratory Immunogenicity Objectives (cont.)	Corresponding Endpoints
• To evaluate potential effects of ADAs during Stage 1	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers during Stage 1 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; PK = pharmacokinetic.

Table 2 Objectives and Corresponding Endpoints for Stage 2

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 2	• ORR, defined as the proportion of patients with a complete response or partial response on two consecutive occasions ≥ 4 weeks apart during Stage 2, as determined by the investigator according to RECIST v1.1 • PFS after initiation of Stage 2, defined as the time from initiation of Stage 2 to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a documented objective response during Stage 2 to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • DCR, defined as the proportion of patients with stable disease for ≥ 12 weeks or a complete or partial response, as determined by the investigator according to RECIST v1.1 and
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 2	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results

DCR = disease control rate; DOR = duration of response; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1.

Table 2 Objectives and Corresponding Endpoints for Stage 2 (cont.)

Exploratory Pharmacokinetic Objective	Corresponding Endpoints
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• Plasma or serum concentration of each drug (as appropriate) at specified timepoints
Exploratory Pharmacokinetic Objective	**Corresponding Endpoints**
• To evaluate potential relationships between drug exposure during Stage 2 and the efficacy and safety of immunotherapy-based treatment combinations	• Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints
Exploratory Immunogenicity Objective	**Corresponding Endpoints**
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline
• To evaluate potential effects of ADAs during Stage 2	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK, endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers during Stage 2 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; PK = pharmacokinetic.

STUDY DESIGN

DESCRIPTION OF STUDY

Overview of Study Design

This is a Phase Ib/II, open-label, multicenter, randomized, umbrella study in patients with mCRC. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status). This study will enroll patients with mCRC who became refractory to first- and second-line standard therapies for mCRC. Eligible patients will initially be assigned to one of several treatment arms (Stage 1; see below). Patients who experience disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may be eligible to continue treatment with a different treatment regimen (Stage 2; see below).

Stage 1

During Stage 1, patients will be randomly assigned to the control arm (regorafenib) or an experimental arm consisting of atezolizumab in combination with idasanutlin (Atezo + Idasa) or regorafenib (Atezo + Regorafenib) or regorafenib and AB928 (Atezo + Regorafenib + AB928) or LOAd703 (Atezo + LOAd703) (see Table 3).

Approximately 111–382 patients will be enrolled during Stage 1. Enrollment within the experimental arms will take place in two phases: a preliminary phase followed by an expansion phase. Approximately 15 patients will be enrolled in the Atezo + Idasa, Atezo + Regorafenib, Atezo + Regorafenib + AB928, and Atezo + LOAd703 arms during the preliminary phase. If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients may be enrolled in that arm during the expansion phase. The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Randomization will be suspended in some arms after enrollment of approximately 6 patients to allow for a safety evaluation (see below for details). The Sponsor may also decide to open enrollment in separate mandatory serial-biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has qualified for the expansion phase (see below for details). Experimental arms with insufficient clinical activity or unacceptable toxicity will not undergo expansion. Additional patients 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 study by amending the protocol.

Patients will be randomly assigned to treatment arms, with the exception of the mandatory serial-biopsy arms, and the randomization ratio will depend on the number of experimental arms that are available (e.g., if an arm is added or enrollment in an arm is suspended, pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control arm will be no more than 35%. Randomization will take into account arm-specific exclusion criteria. Patients will be ineligible for a specific arm if they meet any of the exclusion criteria outlined for that arm (see criteria below).

Table 3 Stage 1 Treatment Regimens

Study Treatment	No. of Patients [a]		
	Preliminary Phase	Expansion Phase [b]	Mandatory Serial-Biopsy Arms [c]
Regorafenib	Variable [a]		
Atezo + Idasa	15 [d, e]	25	15
Atezo + Regorafenib	15 [d]	25	15
Atezo + Regorafenib + AB928	15 [d]	25	15
Atezo + LOAd703	15–21 [d]	25	15

Atezo = atezolizumab; EC = Ethics Committee; IRB = Institutional Review Board; LOAd = Lokon oncolytic adenovirus.

[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), with the stipulation that the likelihood of being allocated to the control arm will be no more than 35%.

[b] If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients may be enrolled in that arm during the expansion phase.

[c] The Sponsor may open enrollment in separate mandatory serial-biopsy arms to enable up to 15 patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase. If a site has not been granted IRB/EC approval for mandatory serial biopsies, these arms will not be opened at that site (see below for details).

[d] Randomization will be suspended after enrollment of approximately 6 patients to allow for a safety evaluation in the Atezo + Idasa, Atezo + Regorafenib, and Atezo + Regorafenib + AB928 arms (see below for details).

[e] Upon implementation of protocol Version 8, the Atezo + Idasa *arm has* been closed for further enrollment.

Patients in the regorafenib control arm will continue to receive treatment until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). Patients in the experimental arms will be treated until unacceptable toxicity or loss of clinical benefit defined as (1) confirmed disease progression in the tumor assessment following the finding of radiographic progression per RECIST v1.1 or (2) lack of continued benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudoprogression) with cancer immunotherapies (CITs; such as atezolizumab), radiographic progression per RECIST v1.1 may not be indicative of true disease progression. After the first tumor assessment meeting the criteria for disease progression per RECIST v1.1, patients receiving treatment with a CIT drug will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Safety Evaluation Phase

To account for potential overlapping toxicities in the Atezo + Idasa, Atezo + Regorafenib, Atezo + Regorafenib + AB928, and Atezo + LOAd703 arms, enrollment within each arm will be suspended after approximately 6 patients have been enrolled to allow for a safety evaluation. The safety evaluation will be based on safety data from a minimum of 6 patients who have received at least one dose of treatment (i.e., one dose of each agent for a given combination) and completed safety follow-up assessments of at least one full treatment cycle. If a combination is determined to be sufficiently safe, enrollment will be resumed in that arm.

Mandatory Serial-Biopsy Arms

If an experimental combination demonstrates clinical activity during the preliminary phase, the Sponsor may decide to test that same combination in a mandatory serial-biopsy arm at the time that arm is open for expansion. This arm will consist of patients at participating sites who are willing to undergo an on-treatment biopsy.

The opening of mandatory serial-biopsy arms is contingent upon the review and approval of the protocol and the mandatory serial biopsy 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 mandatory serial biopsies, these arms will not be opened at that site.

The objective of the mandatory serial-biopsy arms is to analyze serial tissue samples (including pretreatment, on-treatment, and post-progression samples) in an effort to better understand potential biological changes that occur during treatment with CIT combinations (including immune escape), provide evidence of pharmacodynamic effects, or confirm hypothesized mechanisms of action. Biomarkers may include those that inform stromal and immune biology.

Patients entering Stage 1 who are determined by the investigator to be eligible for serial biopsies may be enrolled in a mandatory serial-biopsy arm rather than undergo random assignment to other arms that are open for enrollment. If more than one mandatory biopsy arm is open, patients will be assigned to one of the available arms by the Sponsor.

Approximately 15 patients with serial biopsy samples will be enrolled in each mandatory serial-biopsy arm. However, the number of patients will be reduced if optional on-treatment biopsies have been collected (and determined to be evaluable) from consenting patients treated with that same CIT combination during the preliminary phase, to limit on-treatment biopsy collection to a total of approximately 15 patients per CIT combination.

Patients will undergo the same assessments as other patients receiving the same treatment combination but will have an additional mandatory on-treatment biopsy 4 weeks (±7 days)after initiation of CIT-combination treatment (if deemed clinically feasible by the investigator).

To be eligible for a mandatory serial-biopsy arm, a patient should have at least two accessible tumors that are amenable to excisional, punch, or core-needle biopsy (a minimum of three cores, 18-gauge needle or larger [16-gauge needle preferred]) without unacceptable risk of a major procedural complication. If it is planned that more than one biopsy will be obtained from a single lesion, the lesion should be large enough to permit successive biopsies ≥1 cm apart.

Patients enrolled in a mandatory serial-biopsy arm for whom three evaluable tissue samples cannot be obtained may continue to receive study treatment as scheduled.

Stage 2

During Stage 1, patients who experience disease progression per RECIST v1.1, loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (as described above), or unacceptable toxicity may be eligible to receive a different treatment combination during Stage 2, provided a Stage 2 treatment is available for enrollment and they meet the eligibility criteria of that treatment regimen. A maximum of 40 patients will be enrolled in each of the Stage 2 treatment regimens as outlined in Table 4.

Stage 2 treatment must begin within 3 months after a patient has experienced disease progression per RECIST v1.1 (regorafenib control arm), loss of clinical benefit (experimental arms), or unacceptable toxicity and will continue until unacceptable toxicity or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator. It is recommended that patients begin Stage 2 treatment as soon as possible.

Table 4 Stage 2 Treatment Regimens

Study Treatment
No Stage 2 treatment currently available

The Sponsor may decide to hold or discontinue enrollment in Stage 2 on the basis of a review of safety data, preliminary efficacy data, and supportive information (e.g., biomarker research data), as appropriate.

Assessments and Monitoring

All patients will be closely monitored for adverse events throughout the study, and adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

Patients will undergo tumor assessments every 6 weeks (starting on Day 1 of Cycle 1) for the first 48 weeks and then every 6 or 12 weeks thereafter. Response will be assessed by the investigator using RECIST v1.1. If clinical activity is demonstrated in an experimental arm, the Sponsor may request that tumor assessment scans for that arm *and the corresponding control arm* be submitted for evaluation by an independent reading facility.

Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided that the tissue was obtained from a biopsy performed within 6 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy. Tumor tissue will also be collected from patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1 (regorafenib control arm), or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (experimental arms) if deemed clinically feasible by the investigator. For patients enrolled in a mandatory serial-biopsy arm at participating sites, an additional tumor tissue sample will be collected during treatment (if clinically feasible). These samples, as well as blood samples collected during the study, will be utilized for biomarker research.

To characterize the pharmacokinetic (PK) properties and/or immunogenicity of atezolizumab and other therapeutic agents, blood samples will be obtained 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.

Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will monitor patient 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, 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.

Scientific Oversight Committee

A Scientific Oversight Committee (SOC) will act as a consultative body to the Sponsor, providing external expert opinions on the safety data collected during the study. This committee will consist of an external group of at least three oncology experts in CIT who will advise the Sponsor on the interpretation of study data. For this purpose, the SOC will evaluate aggregate safety data on a periodic basis, approximately every 6 months from the time the first patient is enrolled in the study. Members will follow a charter that outlines their roles and responsibilities. Data being evaluated by the SOC will include demographic, adverse event, serious adverse event, and relevant laboratory data. The SOC may review efficacy data if safety concerns necessitate benefit–risk assessments. The Sponsor will retain all decision-making authority for this study.

NUMBER OF PATIENTS

Approximately 111–382 patients will be enrolled in the study.

TARGET POPULATION

Inclusion Criteria

Patients must meet all of the criteria outlined in Sections 1 and 2 to qualify for Stage 1.
Patients must meet all of the criteria outlined in Sections 2 and 3 to qualify for Stage 2.

Section 1: Inclusion Criteria for Stage 1

Patients must meet all of the following criteria to qualify for Stage 1:

- Age $\geq$ 18 years at the time of signing Informed Consent Form
- ECOG Performance Status of 0 or 1
- Life expectancy $\geq$ 3 months, as determined by the investigator
- Histologically confirmed adenocarcinoma originating from the colon or rectum
- Metastatic disease (Stage IV American Joint Committee on Cancer, Version 7) not amenable to local treatment
- Disease progression during or following not more than two separate lines of treatment for mCRC that consisted of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy in combination with a biologic agent (i.e., bevacizumab, ramucirumab, aflibercept, cetuximab, panitumumab) but not other agents

  For patients who had disease recurrence within 6 months of completing adjuvant chemotherapy, the adjuvant regimen can be considered as one line of treatment for metastatic disease.

The re-introduction of an initially successful induction regimen will not be counted as one additional line of treatment.

Patients who have received first-line induction therapy with FOFOXIRI plus a biologic agent followed by maintenance therapy must have had documented disease progression no less than 3 months after the completion of the first-line induction therapy.

- Availability of a representative tumor specimen that is suitable for determination of programmed death-ligand 1 (PD-L1) and/or additional biomarker status by means of central testing

  Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided that the tissue was obtained from a biopsy performed within 6 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy.

  A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or *10-16* slides *(16 slides preferred)* containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report.

Section 2: Inclusion Criteria for Stage 1 and Stage 2

Patients must meet all of the following criteria to qualify for Stage 1 and to qualify for Stage 2:

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Measurable disease (at least one target lesion) according to RECIST v1.1

  Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support
  - WBC count $\geq 2.5 \times 10^9$/L (2500/μL)
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9.0 g/dL)

    Patients must not have been transfused within 2 weeks prior to screening to meet this criterion.
  - AST, ALT, and alkaline phosphatase (ALP) $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:

    Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN

    Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
  - Bilirubin $\leq 1.5 \times$ ULN, with the following exception:

    Patients with known Gilbert syndrome: bilirubin level $\leq 3 \times$ ULN
  - Albumin ≥ 25 g/L (2.5 g/dL)
  - Creatinine $\leq 1.5 \times$ ULN
  - For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 ULN
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen during the 14 days prior to initiation of study treatment
- Negative HIV test at screening

  Patients without a prior positive HIV test result will undergo an HIV test at screening, unless not permitted per local regulations
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

The HBV DNA test will be performed only for patients who have a positive total HBcAb test.

- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures as outlined for each specific treatment arm
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as outlined for each specific treatment arm

Section 3: Inclusion Criteria for Stage 2

Patients must meet all of the following criteria to qualify for Stage 2:

- ECOG Performance Status of 0–2
- Patients in the control arm: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity or disease progression per RECIST v1.1 while receiving Stage 1 treatment
- Patients in an experimental arm during Stage 1: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity not related to atezolizumab or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator while receiving Stage 1 treatment
- Availability of a tumor specimen from a biopsy performed upon discontinuation of Stage 1 (if deemed clinically feasible by the investigator)

Exclusion Criteria

Patients will be excluded from enrollment during Stage 1 and Stage 2 if they meet any of the applicable criteria outlined in subsequent sections, as summarized by treatment arm in Table 5. If a patient is eligible only for the control arm, the patient will not be enrolled in the study. Event grades in the exclusion criteria are based on NCI CTCAE v4.0.

Table 5 Arm-Specific Exclusion Criteria

Stage	Treatment Arm	Applicable Exclusion Criteria
1	Regorafenib	Sections 1 and 2
	Atezo + Idasa	Sections 1, 2, and 3
	Atezo + Regorafenib	Sections 1 and 2
	Atezo + Regorafenib + AB928	Sections 1, 2, and 4
	Atezo + LOAd703	Sections 1, 2, and 5
2	Not currently available	Not applicable

Atezo = atezolizumab; Idasa = idasanutlin; LOAd = Lokon oncolytic adenovirus.

Section 1: Exclusion Criteria for Stage 1

Patients who meet any of the following criteria will be excluded from Stage 1:

- High microsatellite instability (MSI-H) tumor

  Patients with unknown microsatellite instability (MSI) status will be required to undergo testing at a local laboratory and provide results at screening; genomic testing using polymerase chain reaction (PCR) or sequencing, or immunohistochemistry (IHC) techniques are allowed.
- Presence of $BRAF^{V600E}$ mutation

  Patients with unknown BRAF status will be required to undergo testing at a local laboratory and provide results at screening.

- Prior treatment with any of the protocol-specified study treatments, with the following exception:

  Patients who received bevacizumab for treatment of CRC are eligible for the study.
- Prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies including anti-cytotoxic T lymphocyte–associated protein 4 (anti–CTLA-4), anti-programmed death-1 (anti–PD-1), and anti–PD-L1 therapeutic antibodies
- Biologic treatment (e.g., bevacizumab) within 2 weeks prior to initiation of study treatment, or other systemic treatment for colorectal cancer (CRC) within 2 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Eligibility only for the control arm

Section 2: Exclusion Criteria for Stage 1 and Stage 2

Patients who meet any of the following criteria will be excluded from Stage 1 and from Stage 2:

- Prior allogeneic stem cell or solid organ transplantation
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressant medication during study treatment, with the following exceptions:

  Patients who received acute, low-dose, systemic immunosuppressant medications or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab
- Current treatment with anti-viral therapy for HBV
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Use of an indwelling catheter (e.g., PleurX®) is allowed.
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected serum calcium $>$ ULN)

- Symptomatic, untreated, or actively progressing CNS metastases

  Patients with a history of treated CNS metastases are eligible, provided that all of the following criteria are met:

  - Measurable disease, per RECIST v1.1, must be present outside the CNS.
  - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
  - Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
  - There is no evidence of interim progression between completion of CNS-directed therapy and the screening brain scan.
  - The patient has not received stereotactic radiotherapy within 7 days prior to initiation of study treatment or whole-brain radiotherapy within 14 days prior to initiation of study treatment.
  - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anti-convulsant therapy at a stable dose is permitted.

    Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.
- History of leptomeningeal disease
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

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

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

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

  - Rash must cover $< 10\%$ of body surface area.
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
  - There is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- History of malignancy other than CRC within 2 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year overall survival [OS] rate $> 90\%$), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety
- Treatment with therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to initiation of study treatment

Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable angina or new onset angina within 3 months prior to initiation of study treatment, recent myocardial infarction within 6 months prior to initiation of study treatment, or unstable arrhythmia
- Grade ≥ 3 hemorrhage or bleeding event within 28 days prior to initiation of study treatment
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study

  Placement of central venous access catheter (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.
- Adverse events from prior anti-cancer therapy that have not improved to Grade ≤ 1 or better, with the exception of alopecia of any grade and Grade ≤ 2 peripheral neuropathy
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- History of severe allergic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any of the study drugs or their excipients
- Patients entering Stage 2: inability to tolerate atezolizumab during Stage 1
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Inability to swallow medications
- Malabsorption condition that would alter the absorption of orally administered medications
- Evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (i.e., in the absence of therapeutic anticoagulation)
- Urine dipstick $\geq 2+$ protein or ≥ 3.5 g of protein in a 24-hour urine collection

  Patients discovered to have $\geq 2+$ proteinuria on dipstick urinalysis at screening should undergo a 24-hour urine collection and must demonstrate < 3.5 g of protein in 24 hours to be eligible.

Section 3: Additional Exclusion Criteria for Idasanutlin-Containing Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the idasanutlin-containing arm during Stage 1:

- Prior treatment with an MDM2 antagonist
- TP53 mutation as determined centrally through use of a blood-based NGS ctDNA assay
- Hypersensitivity to idasanutlin active substance or any of the excipients
- Inability to interrupt treatment with moderate to strong CYP2C8 inducers and inhibitors (including gemfibrozil, which is also an inhibitor of UGT1A3), CYP2C8 substrates, strong CYP3A4 inducers or OATP1B1/3 substrates

  These agents must be discontinued 14 days prior to the start of study treatment.
- History of clinically significant liver cirrhosis (e.g., Child-Pugh class B and C)
- Inadequate renal function assessed by either serum creatinine outside local laboratory reference ranges OR creatinine clearance (by Cockcroft Gault formula) < 50 mL/min

- Treatment with oral or parenteral anticoagulants/anti-platelet agents (e.g., warfarin, chronic daily treatment with aspirin [> 325 mg/day], clopidogrel, dabigatran, apixaban, rivaroxaban) within 7 days (or 5 half-lives) prior to treatment start

  Treatment with, or switch to low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is allowed, according to local practice.

  Patients may receive anticoagulant flushes for maintenance of indwelling catheters.
- Unstable seizure disorders
- Active GI conditions, including, but not limited to, uncontrolled inflammatory bowel disease (e.g., Crohn's disease, diverticulosis-associated colitis)
- History of symptomatic clostridium difficile infection that required treatment within 1 month prior to dosing

  Upon clinical response to C. difficile treatment, the stool consistency and frequency must have returned to pretreatment levels.

Section 4: Additional Exclusion Criteria for AB928-Containing Arms during Stage 1

Patients who meet any of the following criteria will be excluded from the AB928-containing arm during Stage 1:

- Prior treatment with an agent targeting the adenosine pathway
- Treatment with strong inhibitors of breast cancer resistance protein (BCRP) (e.g., cyclosporin A, eltrombopag) or BCRP substrates with a narrow therapeutic window, administered orally (e.g., prazosin, rosuvastatin), and within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with strong inhibitors of P-glycoprotein (P-gp) (e.g., itraconazole, quinidine, verapamil, dronedarone, ranolazine) or P-gp substrates with a narrow therapeutic window, administered orally (e.g., digoxin), and within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with known strong UDP-glucuronosyltransferases (UGTs) of UGT1A1, 1A4, 1A9 and 2B4 inhibitors (e.g., atazanavir) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment.
- Treatment with known sensitive substrates of BSEP_within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment.
- Treatment with known sensitive substrates of OCT2 within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment.
- Treatment with known sensitive substrates of MATE-1 within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment.
- Treatment with strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort) and strong CYP3A4 inhibitors (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment

Section 5: Additional Exclusion Criteria for LOAd703-Containing Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the LOAd703-containing arm during Stage 1:

- Prior treatment with an adenovirus-based gene therapy
- Prior treatment with LOAd703 or any other oncolytic virus
- Prior treatment with adenovirus-based vaccines (e.g., ChAdOx1 nCoV-19, Ad26.COV2.S) up to 6 months prior to initiation of study treatment, anticipation of need for such a vaccine during LOAd703 treatment, or up to 6 months after the last dose of LOAd703
- Absence of available lesion that is both measurable according to RECIST v1.1 and injectable (as assessed by the investigator, refer to Section A14–4.1.2.1 for further guidance)

The injected lesion should not be the only measurable lesion

- Known hereditary bleeding diathesis or significant acquired coagulopathy at risk of bleeding (e.g., hemophilia, von Willebrand disease, cancer-associated diffuse intravascular coagulation) when only deep lesions are available for injection
- For procedures with moderate or significant risk of bleeding (deep lesions and/or organs), use of therapeutic doses of anticoagulants prior to the initiation of study treatment

  Long-acting agents such as aspirin or clopidogrel should be discussed on a case-by-case basis with the Sponsor and may need to be discontinued before the start of study treatment.

  Patients on preventive doses of LMWH or direct oral anticoagulant (DOAC) may be eligible if treatment can be suspended 24 hours (for LMWH) or 48 hours (for DOAC) prior to intratumoral injection and resumed 24 hours after the injection.

END OF STUDY

The end of this study is defined as the date when the last patient completes the last visit in both stages, including survival follow-up visits conducted by telephone or on-site visit.

LENGTH OF STUDY

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3–5 years.

INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational medicinal products (IMPs) for this study are atezolizumab, regorafenib, idasanutlin, AB928, and LOAd703.

TEST PRODUCTS (INVESTIGATIONAL DRUGS)

Atezolizumab plus Idasanutlin (Stage 1)

Idasanutlin is planned to be administered orally at a dose of 200 mg QD × 5d Q4W. However, to account for potential toxicities, special caution will be taken by starting idasanutlin at a lower dose of 150 mg QD × 5d during Cycle 1 and continuing idasanutlin at the 200-mg dose in all subsequent cycles in (at a minimum) the first 5 patients. If this regimen is determined to be safe and well tolerated, all subsequent patients will receive 200 mg QD × 5 Q4W in combination with atezolizumab during all cycles. Patients enrolled in the Atezo+Idasa arm will receive treatment until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). It is recommended that treatment be initiated no later than 7 days after randomization. Treatment with Atezo + Idasa when idasanutlin is administered at 150 mg or at 200 mg is described in Table 6 and 7, respectively.

Table 6 Initial Treatment Regimen for Atezo + Idasa Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Idasanutlin 150 mg orally once daily on Days 1–5 of each cycle [a] • Atezolizumab 840 mg IV on Days 1 and 15

Atezo + Idasa = atezolizumab plus idasanutlin.

[a] For details regarding intra-patient dose increase and dose increase after the safety evaluation phase, refer to Section A11–4.1.2.2.

Table 7 Treatment Regimen for Atezo + Idasa Arm after Dose Increase

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Idasanutlin 200 mg orally once daily on Days 1–5 of each cycle • Atezolizumab 840 mg IV on Days 1 and 15

Atezo + Idasa = atezolizumab plus idasanutlin.

Atezolizumab plus Regorafenib (Stage 1)

Patients in the Atezo + Regorafenib arm will receive treatment as outlined in Table 8 until unacceptable toxicity or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator, after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Treatment must be initiated no later than 7 days after treatment assignment.

Table 8 Treatment Regimen for Atezo + Regorafenib Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Atezolizumab 840 mg IV on Days 1 and 15 of each cycle • Regorafenib 120 mg by mouth once daily on Days 1–21 [a]

Atezo = atezolizumab.

[a] Regorafenib should be initiated at 80 mg, allowing sufficient time to monitor drug-related toxicities before considering dose escalation to 120 mg. At least 7 days off regorafenib are required prior to starting a new treatment cycle.

Atezolizumab plus Regorafenib plus AB928 (Stage 1)

Patients in the Atezo + Regorafenib + AB928 arm will receive treatment as outlined in Table 9 until unacceptable toxicity or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator, after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Treatment must be initiated no later than 7 days after treatment assignment.

Table 9 Treatment Regimen for Atezo + Regorafenib + AB928 Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• AB928 150 mg by mouth once daily on Days 1–28 of each cycle • Atezolizumab 840 mg IV on Days 1 and 15 of each cycle • Regorafenib 120 mg by mouth once daily on Days 1–21 of each cycle [a]

Atezo = atezolizumab; IV = intravenous.

[a] Regorafenib should be initiated at 80 mg, allowing sufficient time to monitor drug-related toxicities before considering dose escalation to 120 mg. At least 7 days off regorafenib are required prior to starting a new treatment cycle.

Atezolizumab plus LOAd703 (Stage 1)

It is recommended that treatment be initiated no later than 7 days after randomization.

Table 10 Treatment Regimen for Atezo + LOAd703 Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle [a] • LOAd703 1×10^{11} VP or 5×10^{11} VP [b] intratumoral injection on Day 1 of each cycle [c]

[a] Atezolizumab will be administered preferably prior to LOAd703 injection. If LOAd703 cannot be administered the day of atezolizumab infusion, LOAd703 can be given on another day during the treatment week, after prior consultation with the Medical Monitor. If atezolizumab is administered after LOAd703, it should not be administered until the LOAd703 observation period has ended.

[b] Initially, approximatively 3 to 6 patients will be treated at the dose of 1×10^{11} VP. If this dose is determined to be safe and well tolerated in these first 3–6 patients, the dose may be increased to 5×10^{11} VP in the next enrolled patients according to the considerations described in the protocol.

[c] After the initial six injections of LOAd703 (Cyles 1–6), there is an option to continue treatment with LOAd703 for an additional 6 administrations (Cycles 7–12) for a maximum total number of 12 injections for patients who are deriving clinical benefit as determined by the investigator. In the absence of confirmed PD, atezolizumab treatment can continue after LOAd703 treatment has ended or has been discontinued for reasons other than toxicity, provided the patient is tolerating atezolizumab and is receiving clinical benefit in the opinion of the investigator. *The Medical Monitor is available to advise as needed.*

Control Arm

Patients in the regorafenib (control) arm will receive treatment as outlined in Table 11 until unacceptable toxicity or disease progression per RECIST v1.1. Treatment must be initiated no later than 7 days after treatment assignment.

Table 11 Treatment Regimen for Regorafenib Arm

Cycle Length	Dose, Route, and Regimen
28 days	• Regorafenib 160 mg by mouth once daily on Days 1–21 • Dose escalation to 160 mg during Cycle 1 per institutional guidelines, e.g., from 80 mg in the first week followed by weekly dose increases to 120 mg in the second and 160 in the third week, is allowed.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

For patients in the Atezo + Idasa arm, all patients should receive the premedications outlined in Table 12 to mitigate the risk of idasanutlin-related GI toxicities.

Table 12 Premedication for Idasanutlin

Premedication/Indication	Timepoint	Administration
5-HT3 receptor antagonist: To reduce the incidence and severity of nausea and vomiting	Day 1, 30–60 minutes prior to first administration of study medication (for long-acting anti-emetics, such as palonosetron); otherwise prior to each study medication administration (Days 1–5, for short acting anti-emetics, such as ondansetron or granisetron) [a]	Palonosetron IV 0.25 mg or PO 0.5 mg, or granisetron transdermal system, or oral ondansetron or granisetron [b] according to prescribing information

PO = by mouth

[a] Premedication to be repeated for every cycle.

[b] Palonosetron is the recommended option because of its efficacy against delayed nausea and lack of QT interval–prolonging effects.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary efficacy endpoint is objective response rate (ORR) during Stage 1, as defined in Table 1. Patients with missing or no response assessments will be classified as non-responders.

ORR, defined as the proportion of patients with a complete or partial response, will be calculated for each arm, along with 95% CIs (Clopper–Pearson exact method). The difference in ORR between the experimental arms and the corresponding control arm will also be calculated, along with 95% CIs, *using normal approximation of the binomial distribution*.

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 efficacy, safety, and PK data on immunotherapy-based treatment combinations when administered to patients with mCRC who experienced disease progression during or following two lines of treatment for mCRC that consisted of fluoropyrimidine-, oxaliplatin-, or irinotecan-containing chemotherapy in combination with a biologic agent (e.g., bevacizumab, cetuximab), given in combination as two separate lines of therapy (in either order).

Approximately 111–382 patients will be randomly allocated to the control and experimental arms during the study.

Approximately 15 patients with serial-biopsy samples will be enrolled in each mandatory serial-biopsy arm. However, the number of patients may be reduced if optional on-treatment biopsies have been collected (and determined to be evaluable) from consenting patients treated with that same CIT combination during the preliminary phase, to limit on-treatment biopsy collection to approximately 15 patients per CIT combination within each cohort.

With approximately 15 patients with serial biopsies in each arm, an 80% two-sided CI for a 30% increase in $CD8^+$ T cells in the center of the tumor would range from 22.8% to 37.2%, assuming a standard deviation of 0.20 for the difference in $CD8^+$ T cells between paired samples (i.e., baseline vs. on-treatment samples, baseline vs. post-progression samples, or on-treatment vs. post-progression samples).

INTERIM ANALYSES

It is anticipated that at least one interim analysis will be conducted over the course of the study, with the earliest interim analysis taking place when at least one experimental arm has completed enrollment in the preliminary phase and patients have been followed for a minimum of 6 weeks. A posterior probability will be used to guide further enrollment of 25 additional patients in the experimental arm. Enrollment may be expanded if the posterior probability of demonstrating a given improvement in ORR compared with the control arm is greater than a prespecified threshold. The current considerations are an improvement in ORR of 10% compared with the control arm and a posterior probability of 70%.

An improvement of at least 10% in ORR as compared with control is considered clinically meaningful, and a posterior probability of 70% provides reasonable confidence that the difference will continue to be observed at the final analysis after completion of the expansion phase. If an improvement of at least 10% is not observed in a given arm, enrollment will either be stopped for futility or paused for further evaluation. The Sponsor may make a decision to expand enrollment in an arm based on the totality of available data including, but not limited to, duration of the observed responses, PFS, 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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody, also known as anti-therapeutic antibody
Ad5/35	Adenovirus serotype 5 with a fiber (shaft and knob) from serotype 35
Atezo	Atezolizumab
CAPOX	capecitabine and oxaliplatin
CEA	carcinoembryonic antigen
CIN	chromosomal instability
CIT	cancer immunotherapy
COVID-19	coronavirus *disease* 2019
CRC	colorectal cancer
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte–associated protein 4
DCR	disease control rate
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
FDA	U.S. Food and Drug Administration
FOLFIRI	folinic acid, fluorouracil, and irinotecan
FOLFOX	folinic acid, fluorouracil, and oxaliplatin
FOLFOXIRI	folinic acid, fluorouracil, oxaliplatin, and irinotecan
FFPE	formalin-fixed, paraffin-embedded
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
ICH	International Council for Harmonisation
Idasa	idasanutlin
IFN	interferon
IHC	immunohistochemistry
IMC	Internal Monitoring Committee

Abbreviation	Definition
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IV	intravenous
IxRS	interactive voice or web-based response system
LMWH	low molecular weight heparin
LOAd	Lokon oncolytic adenovirus
mCRC	metastatic colorectal cancer
mOS	median overall survival
MAS	macrophage activation syndrome
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability–high
MSS	microsatellite-stable
NCCN	National Cancer Comprehensive Network
NCI	National Cancer Institute
NCI CTCAE v4.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
NGS	next-generation sequencing
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PBMC	peripheral blood mononuclear cell
PFS	progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SEER	Surveillance, Epidemiology and End Results
SITC	Society for Immunotherapy for Cancer
SOC	Scientific Oversight Committee
T3	triiodothyronine
T4	thyroxine
TAS-102	trifluridine/tipiracil
TMZ	trimerized
UFH	unfractionated heparin
ULN	upper limit of normal

Abbreviation	Definition
VEGF	vascular endothelial growth factor
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON COLORECTAL CANCER

Globally, colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and second in females. CRC is also the fourth leading cause of cancer mortality in males and third in females (Torre et al. 2016). The estimated incidence of new cases in 2012 in developed countries was 736,900, and mortality was 333,200, with the highest incidence rates in North America, Europe, and Australia/New Zealand (Torre et al. 2016).

Mortality from CRC decreased by 35% from 1990 to 2007 (Siegel et al. 2011) and is currently down by about 50% from peak mortality rates (Siegel et al. 2016). Despite the observed improvements in the overall CRC mortality rate, a retrospective cohort study of the Surveillance, Epidemiology and End Results (SEER) CRC registry found that the incidence of CRC in patients younger than 50 years has been increasing; the authors estimate the incidence rates for colon and rectal cancers will increase by 90% and 124%, respectively, for patients 20 to 34 years by 2030 (Bailey et al. 2015).

In the United States, about 40% of CRC patients are diagnosed with early-stage disease, with another 40% diagnosed with regional disease, and 20% diagnosed with distant metastasis. Five-year survival rates are 90%, 71%, and 14%, respectively, with most of these patients dying from metastatic disease (Alberts and Wagman 2008; Kennecke et al. 2014; American Cancer Society 2017). Without treatment, the median survival for patients with metastatic CRC (mCRC) is less than 1 year (Liu et al. 2003). Surgical resection of metastases can improve outcomes. The 5-year survival rates of the small fraction of patients eligible for resection of metastatic lesions are around 27%–41% (Mandalà et al. 2007; Zaydfudim et al. 2015). In the vast majority of mCRC patients, systemic cytotoxic chemotherapy is the mainstay of treatment and median overall survival (mOS) is only around 30 months.

Mechanistically, CRC develops either sporadically (85%), as part of a hereditary cancer syndrome (less than 10%), or in the context of inflammatory bowel disease. With regard to the molecular pathogenesis, two distinct mechanisms that underlie the development of CRC have been identified based on microsatellite instability (MSI) and chromosomal instability (CIN) (Gervaz et al. 2002; Haydon and Jass 2002; Jass et al. 2002; Gervaz et al. 2004). MSI involves the failure of the nucleotide mismatch recognition and repair system (Aaltonen et al. 1993; Ionov et al. 1993). High microsatellite instability (MSI-H) status is observed in approximately 10%–15% of all sporadic CRC (Söreide et al. 2006) and in about 5% of patients with mCRC. In contrast, CIN is characterized by changes in the numbers of chromosomes or profound structural changes of chromosomes and accompanies the development of CRC from dysplastic adenoma in conjunction with somatic mutations in *APC*, *KRAS*, and *TP53* oncogenes (Vogelstein et al. 1989).

1.2 TREATMENT FOR METASTATIC COLORECTAL CANCER

The current management of mCRC involves various active drugs that are used either in combination or as single agents: 5-fluorouracil/leucovorin, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, ziv-aflibercept, regorafenib, and trifluridine/tipiracil. The putative mechanisms of action of these agents are varied and include the interference with DNA replication and inhibition of activities of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR). Current first- and second-line therapies for mCRC include a variety of different oxaliplatin- and irinotecan-based chemotherapy regimens, for example, folinic acid, fluorouracil, and oxaliplatin (FOLFOX) and folinic acid, fluorouracil, and irinotecan (FOLFIRI), which have similar activity, but different toxicity profiles. Patients with mCRC in the first-line setting are typically treated with a cytotoxic doublet such as FOLFOX, capecitabine and oxaliplatin (CAPOX), or FOLFIRI or, possibly, in very select cases, the cytotoxic triplet folinic acid, fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI). Improved outcomes have been demonstrated when combining chemotherapy with cetuximab and panitumumab targeting the EGFR pathway or with bevacizumab, ramucirumab, and ziv-aflibercept targeting the VEGF pathway. In patients in whom the initial chemotherapy regimen failed (i.e., in the second-line setting), the chemotherapy backbone is then changed; patients who received FOLFIRI up front will then receive FOLFOX and vice versa (Benson et al. 2017).

Once patients have exhausted first- and second-line treatment options, their survival is typically less than 6 months. More recently, regorafenib (Stivarga®) and trifluridine/tipiracil (TAS-102 [LONSURF®]) have been approved in these previously treated chemotherapy-refractory mCRC patients. Regorafenib is a multikinase inhibitor that was approved following a randomized, double-blind, placebo-controlled trial in which heavily pretreated mCRC patients showed a survival benefit over best supportive care (mOS 6.4 months for the regorafenib group versus 5.0 months for the placebo group; hazard ratio [HR] = 0.77; 95% CI: 0.64, 0.94; p = 0.0102). The most common adverse events, of all grades observed were hand-foot syndrome (47% of patients), fatigue (47%), diarrhea (34%), hypertension (29%), voice changes (28%), oral mucositis (28%) and rash/desquamation (26%) (Grothey et al. 2013). TAS-102 is an orally administered combination of a thymidine−based nucleic acid analogue, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride. It was approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency based on a randomized, double-blind, placebo-controlled trial demonstrating a survival benefit for TAS-102 over best supportive care (mOS 7.1 months in the TAS-102 group versus 5.3 months in the placebo group; HR = 0.68; 95 % CI: 0.58, 0.81; p < 0.001). The most frequently observed adverse events were neutropenia (38% of patients) and leukopenia (21%) (Mayer et al. 2015). Even with the approvals of these two agents, a high unmet need remains in this patient population for more efficacious treatment options with better safety profiles.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Cancer immunotherapy (CIT) has demonstrated significant survival benefit, observed across multiple advanced malignancies. Currently, the prevailing CIT approach is to circumvent immune evasion mechanisms and reinvigorate anti-tumor responses by targeting T-cell inhibitory factors, such as programmed death-ligand 1/programmed death-1 (PD-L1/PD-1). While these targets have resulted in remarkable clinical therapeutic success for various cancer indications, research indicates that a series of stepwise events is necessary for the generation of a continuous anti-tumor immune response (Chen and Mellman 2013). Each event is critical for an effective response, and each is also susceptible to several tumor immune-evasion mechanisms. Thus, the need to identify and circumvent the various factors that account for the absence of, or escape from, an effective anti-cancer immune response will be critical for propagating cancer immunity and advancing the field of CIT, most likely through combined targeted therapy regimens.

In CRC, single-agent immune checkpoint inhibitors have been shown to have clinical benefit in patients with tumors assessed as having MSI-H status but not with microsatellite-stable (MSS) tumors (Le et al. 2015). The superior efficacy of checkpoint inhibitors in MSI-H CRC has been postulated to be due to a higher number of neo-antigens compared with MSS tumors. The higher number of somatic mutations is thought to increase the immunogenicity of the tumor resulting in increased recruitment of immune effector and antigen presenting cells (Llosa et al. 2015; Zhang et al. 2015). Consistently, the MSI-H cancers have increased $CD8^+$ T cells and PD-L1 expression in the tumor, which may explain why they are responsive to checkpoint inhibitors (Smedt et al. 2015).

While the 4%–8% of CRC patients with MSI-H tumors show clinical benefit from CIT, the remaining CRC patients do not. This appears to also be the case when checkpoint inhibitors, like the anti-PD-1 agent pembrolizumab, are combined with a standard doublet of cytotoxics like FOLFOX (Shahda et al. 2017). Thus, there is a significant unmet medical need for the development of combination treatments that will bring the benefit of cancer immunotherapies with their often long-lasting responses to patients with MSS mCRC.

This randomized Phase Ib/II umbrella study is designed to accelerate the development of CIT combinations by identifying early signals and establishing proof-of-concept clinical data in patients with MSS mCRC. 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. Enrollment of multiple experimental arms within a single study, rather than one or two experimental arms within multiple studies, will result in an overall reduction in the number of patients receiving control-arm treatment. More importantly, 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. To improve the confidence of clinical signal detection in the experimental arms, this study will include a control arm. Moreover, patients who experience disease progression with the initial treatment regimen (Stage 1) may be eligible to continue treatment with a different treatment regimen (Stage 2), which may advance the scientific understanding of immune escape mechanisms in patients who fail to respond to, or experience disease progression during, treatment with a CIT or chemotherapy regimen.

The target and proposed mechanism-of-action classification for each experimental investigational medicinal product (IMP) is summarized in Table 1. The control and experimental treatment regimens are described in Sections 3.1.1 and 3.1.2 (see Table 4 and Table 6). 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 and Table 6.

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	Immune checkpoint inhibitor
Regorafenib	Tyrosine kinase	Multiple kinase inhibitor
Idasanutlin	MDM2	Inhibits p53-MDM2 binding, thus activating p53, which, within the myeloid compartment, promotes the differentiation of cross-presenting cells, and, in tumor cells, promotes a senescence-driven innate immune response [a]
AB928	A2aR/A2bR	Dual adenosine receptor antagonist, reverses immunosuppressive effects caused by high concentrations of adenosine within the tumor microenvironment
LOAd703	CD40; 4-1BB	Oncolytic adenovirus (Ad5/35) with increased cell binding and infectivity of cells expressing CD46; oncolysis of tumor cells with de-regulated RB-pathway; Expression of transgenic TMZ-CD40L and 4-1BBL under the control of CMV promoter in infected tumor and stroma cells which leads to activation of myeloid cells, T cells, and NK cells. [b]

A2aR = adenosine 2a receptor; A2bR = adenosine 2b receptor; Ad5/35 = adenovirus serotype 5 with a fiber (shaft and knob) from serotype 35; CMV = Cytomegalovirus; IMP = investigational medicinal product; LOAd = Lokon oncolytic adenovirus; MDM2 = murine double minute 2; NK=natural killer; PD-L1 = programmed death–ligand 1.

[a] Tovar et al. 2006; Xue et al. 2007; Ianello et al. 2013; Guo et al. 2017; Sharma et al. 2018

[b] Eriksson et al. 2017.

1.4 COVID-19 BENEFIT–RISK ASSESSMENT

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

A possible consequence of 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, 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 (IFN)-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving 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 *CIT* treatment and *COVID-19* vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of *COVID-19* vaccination (Society for Immunotherapy *of* Cancer [SITC] 2020).

Per recommendations of the National Comprehensive Cancer Network® (NCCN®) COVID-19 Vaccination Advisory Committee, *COVID-19* vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of *COVID-19* vaccination in patients who are

receiving CIT (SITC 2020). For patients enrolling in this study and receiving CIT, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving CIT to receive $COVID\text{-}19$ vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering $COVID\text{-}19$ vaccines. When administered, $COVID\text{-}19$ vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the $COVID\text{-}19$ vaccine is considered a concomitant medication and should be documented as such (see respective appendix for that treatment arm [Appendix 7 through Appendix 14]).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of immunotherapy-based treatment combinations in patients with metastatic CRC. Specific objectives and corresponding endpoints for the study are outlined below for Stage 1 (see Table 2) and Stage 2 (see Table 3).

Table 2 Objectives and Corresponding Endpoints for Stage 1

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• ORR, defined as the proportion of patients with a complete response or partial response on two consecutive occasions ≥ 4 weeks apart during Stage 1, as determined by the investigator according to RECIST v1.1
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• PFS after randomization,[a] defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • OS after randomization,[a] defined as the time from randomization to death from any cause • OS at specific timepoints (e.g., 6 months) • DOR, defined as the time from the first occurrence of a documented objective response during Stage 1 to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • DCR, defined as the proportion of patients with stable disease for ≥ 12 weeks or a complete or partial response, as determined by the investigator according to RECIST v1.1

DCR = disease control rate; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

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

[a] For the mandatory serial-biopsy arms, PFS and OS will be determined from the time of treatment initiation (rather than time of randomization).

Table 2 Objectives and Corresponding Endpoints for Stage 1 (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 1	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	• Plasma or serum concentration of each drug (as appropriate) at specified timepoints
• To evaluate potential relationships between drug exposure during Stage 1 and the efficacy and safety of immunotherapy-based treatment combinations	• Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints
Exploratory Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline
• To evaluate potential effects of ADAs during Stage 1	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers during Stage 1 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PK = pharmacokinetic.

Table 3 Objectives and Corresponding Endpoints for Stage 2

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 2	• ORR, defined as the proportion of patients with a complete response or partial response on two consecutive occasions ≥4 weeks apart during Stage 2, as determined by the investigator according to RECIST v1.1 • PFS after initiation of Stage 2, defined as the time from initiation of Stage 2 to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a documented objective response during Stage 2 to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • DCR, defined as the proportion of patients with stable disease for ≥12 weeks or a complete or partial response, as determined by the investigator according to RECIST v1.1
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 2	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results

DCR = disease control rate; DOR = duration of response; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

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

Table 3 Objectives and Corresponding Endpoints for Stage 2 (cont.)

Exploratory Pharmacokinetic Objectives	Corresponding Endpoints
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• Plasma or serum concentration of each drug (as appropriate) at specified timepoints
• To evaluate potential relationships between drug exposure during Stage 2 and the efficacy and safety of immunotherapy-based treatment combinations	• Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints
Exploratory Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline
• To evaluate potential effects of ADAs during Stage 2	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK, endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers during Stage 2 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

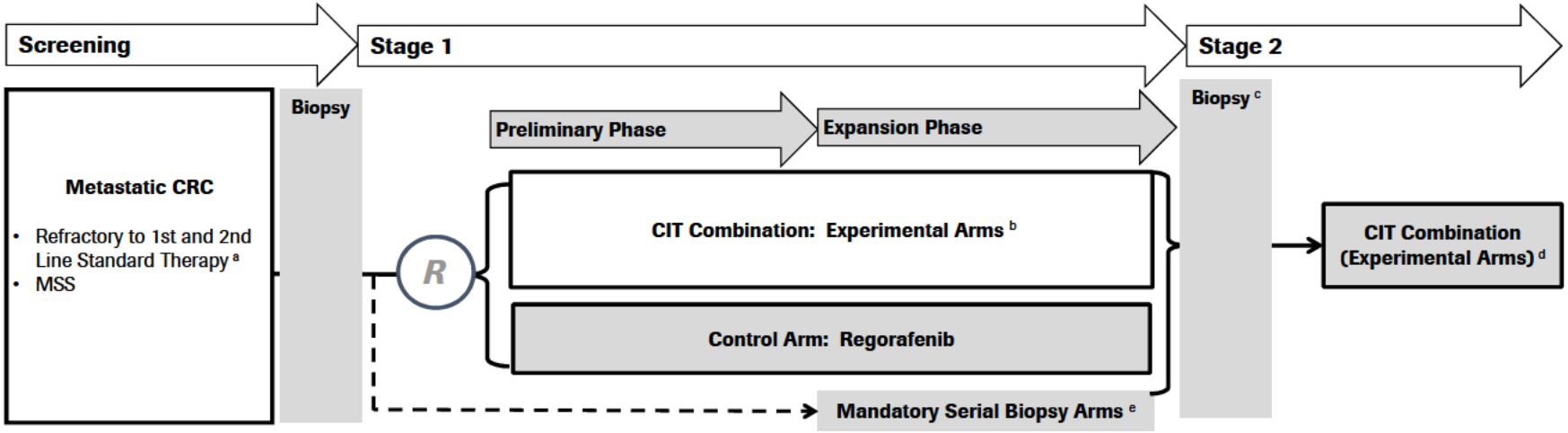
ADA = anti-drug antibody; PK = pharmacokinetic.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase Ib/II, open-label, multicenter, randomized, umbrella study in patients with mCRC. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status). This study will enroll patients with mCRC who became refractory to first- and second-line standard therapies for mCRC. Eligible patients will initially be assigned to one of several treatment arms (Stage 1; see Section 3.1.1). Patients who experience disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may be eligible to continue treatment with a different treatment regimen (Stage 2; see Section 3.1.2).

Figure 1 General Study Design



CIT = cancer immunotherapy; EC = Ethics Committee; IRB = Institutional Review Board; CRC = colorectal cancer; MSS = microsatellite-stable; R = randomization.

[a] Refractory to standard therapies is defined as the progression on not more than two prior lines of treatment (see Section 4.1.1.1).

[b] Refer to Table 4 for a summary of available Stage 1 treatment regimens.

[c] A biopsy will be performed for patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1, or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (if deemed clinically feasible by the investigator).

[d] Refer to Table 6 for a summary of available Stage 2 treatment regimens.

[e] The Sponsor may open enrollment in separate mandatory serial-biopsy arms to enable patients who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase of Stage 1. If a site has not been granted IRB/EC approval for mandatory serial biopsies, these arms will not be opened at that site (see Section 3.1.1.2).

3.1.1 Stage 1

During Stage 1, patients will be randomly assigned to the control arm (regorafenib) or an experimental arm consisting of atezolizumab in combination with idasanutlin (Atezo + Idasa) or regorafenib (Atezo + Regorafenib) or regorafenib and AB928 (Atezo + Regorafenib + AB928) or LOAd703 (Atezo + LOAd703) (see Figure 2). Details on the treatment regimens for Stage 1 are provided in Appendix 7 through Appendix 14, as specified in Table 4. Table 5 lists Stage 1 treatment arms for which enrollment and patient follow-up has been completed.

Approximately 111–382 patients will be enrolled during Stage 1. Enrollment within the experimental arms will take place in two phases: a preliminary phase followed by an expansion phase. Approximately 15 patients will be enrolled in the Atezo + Idasa, Atezo + Regorafenib, Atezo + Regorafenib + AB928, and Atezo + LOAd703 arms during the preliminary phase. If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients may be enrolled in that arm during the expansion phase. The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Randomization will be suspended in some arms after enrollment of approximately 6 patients to allow for a safety evaluation (see Section 3.1.1.1 for details). The Sponsor may also decide to open enrollment in separate mandatory serial-biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has qualified for the expansion phase (see Section 3.1.1.2 for details). Experimental arms with insufficient clinical activity or unacceptable toxicity will not undergo expansion. Additional patients 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 study by amending the protocol.

Patients will be randomly assigned to treatment arms, with the exception of the mandatory serial-biopsy arms, and the randomization ratio will depend on the number of experimental arms that are available (e.g., if an arm is added or enrollment in an arm is suspended, pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control arm will be no more than 35%. Randomization will take into account arm-specific exclusion criteria. Patients will be ineligible for a specific arm if they meet any of the exclusion criteria outlined for that arm (see Section 4.1.2). Details on treatment assignment and randomization are provided in Section 4.2.

Table 4 Stage 1 Treatment Regimens

Study Treatment	No. of Patients [a]			Appendix
	Preliminary Phase	Expansion Phase [b]	Mandatory Serial-biopsy arms [c]	
Regorafenib	Variable [a]			Appendix 7
Atezo + Idasa	15 [d, e]	25	15	Appendix 11
Atezo + Regorafenib	15 [d]	25	15	Appendix 12
Atezo+Regorafenib + AB928	15 [d]	25	15	Appendix 13
Atezo + LOAd703	15–21 [d]	25	15	Appendix 14

Atezo = atezolizumab; EC=Ethics Committee; Idasa = idasanutlin; IRB=Institutional Review Board; LOAd = Lokon oncolytic adenovirus.

[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), with the stipulation that the likelihood of being allocated to the control arm will be no more than 35% (see Section 4.2 for details).

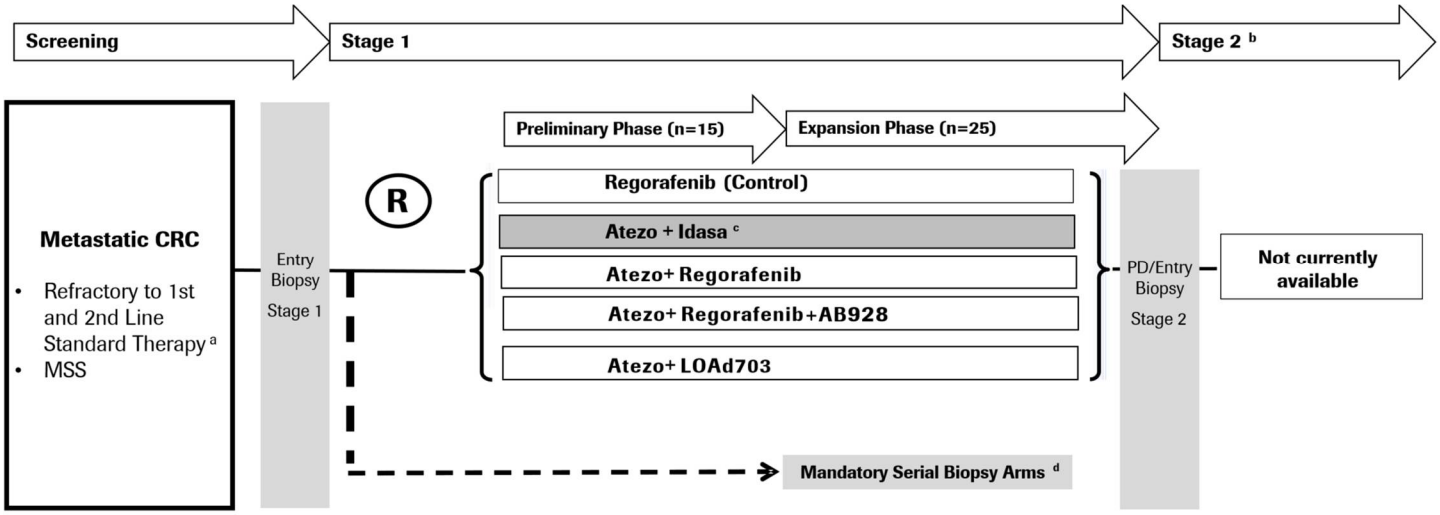
[b] If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients maybe enrolled in that arm during the expansion phase.

[c] The Sponsor may open enrollment in separate mandatory serial-biopsy arms to enable up to 15 patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase. If a site has not been granted IRB/EC approval for mandatory serial biopsies, these arms will not be opened at that site (see Section 3.1.1.2).

[d] Randomization will be suspended after enrollment of approximately 6 patients to allow for a safety evaluation in the Atezo + Idasa, Atezo + Regorafenib, Atezo + Regorafenib + AB928, and Atezo + LOAd703 arms (see Section 3.1.1.1 for details).

[e] Upon implementation of protocol Version 8, the Atezo + Idasa *arm has* been closed for further enrollment.

Figure 2 Detailed Study Design



Atezo = atezolizumab; CRC = colorectal cancer; EC=Ethics Committee; Idasa = idasanutlin; IRB=Institutional Review Board; Isa = isatuximab; LOAd = Lokon adenovirus; PD = progressive disease; R = randomization; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; MSS = microsatellite-stable.

[a] Refractory to standard therapies is defined as the progression on not more than two prior lines of treatment (see Section 4.1.1.1).

[b] Patients who experience disease progression per RECIST v1.1, loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (for details, see Section 3.1.1), or unacceptable toxicity during Stage 1 may be eligible to receive a different treatment during Stage 2, provided a Stage 2 treatment is available for enrolment and they meet the eligibility criteria. Details are provided in the respective appendix for each treatment arm (see Appendix 7 through Appendix 14).

[c] At the time of implementation of protocol Version 8, the Atezo + Idasa arm had been closed for further enrollment.

[d] The Sponsor may open enrollment in separate mandatory serial-biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase. If a site has not been granted IRB/EC approval for mandatory serial biopsies, these arms will not be opened at that site (see Section 3.1.1.2).

Table 5 Treatment Arms with Completed Enrollment and Patient Follow-Up

Stage	Arm Name	Treatment	Number of Patients Enrolled	Protocol Version Describing Arm
1	Atezo + Isa	atezolizumab, isatuximab	15	1–9
1	Atezo + Seli + Bev	atezolizumab, selicrelumab, and bevacizumab	6	1–9
1	*Atezo + Imprime + Bev*	*atezolizumab, Imprime PGG, and bevacizumab*	*15*	*1–10*

Patients in the regorafenib control arm will continue to receive treatment until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; see Appendix 1). Patients in the experimental arms will be treated until unacceptable toxicity or loss of clinical benefit defined as (1) confirmed disease progression in the tumor assessment following the finding of radiographic progression per RECIST v1.1 or (2) lack of continued benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudoprogression) with CITs (such as atezolizumab), radiographic progression per RECIST v1.1 may not be indicative of true disease progression. After the first tumor assessment meeting the criteria for disease progression per RECIST v1.1, patients receiving treatment with a CIT drug will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

3.1.1.1 Safety Evaluation Phase

To account for potential overlapping toxicities in the Atezo + Idasa, Atezo + Regorafenib, Atezo + Regorafenib + AB928, and Atezo + LOAd703 arms, enrollment within each arm will be suspended after approximately 6 patients have been enrolled to allow for a safety evaluation. The safety evaluation will be based on safety data from a minimum of 6 patients who have received at least one dose of treatment (i.e., one dose of each agent for a given combination) and completed safety follow-up assessments of at least one full

treatment cycle. If a combination is determined to be sufficiently safe, enrollment will be resumed in that arm.

3.1.1.2 Mandatory Serial-Biopsy Arms

If an experimental combination demonstrates clinical activity during the preliminary phase, the Sponsor may decide to test that same combination in a mandatory serial-biopsy arm at the time that arm is open for expansion. This arm will consist of patients at participating sites who are willing to undergo an on-treatment biopsy.

Opening of mandatory serial-biopsy arms is contingent upon the review and approval of the protocol and the mandatory serial biopsy 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 mandatory serial biopsies, these arms will not be opened at that site.

The objective of the mandatory serial-biopsy arms is to analyze serial tissue samples (including pretreatment, on-treatment, and post-progression samples) in an effort to better understand potential biological changes that occur during treatment with CIT combinations (including immune escape), provide evidence of pharmacodynamic effects, or confirm hypothesized mechanisms of action. Biomarkers may include those that inform stromal and immune biology (Turley et al. 2015).

Patients entering Stage 1 who are determined by the investigator to be eligible for serial biopsies may be enrolled in a mandatory serial-biopsy arm rather than undergo random assignment to other arms that are open for enrollment. If more than one mandatory biopsy arm is open, patients will be assigned to one of the available arms by the Sponsor.

Approximately 15 patients with serial-biopsy samples will be enrolled in each mandatory serial-biopsy arm. However, the number of patients will be reduced if optional on-treatment biopsies have been collected (and determined to be evaluable) from consenting patients treated with that same CIT combination during the preliminary phase, to limit on-treatment biopsy collection to a total of approximately 15 patients per CIT combination.

Patients will undergo the same assessments as other patients receiving the same treatment combination but will have an additional mandatory on-treatment biopsy 4 weeks (±7 days) after initiation of CIT-combination treatment (if deemed clinically feasible by the investigator). Details about the timing of biopsy sample collection are provided in the schedule of activities for each arm (see Appendix 7 through Appendix 14).

To be eligible for a mandatory serial-biopsy arm, a patient should have at least two accessible tumors that are amenable to excisional, punch, or core-needle biopsy

(a minimum of three cores, 18-gauge needle or larger [16-gauge needle preferred]) without unacceptable risk of a major procedural complication. If it is planned that more than one biopsy will be obtained from a single lesion, the lesion should be large enough to permit successive biopsies ≥ 1 cm apart.

Patients enrolled in a mandatory serial-biopsy arm for whom three evaluable tissue samples cannot be obtained may continue to receive study treatment as scheduled.

3.1.2 Stage 2

During Stage 1, patients who experience disease progression per RECIST v1.1, loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (for details, see Section 3.1.1), or unacceptable toxicity may be eligible to receive a different treatment combination during Stage 2, provided a Stage 2 treatment is available for enrollment and they meet the eligibility criteria of that treatment regimen. Details are provided in the respective appendices for each treatment arm (see Appendix 7 through Appendix 14). A maximum of 40 patients will be enrolled in each of the Stage 2 treatment regimens.

Stage 2 treatment must begin within 3 months after a patient has experienced disease progression per RECIST v1.1 (regorafenib control arm), loss of clinical benefit (experimental arms), or unacceptable toxicity and will continue until unacceptable toxicity or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator. It is recommended that patients begin Stage 2 treatment as soon as possible.

Table 6 Stage 2 Treatment Regimens

Study Treatment	Appendix
No Stage 2 treatment currently available	—

The Sponsor may decide to hold or discontinue enrollment in Stage 2 on the basis of a review of safety data, preliminary efficacy data, and supportive information (e.g., biomarker research data), as appropriate.

3.1.3 Assessments and Monitoring

All patients will be closely monitored for adverse events throughout the study, and adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

Patients will undergo tumor assessments every 6 weeks (starting on Day 1 of Cycle 1) for the first 48 weeks and then every 6 or 12 weeks thereafter (see Section 4.5.6 and Appendix 7 through Appendix 14 for details). Response will be assessed by the investigator using RECIST v1.1 (see Appendix 1). If clinical activity is demonstrated in an experimental arm, the Sponsor may request that tumor assessment scans for that

arm *and the corresponding control arm* be submitted for evaluation by an independent reading facility.

Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided that the tissue was obtained from a biopsy performed within 6 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy. Tumor tissue will also be collected from patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1 (regorafenib control arm), or loss of clinical benefit, defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (experimental arms) if deemed clinically feasible by the investigator. For patients enrolled in a mandatory serial-biopsy arm at participating sites, an additional tumor tissue sample will be collected during treatment (if clinically feasible). These samples, as well as blood samples collected during the study, will be utilized for biomarker research (see rationale for biomarker assessments in Section 3.3.3 and details on tissue sample collection in Section 4.5.7).

To characterize the pharmacokinetic (PK) properties and/or immunogenicity of atezolizumab and other therapeutic agents, blood samples will be obtained 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.

The schedule of activities for each treatment arm is presented in Appendix 7 through Appendix 14.

3.1.4 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will monitor patient 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, 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.

3.1.5 Scientific Oversight Committee

A Scientific Oversight Committee (SOC) will act as a consultative body to the Sponsor, providing external expert opinions on the safety data collected during the study. This committee will consist of an external group of at least three oncology experts in CIT who will advise the Sponsor on the interpretation of study data. For this purpose, the SOC will evaluate aggregate safety data on a periodic basis, approximately every 6 months from the time the first patient is enrolled in the study. Members will follow a charter that outlines their roles and responsibilities. Data being evaluated by the SOC will include demographic, adverse event, serious adverse event, and relevant laboratory data. The SOC may review efficacy data if safety concerns necessitate benefit–risk assessments. The Sponsor will retain all decision-making authority for this study.

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 in both stages, including survival follow-up visits conducted by telephone or on-site visit.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3–5 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

Although the combination of chemotherapy agents and biologics has provided an improvement of the clinical outcomes in patients with mCRC over recent years, treatment beyond the second line remains challenging. A significant unmet medical need exists in this patient population for more efficacious and better tolerated treatments.

The study will enroll patients with mCRC who became refractory to first- and second-line standard therapies for mCRC. While the efficacy of single-agent checkpoint inhibitors in CRC has been limited to the small percentage of patients with MSI-H tumors, no appreciable efficacy has been observed in patients with MSS tumors, hence the need to explore combination therapies. The design of this umbrella trial is expected to allow for rapid signal detection in a defined patient population. This study will exclude patients with MSI-H mCRC tumors and will focus on patients with a high unmet need in second- and third-line therapy.

3.3.2 Rationale for Immunotherapy-Based Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response has been termed pseudoprogression (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some

responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed immune cells and no viable cancer cells. Because of the potential for a response after pseudoprogression, this study will allow patients randomly allocated to immunotherapy-based treatment arms to continue combination treatment after apparent radiographic progression per RECIST v1.1, provided the benefit–risk ratio is judged to be favorable by the investigator (see criteria in Section 3.1.1). Patients should be discontinued for unacceptable toxicity or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1.1 for details).

3.3.3 Rationale for Biomarker Assessments

Blood samples for biomarker assessments will be collected at baseline and during the study. Changes in biomarkers in blood may provide evidence of biologic activity of the specific treatment combinations. Correlations between surrogate biomarkers in blood (such as tumor burden markers, cytokines, chemokines, immune cell subpopulations, gene expression, and circulating tumor DNA) and drug dose and efficacy and safety endpoints may allow for the development of a blood-based biomarker to help define future treatments and predict which patients are more likely to benefit from specific treatment combinations.

Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. Tumor tissue will also be collected for patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 for details) (if deemed clinically feasible by the investigator), to enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of study treatments. Tumor samples will be evaluated for biomarkers such as tumor-infiltrating immune cells, PD-L1, CD8, and expression of targets specific to each drug combination. Evaluation of the tumor microenvironment in response to treatment within each arm, including changes in the number and functional status of tumor-infiltrating immune cells, could provide validation of the postulated mechanism of action and confirmation that an appropriate dose and exposure for the specific treatment combination have been achieved.

Tumor tissue and blood samples may be analyzed through use of next-generation sequencing (NGS) methods, such as whole exome sequencing (WES), to identify somatic mutations 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, or can increase the knowledge and understanding of disease biology.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet all of the criteria outlined in Sections 4.1.1.1 and 4.1.1.2 to qualify for Stage 1. Patients must meet all of the criteria outlined in Sections 4.1.1.2 and 4.1.1.3 to qualify for Stage 2.

4.1.1.1 Inclusion Criteria for Stage 1

Patients must meet all of the following criteria to qualify for Stage 1:

- Age ≥ 18 years at the time of signing Informed Consent Form
- ECOG Performance Status of 0 or 1 (see Appendix 3)
- Life expectancy ≥ 3 months, as determined by the investigator
- Histologically confirmed adenocarcinoma originating from the colon or rectum
- Metastatic disease (Stage IV American Joint Committee on Cancer, Version 7) not amenable to local treatment
- Disease progression during or following not more than two separate lines of treatment for mCRC that consisted of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy in combination with a biologic agent (i.e., bevacizumab, ramucirumab, aflibercept, cetuximab, panitumumab) but not other agents

  For patients who had disease recurrence within 6 months of completing adjuvant chemotherapy, the adjuvant regimen can be considered as one line of treatment for metastatic disease.

  The re-introduction of an initially successful induction regimen will not be counted as one additional line of treatment.

  Patients who have received first-line induction therapy with FOFOXIRI plus a biologic agent followed by maintenance therapy must have had documented disease progression no less than 3 months after the completion of the first-line induction therapy.
- Availability of a representative tumor specimen that is suitable for determination of PD-L1 and/or additional biomarker status by means of central testing

  Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided that the tissue was obtained from a biopsy performed within 6 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy.

  A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or *10–16* slides *(16 slides preferred)* containing unstained, freshly cut, serial sections must be submitted along with an associated pathology

report. Refer to Section 4.5.7 for additional information on tumor specimens collected at screening.

4.1.1.2 Inclusion Criteria for Stage 1 and Stage 2

Patients must meet all of the following criteria to qualify for Stages 1 and 2:

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Measurable disease (at least one target lesion) according to RECIST v1.1

  Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support
  - WBC count $\geq 2.5 \times 10^9$/L (2500/μL)
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9.0 g/dL)

    Patients must not have been transfused within 2 weeks prior to screening to meet this criterion.
  - AST, ALT, and alkaline phosphatase (ALP) $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:

    Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN

    Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
  - Bilirubin $\leq 1.5 \times$ ULN, with the following exception:

    Patients with known Gilbert syndrome: bilirubin level $\leq 3 \times$ ULN
  - Albumin ≥ 25 g/L (2.5 g/dL)
  - Creatinine $\leq 1.5 \times$ ULN
  - For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 ULN
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen during the 14 days prior to initiation of study treatment
- Negative HIV test at screening

  Patients without a prior positive HIV test result will undergo an HIV test at screening, unless not permitted per local regulations.
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

The HBV DNA test will be performed only for patients who have a positive total HBcAb test.

- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures as outlined for each specific treatment arm in Appendix 7 through Appendix 14
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as outlined for each specific treatment arm in Appendix 7 through Appendix 14

4.1.1.3 Inclusion Criteria for Stage 2

Patients must meet all of the following criteria to qualify for Stage 2:

- ECOG Performance Status of 0–2 (see Appendix 3)
- Patients in the control arm: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity or disease progression per RECIST v1.1 while receiving Stage 1 treatment
- Patients in an experimental arm during Stage 1: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity not related to atezolizumab or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 for details) while receiving Stage 1 treatment
- Availability of a tumor specimen from a biopsy performed upon discontinuation of Stage 1 (if deemed clinically feasible by the investigator)

4.1.2 Exclusion Criteria

Patients will be excluded from enrollment during Stage 1 and Stage 2 if they meet any of the applicable criteria outlined in subsequent sections, as summarized by treatment arm in Table 7. If a patient is eligible only for the control arm, the patient will not be enrolled in the study. Event grades in the exclusion criteria are based on NCI CTCAE v4.0.

Table 7 Arm-Specific Exclusion Criteria

Stage	Treatment Arm	Applicable Exclusion Criteria
1	Regorafenib	Sections 4.1.2.1 and 4.1.2.2
	Atezo + Idasa	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.3
	Atezo + Regorafenib	Sections 4.1.2.1 and 4.1.2.2
	Atezo + Regorafenib + AB928	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.4
	Atezo + LOAd703	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.5
2	Not currently available	Not applicable

Atezo = atezolizumab; Idasa=Idasanutlin; LOAd = Lokon oncolytic adenovirus.

4.1.2.1 Exclusion Criteria for Stage 1

Patients who meet any of the following criteria will be excluded from Stage 1:

- High microsatellite instability (MSI-H) tumor

  Patients with unknown MSI status will be required to undergo testing at a local laboratory and provide results at screening; genomic testing using polymerase chain reaction (PCR) or sequencing, or immunohistochemistry (IHC) techniques are allowed.

- Presence of $BRAF^{V600E}$ mutation

  Patients with unknown *BRAF* status will be required to undergo testing at a local laboratory and provide results at screening.

- Prior treatment with any of the protocol-specified study treatments, with the following exception:

  Patients who received bevacizumab for treatment of CRC are eligible for the study.

- Prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Biologic treatment (e.g., bevacizumab) within 2 weeks prior to initiation of study treatment, or other systemic treatment for CRC within 2 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Eligibility only for the control arm

4.1.2.2 Exclusion Criteria for Stage 1 and Stage 2

Patients who meet any of the following criteria will be excluded from Stage 1 and from Stage 2:

- Prior allogeneic stem cell or solid organ transplantation
- Treatment with systemic immunostimulatory agents (including, but not limited to, IFN and IL-2) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressant medication during study treatment, with the following exceptions:

  Patients who received acute, low-dose, systemic immunosuppressant medications or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.

Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab
- Current treatment with anti-viral therapy for HBV
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Use of an indwelling catheter (e.g., PleurX®) is allowed.
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected serum calcium $>$ ULN)
- Symptomatic, untreated, or actively progressing CNS metastases

  Patients with a history of treated CNS metastases are eligible, provided that all of the following criteria are met:

  – Measurable disease, per RECIST v1.1, must be present outside the CNS.
  – The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
  – Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
  – There is no evidence of interim progression between completion of CNS-directed therapy and the screening brain scan.
  – The patient has not received stereotactic radiotherapy within 7 days prior to initiation of study treatment or whole-brain radiotherapy within 14 days prior to initiation of study treatment.
  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anti-convulsant therapy at a stable dose is permitted.

Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.

- History of leptomeningeal disease
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 4 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

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

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

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

  – Rash must cover $<10\%$ of body surface area.
  – Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
  – There is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

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

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

- History of malignancy other than CRC within 2 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year overall survival [OS] rate $>90\%$), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety

- Treatment with therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable angina or new onset angina within 3 months prior to initiation of study treatment, recent myocardial infarction within 6 months prior to initiation of study treatment, or unstable arrhythmia
- Grade ≥ 3 hemorrhage or bleeding event within 28 days prior to initiation of study treatment
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study

  Placement of central venous access catheter (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.

- Adverse events from prior anti-cancer therapy that have not improved to Grade ≤ 1 or better, with the exception of alopecia of any grade and Grade ≤ 2 peripheral neuropathy
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- History of severe allergic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any of the study drugs or their excipients
- Patients entering Stage 2: inability to tolerate atezolizumab during Stage 1
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

- Inability to swallow medications
- Malabsorption condition that would alter the absorption of orally administered medications
- Evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (i.e., in the absence of therapeutic anticoagulation)

- Urine dipstick ≥ 2+ protein or ≥ 3.5 g of protein in a 24-hour urine collection

  Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at screening should undergo a 24-hour urine collection and must demonstrate < 3.5 g of protein in 24 hours to be eligible.

4.1.2.3 Additional Exclusion Criteria for Idasanutlin-Containing Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the idasanutlin-containing arm during Stage 1:

- Prior treatment with an MDM2 antagonist
- *TP53* mutation as determined centrally through use of a blood-based NGS ctDNA assay
- Hypersensitivity to idasanutlin active substance or any of the excipients
- Inability to interrupt treatment with moderate to strong CYP2C8 inducers and inhibitors (including gemfibrozil, which is also an inhibitor of UGT1A3), CYP2C8 substrates, strong CYP3A4 inducers or OATP1B1/3 substrates (see Tables 6–8 in Appendix 11 for more details)

  These agents must be discontinued 14 days prior to the start of study treatment.
- History of clinically significant liver cirrhosis (e.g., Child-Pugh class B and C)
- Inadequate renal function assessed by either serum creatinine outside local laboratory reference ranges OR creatinine clearance (by Cockcroft Gault formula) < 50 mL/min
- Treatment with oral or parenteral anticoagulants/anti-platelet agents (e.g., warfarin, chronic daily treatment with aspirin [> 325 mg/day], clopidogrel, dabigatran, apixaban, rivaroxaban) within 7 days (or 5 half-lives) prior to treatment start

  Treatment with, or switch to low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is allowed, according to local practice.

  Patients may receive anticoagulant flushes for maintenance of indwelling catheters.
- Unstable seizure disorders
- Active GI conditions, including, but not limited to, uncontrolled inflammatory bowel disease (e.g., Crohn's disease, diverticulosis-associated colitis)
- History of symptomatic clostridium difficile infection that required treatment within 1 month prior to dosing

  Upon clinical response to C. difficile treatment, the stool consistency and frequency must have returned to pretreatment levels.

4.1.2.4 Additional Exclusion Criteria for AB928-Containing Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the AB928-containing arm during Stage 1:

- Prior treatment with an agent targeting the adenosine pathway
- Treatment with strong inhibitors of breast cancer resistance protein (BCRP) (e.g., cyclosporin A, eltrombopag) or BCRP substrates with a narrow therapeutic window, administered orally (e.g., prazosin, rosuvastatin), and within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with strong inhibitors of P-glycoprotein (P-gp) (e.g., itraconazole, quinidine, verapamil, dronedarone, ranolazine) or P-gp substrates with a narrow therapeutic window, administered orally (e.g., digoxin), and within 4 weeks or 5 half-lives of the drug (whichever is longer), prior to initiation of study treatment
- Treatment with known strong UDP-glucuronosyltransferases (UGTs) of UGT1A1, 1A4, 1A9 and 2B4 inhibitors (e.g., atazanavir) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment.
- Treatment with known sensitive substrates of BSEP within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment.
- Treatment with known sensitive substrates of OCT2 within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment.
- Treatment with known sensitive substrates of MATE-1 within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment.
- Treatment with strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort) and strong CYP3A4 inhibitors (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment

4.1.2.5 Additional Exclusion Criteria for LOAd703-Containing Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the LOAd703-containing arm during Stage 1:

- Prior treatment with an adenovirus-based gene therapy
- Prior treatment with LOAd703 or any other oncolytic virus
- Prior treatment with adenovirus-based vaccines (e.g., ChAdOx1 nCoV-19, Ad26.COV2.S) up to 6 months prior to initiation of study treatment, anticipation of need for such a vaccine during LOAd703 treatment or up to 6 months after the last dose of LOAd703
- Absence of available lesion that is both measurable according to RECIST v1.1 and injectable (as assessed by the investigator, refer to Section A14–4.1.2.1 for further guidance)

  The injected lesion should not be the only measurable lesion
- Known hereditary bleeding diathesis or significant acquired coagulopathy at risk of bleeding (e.g., hemophilia, von Willebrand disease, cancer-associated diffuse intravascular coagulation) when only deep lesions are available for injection

- For procedures with moderate or significant risk of bleeding (deep lesions and/or organs), use of therapeutic doses of anticoagulants prior to the initiation of study treatment

    Long-acting agents such as aspirin or clopidogrel should be discussed on a case-by-case basis with the Sponsor and may need to be discontinued before the start of study treatment.

    Patients on preventive doses of LMWH or direct oral anticoagulant (DOAC) may be eligible if treatment can be suspended 24 hours (for LMWH) or 48 hours (for DOAC) prior to intratumoral injection and resumed 24 hours after the injection.

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a randomized, open-label study. After initial written informed consent has been obtained, prescreen testing (if applicable; see Section 4.5.2) has been completed, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and Stage 1 treatment assignment from the interactive voice or web-based response system (IxRS). Patients who enroll in Stage 2 will be assigned to treatment per investigator's choice if more than one treatment option is available and will retain the same patient identification number that was assigned in Stage 1.

For Stage 1, this study will employ a permuted-block randomization method with dynamically changing randomization ratios to account for fluctuation in the number of treatment arms that are open for enrollment over the course of the study. 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), with the stipulation that the likelihood of being allocated to control arm is no more than 35%. The randomization ratios may be altered to increase enrollment into a given experimental arm.

Randomization will take into account general exclusion criteria and arm-specific exclusion criteria as outlined in Sections 4.1.1 and 4.1.2. For example, the Atezo + *Regorafenib* arm will be removed as an option for patients who are ineligible for that arm. If a patient is only eligible for the control arm, the patient will not be enrolled in the study. If the Atezo + Idasa arm is open, the Sponsor may decide to limit randomization to the Atezo + Idasa arm and the regorafenib arm for patients who have a *TP53* wild-type status and are eligible for this arm.

If more than one mandatory serial-biopsy arm is open for enrollment at a time, eligible patients at participating sites will be assigned to one of the available arms by the Sponsor.

Patients 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 patients may be enrolled in Stage 1 to reach the target number of treated patients 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 and Table 6.

4.3.1 Investigational Medicinal Product Accountability

The IMPs for this study are atezolizumab, regorafenib, idasanutlin, AB928, and LOAd703.

All IMPs required for completion of this study will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (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 Inventory Log.

4.3.2 Post-Trial Access to Study Treatment

Currently, the Sponsor does not have any plans to provide study treatments or interventions to patients 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 web site:

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 (see Appendix 7 through Appendix 14).

4.5 STUDY ASSESSMENTS

A schedule of activities to be performed during the study is provided for each treatment arm in Appendix 7 through Appendix 14. All activities must be performed and

documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each infusion; 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 obtained before performing any study-related procedures (including prescreen testing [if applicable; see Section 4.5.2] and screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Written informed consent must also be obtained from patients before performing screening evaluations and study-related procedures for Stage 2.

Screening evaluations for Stage 1 and Stage 2 are to be performed within 28 days prior to initiation of study treatment (Day 1). All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment.

Patients who fail their first screening for study eligibility (Stage 1 or Stage 2) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the consent form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within a specified time prior to Day 1 (see the schedule of activities for each arm in Appendix 7 through Appendix 14) may be used; such tests do not need to be repeated for screening or re-screening.

4.5.2 Prescreen Testing for *TP53* Mutation Status for Atezo+Idasa Arm

If additional experimental treatment arms are open for enrollment, patients will proceed directly into screening after written consent for screening has been obtained (see Section 4.5.1). In addition, the option for prescreening for *TP53* mutation status may be available. By signing the prescreening consent form, patients may specifically allow for the collection and genetic testing of a fresh blood sample. Only if prescreening shows that there are no *TP53* alterations and the Atezo+Idasa arm is the only experimental arm open, patients may proceed to the 28-day screening period provided prior written consent for the screening of the study has been obtained (see Section 4.5.1).

4.5.3 Medical History, Molecular Profile, 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. The molecular profile of the patient's cancer, if available, will be recorded at screening and

updated whenever information becomes available during the study. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within a specified time prior to initiation of study treatment will be recorded (as outlined for each arm in Appendix 7 through 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/ethnicity.

4.5.4 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. 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.

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

4.5.5 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature.

Vital signs should be measured at specified timepoints, as outlined for each arm in the schedules of activities (see Appendix 7 through Appendix 14), and as clinically indicated.

4.5.6 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following initiation of combination treatment, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons

other than disease progression or loss of clinical benefit, even if they start new, non–protocol-specified anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). For patients eligible for Stage 2, tumor assessments performed prior to or at the time of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.

All measurable and/or evaluable lesions should be assessed and documented at screening (in both Stage 1 and Stage 2). Brain metastases treated with radiotherapy or surgery will not be considered measurable or evaluable but will be documented at screening as a site of metastatic disease. 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, pelvis, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head should be performed. A CT scan with contrast or MRI scan with contrast of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if contrast 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 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. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus subsequent 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). To facilitate evaluation of *post-progression tumor changes while treatment is ongoing*, tumor assessments must be continued after disease progression per RECIST v1.1 for patients who receive

treatment beyond progression. This includes continued measurement of target lesions, evaluation of non-target lesions (including monitoring for further worsening of any non-target lesions that have shown unequivocal progression), and evaluation of any newly identified lesions (including measurements, if lesions are measurable) at all subsequent assessments.

Overall response at a given timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Available results must be reviewed by the investigator before further dose administration.

4.5.7 Laboratory, Biomarker, and Other Biologic Samples

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide (as per standard of care for the region), glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST in all arms and CPK, lipase, and amylase in specified arms
- Coagulation: INR and aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- Ferritin (performed for specified arms only; details provided in schedules of activities)
- HIV serology, unless not permitted per local regulations
- HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- C-reactive protein
- Lactate dehydrogenase
- Carcinoembryonic antigen (CEA)
- Pregnancy test

All women of childbearing potential will have a serum pregnancy test at Stage 1 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 postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

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

  For patients in a bevacizumab- or regorafenib-containing arm, 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.

- For patients with unknown status: MSI/MSS and *BRAF* status through testing performed on tumor tissue collected at baseline

Samples for the following laboratory test will be sent to a central laboratory for analysis:

- Blood sample for blood-based NGS ctDNA assay performed by Foundation Medicine

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

- Archival or fresh tumor tissue sample collected at baseline for determination of PD-L1 expression and for exploratory research on biomarkers

  Baseline tumor tissue samples from the primary lesion or a metastatic lesion will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided that the tissue was obtained from a biopsy performed within 6 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy.

  A representative FFPE tumor specimen in a paraffin block (preferred) or *10–16* slides *(16 slides preferred)* containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

Tumor tissue from bone metastases that have been decalcified is not acceptable.

Remaining archival tumor tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first.

- Serum sample for analysis of autoantibodies: anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody in all arms

  The serum autoantibody sample collected at screening will be analyzed only if a patient experiences a suspected immune-related adverse event and the serum autoantibody results are positive during the treatment period.
- Plasma or serum samples for PK analysis (see Appendix 7 through Appendix 14)
- Plasma or serum samples for immunogenicity analysis (see Appendix 7 through Appendix 14)
- Plasma, serum, and peripheral blood mononuclear cell (PBMC) samples for exploratory research on biomarkers (see Appendix 7 through Appendix 14)
- Serum and urine samples, oral and rectal swabs for LOAd703 shedding analysis (see Appendix 14, Table 9)
- Mandatory serial-biopsy arms at participating sites: tumor tissue sample collected 4 weeks (±7 days) after initiation of Stage 1 treatment (if deemed clinically feasible by the investigator) for exploratory research on biomarkers

  Patient should have at least two accessible tumors that are amenable to excisional, punch, or core-needle biopsy (a minimum of three cores, 18-gauge needle or larger [16-gauge needle preferred]) without unacceptable risk of a major procedural complication. If it is planned that more than one biopsy will be obtained from a single lesion, the lesion should be large enough to permit successive biopsies ≥1 cm apart.
- Tumor tissue sample collected during Stage 1, at the time of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 for details) (if deemed clinically feasible by the investigator) for exploratory research on biomarkers

  Biopsies should be performed within 40 days after determination of unacceptable toxicity, disease progression, or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

Exploratory biomarker research may include, but will not be limited to, analysis of genes or gene signatures associated with tumor immunobiology, PD-L1, cytokines associated with T-cell activation, T-cell receptor repertoire, CEA, or density, localization, and activation status of immune cells and their subsets. *Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms,*

and other genomic variants; and genomic profiling through use of NGS of a comprehensive panel of genes. DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. NGS methods may include whole genome sequencing (WGS) or WES of tissue and blood samples, but WGS or WES of blood samples will be performed only at participating sites (see Section 4.5.9).

NGS may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator can obtain results from these analyses in the form of an NGS report, which is available upon request directly from Foundation Medicine. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results may not be available for samples that do not meet testing criteria.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum or plasma, and shedding samples collected for PK analysis, immunogenicity analysis, or LOAd703 shedding analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Plasma, serum, PBMC, and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the exception of the samples that undergo WES, which will be stored until they are no longer needed or until they are exhausted. However, the storage period for the WES samples will be in accordance with the Institutional Review Board or Ethics Committee (IRB/EC)-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

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

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

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

4.5.8 Electrocardiograms

An ECG will be performed at screening and as outlined for each arm in the schedules of activities (see Appendix 7 through Appendix 14). ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. It is recommended that patients 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 patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

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

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research may include exploration of germline 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 4.5.9) will not be applicable at that site.

Genomics is increasingly informing researcher's 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).

Data generated from blood samples collected for WGS or WES will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.10 Optional Tumor Biopsies

Consenting patients will undergo optional tumor biopsies 4 weeks (±7 days) after treatment initiation, or as otherwise indicated in the schedules of activities, and may undergo additional on-treatment biopsies at any other time at the investigator's discretion (if deemed clinically feasible by the investigator). Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies.

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

Samples may be used for exploratory biomarker research as described in Section 4.5.7. Refer to Section 4.5.7 for details on sample storage, use of samples after patient

withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 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 biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR 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 4.5.11) will not be applicable at that site.

4.5.11.3 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:

- Blood samples collected on Day 1 of Cycle 1 during Stage 1 and Stage 2
- Leftover blood, serum, plasma, PBMC, and tumor tissue samples (with the exception of leftover tissue from archival FFPE blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides) collected during Stage 1 or Stage 2 of the study, including leftover tissue samples from additional tumor biopsies or medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via WGS, NGS, or other genomic analysis methods.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

RBR specimens 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).

4.5.11.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

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

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

Data generated from RBR specimens 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.

4.5.11.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any

time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

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

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

4.5.11.6 Withdrawal from the Research Biosample Repository

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

If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from this study.

4.5.11.7 Monitoring and Oversight

RBR specimens 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 specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Experimental arms: loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details)
- Regorafenib control arm: radiographic disease progression per RECIST v1.1

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

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease or loss of clinical benefit may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities provided for each arm in Appendix 7 through Appendix 14.

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

4.6.2 Patient Discontinuation from Study

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

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

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

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

A safety plan for each treatment arm, including a summary of risks and management guidelines for patients who experience specific adverse events, is provided in the respective appendix for that treatment arm (see Appendix 7 through Appendix 14).

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to

and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

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 patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.

- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

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 (see Appendix 7 through 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 patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment, 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 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days (180 days for patients in the Atezo+LOAd703 arm; see Section A14-5.1) after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 8 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 8 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 (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 9):

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

Table 9 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related or Injection-Site 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 or injection should be captured on the Adverse Event eCRF *as a diagnosis (e.g., "infusion-related reaction," "injection-site 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 or Injection-Site Reaction eCRF *or Cytokine Release Syndrome eCRF*. If a patient 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 *associated* signs and symptoms also

recorded separately on the dedicated Infusion-Related or Injection 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 6.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related or injection reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be

recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), 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 mCRC 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 Metastatic Colorectal Cancer

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

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

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

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

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

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

5.3.5.12 Reporting Requirements for 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 patient, drug misuse could involve the drug being administered to someone other than the patient.

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 the IMPs studied in this trial (see Section 4.3.1), 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 the IMPs studied in this trial (see Section 4.3.1) 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 patient: 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 on both eCRF pages.

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 Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Primary Medical Monitor/ Roche Medical Responsible:	[redacted], M.D., Ph.D.
Email:	[redacted]
Mobile Telephone No.:	[redacted]
Backup Medical Monitor:	[redacted]
Email:	[redacted]
Mobile Telephone No.:	[redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, 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, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days (180 days for patients in the Atezo+LOAd703 arm; see Section A14-5.1) after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. 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 > 135 days (180 days for patients in the Atezo + LOAd703 arm; see Section A14-5.1) after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

Reporting requirements for pregnancies are described for each treatment arm in the respective appendix for that treatment arm (see Appendix 7 through Appendix 14).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, 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 adverse event reporting period (defined as 135 days [180 days for patients in the Atezo + LOAd703 arm; see Section A14-5.1] after the last dose of study treatment or until initiation of new, systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the

investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/*Special Situations* Form using the fax number or email address provided to investigators.

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Atezolizumab Investigator's Brochure
- Idasanutlin Investigator's Brochure
- AB928 Investigator's Brochure
- LOAd703 Investigator's Brochure
- Summary of Product Characteristics for regorafenib

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

The analysis results will be summarized by the treatment that patients actually received, as well as by stage (Stage 1 or Stage 2). Data will be described and summarized as warranted by sample size. Continuous variables will be summarized through use of means, standard deviations, medians, and minimum and maximum values. 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.

New baseline values will be established for the Stage 2 efficacy and safety analyses. For evaluation of tumor response, new baseline tumor assessments will be established as described in Section 4.5.6. For other endpoints (e.g., change from baseline in vital signs or laboratory test results), the last non-missing value prior to the patient's first dose during Stage 2 will serve as the new baseline.

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 efficacy, safety, and PK data on immunotherapy-based treatment combinations when administered to patients with mCRC who experienced disease progression during or following two lines of treatment for mCRC that consisted of fluoropyrimidine-, oxaliplatin-, or irinotecan-containing chemotherapy in combination with a biologic agent (e.g., bevacizumab, cetuximab), given in combination as two separate lines of therapy (in either order).

Approximately 111−382 patients will be randomly allocated to the control and experimental arms during the study.

Approximately 15 patients with serial biopsy samples will be enrolled in each mandatory serial-biopsy arm. However, the number of patients may be reduced if optional on-treatment biopsies have been collected (and determined to be evaluable) from consenting patients treated with that same CIT combination during the preliminary phase, to limit on-treatment biopsy collection to approximately 15 patients per CIT combination within each cohort.

With approximately 15 patients with serial biopsies in each arm, an 80% two-sided CI for a 30% increase in $CD8^+$ T cells in the center of the tumor would range from 22.8% to 37.2%, assuming a standard deviation of 0.20 for the difference in $CD8^+$ T cells between paired samples (i.e., baseline vs. on-treatment samples, baseline vs. post-progression samples, or on-treatment vs. post-progression samples).

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment will be summarized by region, country, and investigator by treatment arm within the two stages. Patient 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 within each stage.

For safety-evaluable patients, study drug administration data will be tabulated or listed by treatment arm within each stage, 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. Reasons for discontinuation of study drugs 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, primary tumor sidedness, and baseline ECOG Performance Status) will be summarized overall and by treatment arm within each stage.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is ORR during Stage 1, as defined in Section 2 (see Table 2). Patients with missing or no response assessments will be classified as non-responders.

ORR, defined as the proportion of patients with a complete or partial response, will be calculated for each arm, along with *95%* CIs (Clopper–Pearson exact method). The difference in ORR between the experimental arms and the corresponding control arm will also be calculated, along with *95%* CIs*, using normal approximation of the binomial distribution.*

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are progression-free survival (PFS), OS, OS at specific timepoints (e.g., 6 months), duration of response (DOR), and disease control rate (DCR) during Stage 1, as defined in Section 2 (see Table 2). PFS, DOR, and DCR are determined by the investigator according to RECIST v1.1.

DOR will be derived for efficacy-evaluable patients with a complete or partial response.

For patients who do not have documented disease progression or death in a study stage, PFS and DOR will be censored at the day of the last tumor assessment.

Patients 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 PFS, OS, and DOR, with *95%* CIs constructed through use of the Brookmeyer and Crowley method. OS rate at specific timepoints will also be estimated through use of the Kaplan-Meier method, with *95%* CIs calculated on the basis of the Greenwood estimate for the variance.

DCR, defined as the proportion of patients with stable disease for $\geq$12 weeks, a partial response, or a complete response, will be calculated for each treatment arm, with *95%* CIs estimated through use of the Clopper-Pearson exact method.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are ORR, PFS, DOR, and DCR *during Stage 2*, as determined by the investigator according to RECIST v1.1 (see Table 3).

Objective response, PFS, DOR, and DCR will be analyzed through use of the same methods described in Sections 6.4.1 and 6.4.2. DOR will be derived for efficacy-evaluable patients with a complete or partial response.

6.5 SAFETY ANALYSES

Verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v4.0.

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 within each stage.

Treatment-emergent adverse events occurring after initiation of treatment will be summarized. For each patient, 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, blood pressure, 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.

6.6 PHARMACOKINETIC ANALYSES

Sparse samples will be collected for PK analyses of atezolizumab (patients who receive at least one dose of atezolizumab) and drugs given in combination with atezolizumab (patients who receive at least one dose of the drug). Serum or plasma concentrations of the various study drugs will 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 will be plotted by treatment arm and cycle and day. PK data for combination drugs may be compared with available historical data from internal and published previous studies. Atezolizumab concentration data may be pooled with data from other studies using an established population PK model to derive PK parameters such as clearance, volume of distribution, and area under the curve.

6.7 IMMUNOGENICITY ANALYSES

Immunogenicity will be assessed for atezolizumab and other study treatments as appropriate (refer to arm-specific appendices for details). The immunogenicity analyses will include all patients with at least one anti-drug antibody (ADA) assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

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

For other study treatments where ADA is tested, positivity will be determined according to standard methods established in previous studies of that drug.

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

6.8 SHEDDING ANALYSES

The presence of LOAd703 viral particles in the oral cavity, feces and urine are evaluated at baseline and at different time points during and after LOAd703 treatments to understand possible shedding and route. The results will be compared to baseline levels and differences will be estimated.

6.9 BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of these biomarkers with response to study drugs, taking into account efficacy and safety endpoints.

6.10 INTERIM ANALYSES

It is anticipated that at least one interim analysis will be conducted over the course of the study, with the earliest interim analysis taking place when at least one experimental arm has completed enrollment in the preliminary phase and patients have been followed for a minimum of 6 weeks. A posterior probability will be used to guide further enrollment of 25 additional patients in the experimental arm. Enrollment may be expanded if the posterior probability of demonstrating a given improvement in ORR compared with the

control arm is greater than a prespecified threshold. The current considerations are an improvement in ORR of 10% compared with the control arm and a posterior probability of 70%.

An improvement of at least 10% in ORR as compared with control is considered clinically meaningful, and a posterior probability of 70% provides reasonable confidence that the difference will continue to be observed at the final analysis after completion of the expansion phase. If an improvement of at least 10% is not observed in a given arm, enrollment will either be stopped for futility or paused for further evaluation. The Sponsor may make a decision to expand enrollment in an arm based on the totality of available data including, but not limited to, duration of the observed responses, PFS, 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 patient 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 patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-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, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMPs, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

Roche will retain study data for 25 years after the final 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 applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) 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 patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their

consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

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

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

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

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

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

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

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

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

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., last patient, last visit).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 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, biomarker analyses, and PK analyses), as specified in Section 4.5.7. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC and an SOC will be employed to monitor and evaluate patient safety throughout the study (see Sections 3.1.4 and 3.1.5).

9.5 PUBLICATION 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, both at scientific congresses, in clinical trial registries of the U.S. National Institutes of Health and the

European Medicines Agency, 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, and redacted clinical study reports and other summary reports will be provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.6 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 patients 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) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

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

METHODS FOR ASSESSING LESIONS

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

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

Clinical Lesions

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

Chest X-Ray

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

CT and MRI Scans

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

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

non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

Endoscopy, Laparoscopy, Ultrasound, Tumor Markers, Cytology, Histology

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

ASSESSMENT OF TUMOR BURDEN

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

Identification of Target and Non-Target Lesions

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

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

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

but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

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

Calculation of Sum of Diameters

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

Measuring Lymph Nodes

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

Measuring Lesions That Become Too Small to Measure

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

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

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

Measuring Lesions That Split or Coalesce on Treatment

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

Evaluation of Non-Target Lesions

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

RESPONSE CRITERIA

Criteria for Target Lesions

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

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

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

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

Criteria for Non-Target Lesions

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the 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 patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

Criteria for Overall Response at a Single Timepoint

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

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

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

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

Missing Assessments and Not-Evaluable Designation

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

Special Notes on Response Assessment

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1.

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

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Appendix 2
Placeholder for Future Arm

The Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST) appendix has been removed as the Sponsor no longer plans to perform these analyses. Appendix 2 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 3
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 4
Preexisting Autoimmune Diseases and Immune Deficiencies

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

Autoimmune Diseases and Immune Deficiencies

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

Appendix 5
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

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

1. Stop the study treatment infusion.
2. Maintain an adequate airway.
3. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations.

Appendix 6
Risks Associated with Atezolizumab and Guidelines for Management of Atezolizumab-Specific Adverse Events

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

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

The investigator should consider the benefit–risk balance for a given patient prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

Guidelines for managing patients who experience selected adverse events are provided in the following sections. Management guidelines are presented by adverse event severity based on the National Cancer Institute Common Terminology Criteria for Adverse Events.

Pulmonary Events

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

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

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • *For Grade 1 pneumonitis, consider withholding atezolizumab.*
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events *or events with no improvement after 48–72 hours of corticosteroids,*, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day *IV methylprednisolone.* • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

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

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

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

Hepatic Events

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

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

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

Table 2 Management Guidelines for Hepatic Events

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

GI = gastrointestinal; LFT = liver function test.

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

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

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

Gastrointestinal Events

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

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

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

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

GI = gastrointestinal.

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

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

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

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

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

GI = gastrointestinal.

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

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

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

Endocrine Events

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

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

magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • *Consider patient referral to endocrinologist.* **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism. • *Consider patient referral to endocrinologist.*
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

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

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

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

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

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact 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.

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

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

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

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

Table 4 Management Guidelines for Endocrine Events (cont.)

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

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

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

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

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

Ocular Events

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

Table 5 Management Guidelines for Ocular Events

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

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

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

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

Immune-Mediated Myocarditis

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

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

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

Table 6 Management Guidelines for Immune-Mediated Myocarditis

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

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

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

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, anti-pyretics, 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 medical management of IRRs and CRS are provided in Table 7.

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

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

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** 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 Medical Monitor. [e] • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

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 Medical Monitor. [f] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

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

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

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

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

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

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

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *The* Medical Monitor *available to advise as needed*. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after *assessing* the benefit–risk ratio.

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

Pancreatic Events

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

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

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

GI = gastrointestinal.

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

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

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

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

GI = gastrointestinal.

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

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

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

Dermatologic Events

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

Table 9 Management Guidelines for Dermatologic Events

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

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

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

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

Neurologic Disorders

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

Table 10 Management Guidelines for Neurologic Disorders

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

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

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

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

Immune-Mediated Meningoencephalitis

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

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

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

Table 11 Management Guidelines for Immune-Mediated Meningoencephalitis

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

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

Renal Events

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as

non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

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

Table 12 Management Guidelines for Renal Events

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

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

Immune-Mediated Myositis

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

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

Table 13 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • 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 Medical Monitor. [c]

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

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

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

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

Hemophagocytic lymphohistiocytosis and Macrophage Activation Syndrome

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

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

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

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

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

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

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

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

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact 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; MAS = macrophage activation syndrome.

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Appendix 7
Study Details Specific to the Regorafenib Arm (Control)

TABLE OF CONTENTS

A7–1. MATERIALS AND METHODS SPECIFIC TO REGORAFENIB ARM

A7–1.1 TREATMENT IN REGORAFENIB ARM

A7–1.1.1 Formulation, Packaging, and Handling

For information on the formulation, packaging, and handling of regorafenib, refer to the local prescribing information.

A7–1.1.2 Dosage, Administration, and Compliance

Patients in the regorafenib arm will receive treatment as outlined in Table 1 until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). It is recommended that treatment be initiated no later than 7 days after randomization.

Table 1 Treatment Regimen for Regorafenib Arm

Cycle Length	Dose, Route, and Regimen
28 days	• Regorafenib 160 mg by mouth once daily on Days 1–21 • Dose escalation to 160 mg during Cycle 1 per institutional guidelines, e.g., from 80 mg in the first week followed by weekly dose increases to 120 mg in the second and 160 in the third week, is allowed.

Regorafenib will be used in the commercially available formulation.

Patients will receive regorafenib at the approved dose level of 160 mg (four tablets of 40 mg each) orally once daily on Days 1−21 of a 28-day cycle (see Table 1). This 4-week period is considered a treatment cycle.

Regorafenib should be taken at the same time each day. The tablets should be swallowed whole with water after a light meal that contains < 30% fat. An example of a light (low-fat) meal would include one portion of cereal (about 30 g), one glass of skimmed milk, one slice of toast with jam, one glass of apple juice, and one cup of coffee or tea (520 calories, 2 g fat).

Guidelines for regorafenib dose modification and treatment interruption or discontinuation because of toxicities are provided in Sections A7–2.1.2.1 and A7–2.1.2.2. Regorafenib treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. The highest dose of regorafenib studied clinically is 220 mg per day. The most frequently observed adverse drug reactions at this dose were dermatologic events, dysphonia, diarrhea, mucosal inflammation, dry mouth, decreased appetite, hypertension, and fatigue. There is no specific antidote for regorafenib overdose. In the event of suspected overdose, interrupt regorafenib, institute supportive care, and observe until clinical stabilization.

A7–1.1.3 Stage 2 Treatment

Patients who experience disease progression per RECIST v1.1 or unacceptable toxicity, may be eligible to receive a different treatment combination during Stage 2, provided a Stage 2 treatment is available for enrolment and they meet the eligibility criteria of that treatment regimen. Stage 2 treatment must begin within 3 months after the patient has experienced disease progression. It is recommended that patients begin Stage 2 treatment as soon as possible, but no earlier than 2 weeks after the last dose of treatment in Stage 1.

Tumor assessments performed prior to or at the time of disease progression during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table 2 Stage 2 Treatment Regimens Available for the Regorafenib Arm

Study Treatment	Appendix
No Stage 2 treatment currently available	—

A7–1.2 Concomitant Therapy for Regorafenib 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 patient 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.

Regorafenib is metabolized by CYP3A4, therefore concomitant use of strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort) and strong inhibitors of CYP3A4 activity (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) is to be avoided. For more detailed information on permitted, prohibited, or cautionary therapy, prohibited foods, and other restrictions (as applicable) for regorafenib, refer to the local prescribing information.

Regorafenib is metabolized by UGT1A1, and regorafenib and its metabolites are inhibitors of UGT1A1 and UGT1A9. Therefore, inhibitors of UGT1A1 (e.g., erlotinib, nilotinib, pazopanib, lapatinib, sorafenib) and substrates of UGT1A1 (e.g., irinotecan with its active metabolite SN-38, raltegravir, bazedoxifene, eltrombopag) and substrates of UGT1A9 (e.g., sorafenib, mycophenolic acid) should be used with caution. Also, patients receiving substrates of the BCRP transporter (e.g., methotrexate, fluvastatin, atorvastatin) should be monitored for signs and symptoms of increased exposure.

Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent as per Section 4.1.2.1, and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment. Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.

A7–1.3 Contraception Requirements for Regorafenib Arm

Contraception requirements for women and men in the regorafenib arm are outlined below:

- Women of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 2 months after the last dose of regorafenib. Women must refrain from breastfeeding during this same period of time.

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

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

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

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 2 months after the last dose of regorafenib to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

A7–2. ASSESSMENT OF SAFETY FOR REGORAFENIB ARM

A7–2.1 SAFETY PLAN FOR REGORAFENIB ARM

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Adverse events will be reported as described in Sections 5.2–5.6 in the protocol body.

A7–2.1.1 Risks Associated with Regorafenib

The overall safety profile of regorafenib is based on data from more than 4800 treated patients in clinical trials including placebo-controlled Phase III data for 636 patients with metastatic colorectal cancer, 132 patients with gastrointestinal (GI) stromal tumors, and 374 patients with hepatocellular carcinoma. The most serious adverse drug reactions in patients receiving regorafenib are severe liver injury, hemorrhage, GI perforation, and infection. The most frequently observed adverse drug reactions (≥30%) in patients receiving regorafenib are pain, hand-foot skin reaction, asthenia/fatigue, diarrhea, decreased appetite and food intake, hypertension, and infection.

Please refer to the regorafenib prescribing information for complete information regarding clinical safety.

A7–2.1.2 Management of Patients Who Experience Specific Adverse Events in Regorafenib Arm

A7–2.1.2.1 Dose Modifications

The dose of regorafenib can be reduced by decrements of 40 mg once a day (one dose level) up to two times for management of drug-related toxicities (i.e., from 160 to 120 mg and then from 120 to 80 mg). During the allowed dose escalation in Cycle 1 (Section A7–1.1.2), the continuation of a dose below 160 mg for more than 1 week for the management of drug-related toxicities is also allowed. If further dose reduction is indicated after two dose reductions, the patient must discontinue regorafenib. After dose reduction, the dose of regorafenib may be re-escalated at the investigator's discretion, provided there are no safety concerns.

A7–2.1.2.2 Treatment Interruption for Toxicities

Regorafenib treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table 3). If regorafenib has been withheld for >42 days because of toxicity, the patient should be discontinued from regorafenib.

Refer to Section A7–1.1.2 for information on dose interruptions for reasons other than toxicity (e.g., surgical procedures).

A7–2.1.2.3 Management Guidelines for Adverse Events

Toxicities associated or possibly associated with regorafenib treatment should be managed according to standard medical practice. Guidelines for the management of patients who experience adverse events are provided in Table 3. Please refer to the regorafenib prescribing information for further guidance.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in the Regorafenib Arm

Event	Action to Be Taken
Dermatologic toxicity (hand-foot skin reaction/ palmar-plantar erythrodysesthesia)	
Dermatologic event, Grade 1	• Continue regorafenib at the same dose level. • Immediately institute supportive measures for symptomatic relief.
Dermatologic event, Grade 2	• First occurrence: Decrease dose by one level and immediately institute supportive measures. • If no improvement occurs despite dose reduction, withhold regorafenib for a minimum of 7 days until toxicity resolves to Grade ≤ 1. • A dose re-escalation is permitted at the investigator's discretion. • If no improvement within 7 days or second occurrence: Withhold regorafenib for a minimum of 7 days until toxicity resolves to Grade ≤ 1. • When restarting treatment, decrease dose by one level. • A dose re-escalation is permitted at the investigator's discretion. • Third occurrence: Withhold regorafenib for a minimum of 7 days, until toxicity resolves to Grade ≤ 1. • When restarting treatment, decrease dose by one level. • A dose re-escalation is permitted at the investigator's discretion. • Fourth occurrence: Discontinue regorafenib permanently.
Dermatologic event, Grade 3 or 4	• First occurrence: Institute supportive measures immediately and withhold regorafenib for a minimum of 7 days until toxicity resolves to Grade ≤ 1. • When restarting treatment, decrease dose by one level. • A dose re-escalation is permitted at the investigator's discretion. • Second occurrence: Institute supportive measures immediately and withhold regorafenib for a minimum of 7 days, until toxicity resolves to Grade ≤ 1. • When restarting treatment, decrease dose by one level. • Third occurrence: Discontinue regorafenib permanently.

GI = gastrointestinal; ULN = upper limit of normal.

[a] Resumption of regorafenib may be considered in patients who are deriving benefit at the investigator's discretion if the potential benefit outweighs the risks.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in the Regorafenib Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin	
$\leq 5 \times$ ULN elevations in ALT/AST (maximum Grade 2)	• Continue regorafenib treatment. • Monitor liver function weekly until transaminases return to < 3 ULN (Grade 1) or baseline.
$> 5 \times$ ULN but $\leq 20 \times$ ULN elevations in ALT/AST (Grade 3)	• First occurrence: Withhold regorafenib treatment. • Monitor liver function weekly until transaminases return to < 3 ULN (Grade 1) or baseline. • If restarting treatment [a], decrease dose by one level and monitor liver function weekly for at least 4 weeks. • Re-occurrence: Discontinue regorafenib permanently.
$> 20 \times$ ULN (Grade 4) elevations in ALT/AST	• Discontinue regorafenib permanently.
$> 3 \times$ ULN (Grade 2 or higher) with concurrent bilirubin $> 2 \times$ ULN elevations in ALT/AST	• Discontinue regorafenib permanently. • Monitor liver function weekly until resolution or return to baseline. • Exception: Patients with Gilbert syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.
Infection	
Grade 3 or 4 infections, or worsening infection of any grade	• Withhold regorafenib treatment. • Resume regorafenib at the same dose following resolution of infection.
Hemorrhage	
Grade 3 or 4 hemorrhage	• Discontinue regorafenib permanently. [a] • Monitor INR levels more frequently in patients receiving warfarin.
GI perforation or fistula	
Any GI perforation or fistula	• Discontinue regorafenib permanently.

GI = gastrointestinal; ULN = upper limit of normal.

[a] Resumption of regorafenib may be considered in patients who are deriving benefit at the investigator's discretion if the potential benefit outweighs the risks.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in the Regorafenib Arm (cont.)

Event	Action to Be Taken
Hypertension	
General guidance	• Grade 2 or above, start antihypertensive therapy.
Hypertension, Grade 2	• Withhold regorafenib treatment. • Once blood pressure is < 150/100 mmHg, patient may continue regorafenib treatment, and consider reducing dose by one level at the investigator's discretion.
Hypertension, Grade 3	• If blood pressure is not controlled to 150/100 mmHg with medication, discontinue regorafenib.
Hypertension, Grade 4 (includes hypertensive crisis and hypertensive encephalopathy)	• Discontinue regorafenib permanently. [a]
Cardiac ischemia and infarction	
New or acute onset cardiac ischemia or infarction	• Withhold regorafenib treatment. • Resume regorafenib only after resolution of acute cardiac ischemic events and if the potential benefits outweigh the risks of further cardiac ischemia.
Reversible posterior leukoencephalopathy syndrome	
Reversible posterior leukoencephalopathy syndrome	• Discontinue regorafenib permanently.
Wound dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	• Discontinue regorafenib permanently.
Regorafenib-related toxicities not described above	
Grade 1 or Grade 2 (tolerable)	• Continue regorafenib treatment at the same dose.
Grade 2 (intolerable) or Grade 3	• First occurrence: Withhold regorafenib until toxicity resolves to Grade ≤ 1. • When restarting treatment, decrease dose by one level. • Second occurrence: Withhold regorafenib until toxicity resolves to Grade ≤ 1. • When restarting treatment, decrease dose by one level. • Third occurrence: Consider permanent discontinuation.
Grade 4	• Discontinue regorafenib permanently. [a]

GI = gastrointestinal; ULN = upper limit of normal.

[a] Resumption of regorafenib may be considered in patients who are deriving benefit at the investigator's discretion if the potential benefit outweighs the risks.

A7–2.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR REGORAFENIB 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 in the protocol body for reporting instructions). Adverse events of special interest for the regorafenib arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7 in the protocol body)
- 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.

A7–2.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN REGORAFENIB ARM

A7–2.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 2 months after the last dose of regorafenib. 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 regorafenib and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A7–2.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 2 months after the last dose of regorafenib. 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 patient exposed to regorafenib. 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 patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A7–2.3.3 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 in the protocol body).

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.

A7–2.3.4 Congenital Anomalies/Birth Defects

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

A7–3. SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR REGORAFENIB ARM

Table 4 Schedule of Activities for Regorafenib Arm

Assessment/Procedure	Screening Days –28 to –1	Treatment Cycles (28-Day Cycles) [a]								Stage 2 Screen. [c] or Treat. Discon. [d]	Follow-Up Every 3 Months (±7 days)
		Cycle 1 [b]				Cycle 2			Cycles ≥3		
		Days				Days					
		1	8 (±3 d)	15 (±3 d)	22 (±3 d)	1 (±3 d)	8 (±3 d)	15 (±3 d)	Day 1 (±3 days)		
Molecular profile of CRC (if available)	See Appendix 15	Whenever updated information becomes available									
Vital signs [e]		x [f]	x [f]	x [f]	x [f]	x [f]	x [f]		x	x	
Weight		x [g]				x [g]			x [g]	x	
Height											
Complete physical examination [h]										x	
Limited physical examination [i]		x [g]				x [g]			x [g]		
ECOG Performance Status		x [g]				x [g]			x [g]	x	
ECG [j]		Perform as clinically indicated [g]								x [k]	
Hematology [l]		x [m, n]				x [m]			x [m]	x	
Chemistry		x [m, n, o]		x [m, p]		x [m, o]		x [m, p]	x [m, o]	x [o]	
Coagulation (INR and aPTT) [q]		x [m, n]				x [m]			x [m]	x [k]	
TSH, free T3 (or total T3), and free T4 [r]										x [k]	
Viral serology [s]										x [k]	
C-reactive protein										x [k]	
Plasma CEA [t]		x [m]							x [m, t]		

Table 4 Schedule of Activities for Regorafenib Arm (cont.)

Assessment/Procedure	Screening Days –28 to –1	Treatment Cycles (28-Day Cycles) [a]								Stage 2 Screen. [c] or Treat. Discon. [d]	Follow-Up Every 3 Months (±7 days)
		Cycle 1 [b]				Cycle 2			Cycles ≥3		
		Days				Days					
		1	8 (±3 d)	15 (±3 d)	22 (±3 d)	1 (±3 d)	8 (±3 d)	15 (±3 d)	Day 1 (±3 days)		
LDH	See Appendix 15									x [k]	
Pregnancy test [u]		x [m]				x [m]			x [m]	x	x [u]
Urinalysis [v]		x				x			x	x [k]	
Serum autoantibody sample [w]										x [k]	
Blood sample for RBR (optional) [x]		x									
Plasma, serum, and PBMC samples for biomarkers		Refer to Table 5 below									
Tumor biopsy		x [y]									
Tumor biopsy (optional)		x [z]									
Tumor response assessments		x [aa, bb, cc]									
Concomitant medications [dd]		x				x			x	x	
Adverse events [ee]		x	x	x	x	x	x	x	x	x [ee]	x [ee]
Dispense regorafenib [ff, gg]		x				x			x		
Survival follow-up and anti-cancer treatment											x [hh]

CEA = carcinoembryonic antigen; CRC = colorectal cancer; CT = computed tomography; d = days; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LDH = lactate dehydrogenase; PBMC = peripheral blood mononuclear cell; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen. = screening; T3 = triiodothyronine; T4 = thyroxine; Treat. = treatment; TSH = thyroid-stimulating hormone.

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

Table 4 Schedule of Activities for Regorafenib Arm (cont.)

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

[b] It is recommended that treatment be initiated no later than 7 days after randomization.

[c] Patients who experience disease progression per RECIST v1.1 or unacceptable toxicity will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.2 in the protocol body provided Stage 2 is open for enrollment) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which disease progression is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments after completing the treatment discontinuation visit.

[e] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[f] Monitor vital signs weekly for the first 6 weeks and then on Day 1 of every cycle thereafter.

[g] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[h] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[j] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[k] Assessments to be performed only for patients undergoing Stage 2 screening.

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

[m] *Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.*

[n] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

Table 4 Schedule of Activities for Regorafenib Arm (cont.)

[o] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide (per standard of care in the region), glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Additionally, CPK, amylase, and lipase will be performed on Day 1 of each cycle.

[p] Only liver function (ALP, ALT, AST, and total bilirubin) will be tested on Day 15 of Cycles 1 and 2.

[q] Monitoring of INR/aPTT should be performed more frequently if clinically indicated.

[r] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening.

[s] At Stage 2 screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[t] CEA will be assessed on Day 1 of Cycle 1 and every 2 cycles thereafter (i.e., Cycles 3, 5, 7, etc.) until disease progression.

[u] 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 and at 3 months and 6 months after treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[v] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. Patients with $\geq$ 2+ protein on dipstick urinalysis must undergo a 24-hour urine collection and demonstrate $<$ 3.5 g of protein in 24 hours.

[w] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[x] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate. RBR sample should be collected prior to study treatment.

[y] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or disease progression per RECIST v1.1, if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or disease progression, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.7 in the protocol body for tissue sample requirements.

[z] Consenting patients will undergo optional tumor biopsy sample collection 4 weeks ($\pm$7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[aa] Patients will undergo tumor assessments at baseline, every 6 weeks ($\pm$1 week) for the first 48 weeks following treatment initiation, and every 12 weeks ($\pm$2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1. Tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression, even if they start new non–protocol-specified anti-cancer therapy.

Table 4 Schedule of Activities for Regorafenib Arm (cont.)

[bb] All measurable and/or evaluable lesions should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head CT 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).

[cc] For patients who undergo screening for Stage 2, tumor assessments performed prior to or at the time of disease progression during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

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

[ee] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6 in the protocol body). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[ff] Patients will receive regorafenib at a dose of 160 mg (four tablets) orally once a day on Days 1–21 of each cycle. At least 7 days off regorafenib are required prior to starting a new treatment cycle. Dose escalation to 160 mg during Cycle 1 per institutional guidelines is allowed. Regorafenib should be taken approximately the same time each day and no later than 12 hours after the scheduled time. The tablets should be swallowed whole with water and a light meal (< 30% fat).

[gg] Treatment will continue until unacceptable toxicity or disease progression per RECIST v1.1 (see Section 3.1.1 in the protocol body for details).

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

Table 5 Schedule of Biomarker Samples for Patients Treated with Regorafenib

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 2	Prior to study treatment	• Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 4	Prior to study treatment	• Biomarkers (plasma, serum)
Day 1 of Cycle 8	Prior to study treatment	• Biomarkers (plasma, serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Biomarkers (plasma, serum)

PBMC = peripheral blood mononuclear cell.

Note: No pharmacokinetic samples are being collected for this treatment arm.

Appendix 8
Placeholder for Future Arm

The atezolizumab plus Imprime PGG plus bevacizumab (Atezo +Imprime +Bev) arm has been removed because enrollment and patient follow-up has been completed for that arm, and the content of Appendix 8 (previously entitled "Study Details Specific to the Atezo +Imprime +Bev Arm") has been deleted. Appendix 8 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 9
Placeholder for Future Arm

The atezolizumab plus isatuximab (Atezo + Isa) arm has been removed because enrollment and patient follow-up has been completed for that arm, and the content of Appendix 9 (previously entitled “Study Details Specific to the Atezo + Isa Arm”) has been deleted. Appendix 9 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 10
Placeholder for Future Arm

The atezolizumab plus selicrelumab plus bevacizumab (Atezo + seli + bev) arm has been removed because enrollment and patient follow-up has been completed for that arm, and the content of Appendix 10 (previously entitled “Study Details Specific to Atezo + seli + bev Arm”) has been deleted. Appendix 10 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 11
Study Details Specific to Atezo+Idasa Arm

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A11–1 BACKGROUND FOR ATEZO+IDASA ARM

A11–1.1 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 CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody mediated clearance of activated effector T cells.

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

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

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

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

A11–1.2 BACKGROUND ON IDASANUTLIN

Idasanutlin belongs to a class of small-molecule compounds, termed nutlins, and was identified as a potent and selective inhibitor of the p53-murine double minute 2 (MDM2) interaction (Vassilev et al. 2004) with a median inhibitory concentration [IC50] of 17 nM. Idasanutlin binds to the surface of MDM2 in the p53-binding pocket, thus preventing the p53-MDM2 protein-protein interaction (Kussie et al. 1996).

In nonclinical models, exposure of solid tumor cell lines expressing functional p53 to idasanutlin resulted in a dose-dependent stabilization and accumulation of p53 protein and activation of p53 and its transcriptional targets. This in turn led to inhibition of proliferation and/or apoptosis. In vivo, idasanutlin, as a single agent, demonstrated

anti-tumor activity in an established osteosarcoma xenograft model, increased efficacy and survival when given in combination with cytarabine in an acute myeloid leukemia (AML) model in immunodeficient mice, and increased efficacy when given in combination with obinutuzumab in a non-Hodgkin lymphoma (NHL) model in immunodeficient mice.

Idasanutlin has been investigated as a single agent in patients with solid tumors in three Phase I Studies: NP27872 (99 patients), NP28902 (61 patients), and NP29910 (8 patients) and in a Phase I study in 122 patients with AML (NP28679). A bioequivalence study in patients with solid tumors (Study NP39051) and a single-agent Phase I/II study in patients with polycythemia vera (NP39761) are ongoing. Idasanutlin is also currently being investigated in combination with cytarabine in fit patients with relapsed or refractory (R/R) AML in a Phase III study (WO29519) and in combination with venetoclax in a Phase Ib/II study (GH29914) in unfit patients with R/R AML. In addition, two Phase Ib/II studies are being conducted in combination with obinutuzumab or rituximab (Study BH29812) and in combination with obinutuzumab or rituximab and venetoclax (Study BH39174) in patients with follicular lymphoma and diffuse large B-cell lymphoma.

The majority of the adverse events recorded for idasanutlin treatment are transient in nature and reversible.

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

A11–2 RATIONALE FOR ATEZO+IDASA ARM

A11–2.1 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, urothelial carcinoma, renal cell carcinoma, melanoma, CRC, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

Early clinical data had shown encouraging results with the anti–PD-1 checkpoint inhibitor pembrolizumab as a single agent in patients with mCRC assessed as having high microsatellite instability (MSI-H) status but not with microsatellite stable (MSS) status (Le et al. 2015). These data resulted in the May 2017 approval of pembrolizumab in adult and pediatric patients with tumors characterized as MSI-H or deficient for mismatch repair genes based on objective response rate (ORR) and durability of the response. ORR was similar irrespective of whether patients were diagnosed with CRC (36%) or a different cancer type (46% across the 14 other MSI-H cancer types). Similar response rates were observed in patients with second line or later mCRC enrolled in a Phase Ia study investigating atezolizumab as single agent (Roche Study PCD4989g) and a Phase Ib study investigating the combination of atezolizumab plus bevacizumab (Roche Study GP28328, Arm A). In Study PCD4989g, there was 1 responder reported in 14 patients with MSS status per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). In the 10 patients with MSI-H status enrolled in Study GP28328, the investigator assessed confirmed ORR per RECIST v1.1 was 40% (95% CI: 12.2, 73.8), with all 4 responders having partial responses. No objective responses were seen in the 14 patients with MSS tumors.

A11–2.2 MDM2 ANTAGONISM

MDM2 was identified as a major negative regulator of the tumor suppressor p53. p53 is a transcription factor whose best understood function is the ability to arrest or eliminate cells in response to DNA damage or other cellular stresses (e.g., dysregulated oncogenes) that can promote malignant transformation. In response to cellular stress, p53 regulates the expression of cell cycle and survival genes, the end result of which is either transient cell cycle arrest, senescence, or apoptosis, depending on the nature and the severity of the stress, the cell type and genetic context (Kastenhuber and Lowe 2017).

While *TP53* is the most frequently mutated gene in human cancer, around 50% of cancers retain wild-type p53 (Kastenhuber and Lowe 2017), including approximately 22%

of CRC tumors (based on an unpublished *TP53* mutation analysis in the IMblaze 370 trial). In these tumors, amplification of the MDM2 gene or overexpression of the MDM2 protein was frequently found (Wade et al. 2013), and the interaction between MDM2 and p53 is considered to be the primary mechanism for inhibition of the p53 function (Wade et al. 2013).

MDM2 inhibits p53 activity by interfering with p53 transactivation function and targeting it for degradation by the ubiquitin-proteasome system (Shangary and Wang. 2008). This keeps p53 levels and activity low in unstressed cells. In the presence of cellular stress, p53 becomes rapidly stabilized by a mechanism that prevents its interaction with MDM2. p53 then accumulates in the nucleus and activates the transcription of the MDM2 gene. Subsequently, MDM2 inactivates p53, which results in a dampening of p53 back to baseline levels, establishing a feedback loop that prevents the potential detrimental effects of excessive p53 activation. In tumors that overexpress MDM2, this negative feedback loop is disrupted and stress-induced p53 activation mechanisms become insufficient to overcome the negative control of MDM2, resulting in unrestrained proliferation of cancer cells. Therefore, blocking the p53-MDM2 interaction is expected to restore p53 function, resulting in effective proliferation inhibition and/or killing of wild-type p53 cancer cells.

In addition to its tumor cell intrinsic effects, several lines of evidence indicate that p53 can contribute to anti-cancer immunity through different mechanisms. First, as mentioned above, p53 can induce cellular senescence, which is a tumor-suppressive program that involves stable cell-cycle arrest and secretion of a variety of immune modulators and inflammatory cytokines (Coppe 2008). The latter property, called Senescence Associated Secretory Phenotype (SASP), turns senescent cells into proinflammatory cells. Accordingly, the ability of the p53-driven senescence program to elicit an anti-tumor immune response was demonstrated in a mouse model of RAS driven liver carcinoma in which endogenous p53 expression was conditionally regulated by RNA interference (RNAi). Reactivation of endogenous p53 in p53-deficient tumors, led to complete tumor regression. Importantly, the primary tumor cell response was senescence, which was associated with the clearance of the senescent tumor cells by components of the innate immune system, including macrophages, neutrophils, and NK cells (Xue et al. 2007). Subsequent work focusing on the role of NK cells showed that the elimination of senescent tumor cells was dependent on p53-induced secretion of the chemokine CCL2, a potent chemoattractant for NK cells. p53-driven senescent tumor cells also upregulated cytokines known to activate NK cells, such as interleukin (IL)-12, IL-15, and IL-18 (Iannello et al. 2013). As nutlin was shown to induce a senescence-like state in p53 wild-type solid tumor cell lines (Shen and Maki 2010), MDM2 antagonism has the potential to re-establish the p53-mediated senescence program and promote an innate immune tumor attack in patients with p53 wild-type cancers.

More recent work has expanded the role of p53 in anti-tumor immunity to actions in the immune cells themselves. Intra-tumoral injection of nutlin-3a was shown to result in complete tumor regression and resistance to tumor re-challenge, indicating the establishment of an anti-tumor immune memory. This effect was dependent on p53 expression in immune cells and relied on two p53-driven effects: the induction of tumor cell immunogenic cell death (ICD) and a reduction in the number and function of tumor-infiltrating myeloid-derived suppressor cells (MDSCs) (Guo et al. 2017).

Moreover, p53 was shown to promote the differentiation of myeloid cells into immune cells with cross-presenting properties that are considered to be required for turning a cold tumor microenvironment into an inflamed one. A particular type of dentritic cell (DC), called a type 1 conventional dendritic cell (cDC1, also known as CD103+ DC in mice or CD141+ DC in humans), is capable of cross-presenting tumor antigens to activate naive CD8+ T cells and therefore is considered to be essential for the establishment of adaptive anti-tumor immunity and response to cancer immunotherapy (Broz et al. 2014, Barry et al. 2018). The cDC1 cells derive from a common DC progenitor. A recent study identified a phenotypically similar CD103+ DC population (defined as Ly6c+ CD11c+ CD103+) emerging in a mouse melanoma model treated by a combination of cyclophosphamide (which induces ICD) and a T–regulatory cell targeting drug. In contrast to cDC1, this DC subset was shown to stem from from monocyte precursors and tumor-associated MDSCs. Importantly the emergence of the Ly6c+ CD11c+ CD103+ cells was dependent on p53, as conditional deletion of *TP53* in the myeloid compartment resulted in the complete absence of these cells from the tumor and the loss of therapeutic efficacy of the chemo-immunotherapy combination. Conversely, inducing p53 using nutlin-3a was synergistic with checkpoint blockade in an otherwise CPI resistant mouse melanoma model (Sharma et al. 2018). Thus p53-driven differentiation of a cross-presenting, DC-like subpopulation and the resulting anti-tumor adaptive immune response represents yet another mechanism by which MDM2 antagonism can promote anti-tumor immunity.

A11–2.3 RATIONALE FOR COMBINING IDASANUTLIN WITH CHECKPOINT INHIBITION

As discussed above, by promoting senescence of tumor cells, idasanutlin is expected to initiate a NK cell response that is likely to be reinforced by PD-L1 blockade. Indeed, increased PD-1 expression was observed in peripheral and tumor-infiltrating NK cells in patients with GI tumors, including CRC (Liu et al. 2017). Moreover, PD-1 was shown to function as a checkpoint for NK cells, and PD-1 blockade in tumor models, whose tumor surveillance was dependent on NK cells, showed significant anti-tumor activity (Hsu et al. 2018).

Furthermore, idasanutlin has been shown to promote the differentiation of myeloid cells to antigen presenting cells that are capable of antigen cross presentation to CD8+

T cells thereby initiating an anti-tumor response. This mechanism of action could restore antigen presentation and T-cell priming, which are steps that are considered to be missing in MSS CRC, resulting in resistance to immune checkpoint inhibitors (Legitimo et al., 2014). The tumor-specific, cytotoxic CD8+ T-cells thus primed will eventually experience T-cell exhaustion due to the negative feedback regulation by the PD-1/PD-L1 axis that invariably occur in the tumor bed (Ribas and Wolchok 2018), an effect that can be counteracted by PD-L1 blockade.

Therefore, the two key effectors of the anti-tumor immunity activated by idasanutlin–NK cells and CD8+ T-cells are expected to act synergistically to initiate an anti-tumor immune response. In order to prevent the exhaustion of activated NK cells and T-cells, resulting from the upregulation of the PD1/PDL1 axis, idasanutlin will be combined with atezolizumab to promote a sustainable immune response.

A11–2.4 BENEFIT–RISK ASSESSMENT

This study will enroll patients with mCRC who have become refractory to first- and second-line standard therapies. This patient population has a median OS of less than 6 months with currently available treatments. Treatment options have shown limited efficacy and are often poorly tolerated.

Despite the success of single agent checkpoint inhibition (CPI) in the MSI-H patient population, the vast majority of CRC patients have MSS tumors and do not respond to single agent CPI, highlighting the need for safe and effective combination treatments. As discussed in detail above, the combination of idasanutlin and atezolizumab is expected to boost anti-cancer immunity in this patient population with high unmet medical need by mobilizing two key effectors of the anti-tumor immune response, NK-cells and CD8+ T-cells, providing the necessary ground for anti–PD-L1 efficacy.

As of 13 September 2018, a total of 205 adult patients with solid tumors have been treated with idasanutlin in four studies (NP27872, NP28902, NP29910, and NP39051), which tested a dose range of 100 mg to 3200 mg. Across these four studies in solid tumors, 97% of patients had at least one adverse event with an incidence rate of at least 10%. Diarrhea, nausea, vomiting, decreased appetite, and fatigue were the most frequently reported adverse events. The most common (≥30%) treatment-related adverse events were diarrhea, nausea, and vomiting.

Grade ≥3 adverse events were reported in 50% of patients, most commonly within the system organ classes of blood and lymphatic system disorders, gastrointestinal (GI) disorders, and metabolism and nutrition disorders. Thrombocytopenia, anemia, neutropenia, and nausea were the most common (≥5% of patients) Grade ≥3 adverse events reported. Serious adverse events were reported in 26% of patients in the pooled dataset. The most commonly reported serious adverse events (≥2% of patients) were

thrombocytopenia (6.3%), febrile neutropenia (2.4%), pyrexia (2.4%), and anemia (2.0%). In 14% of patients, serious adverse events were considered related to idasanutlin, with the most commonly reported (≥2% of patients) being thrombocytopenia (6.3%) and febrile neutropenia (2.4%). A total of 13 patient deaths were recorded across all four studies, of which 9 deaths were attributed to progressive disease. Of the remaining 4 deaths, 1 death was considered remotely related to idasanutlin (pulmonary embolism); the other three deaths were considered unrelated (intracranial hemorrhage, intra-abdominal hemorrhage, and aspiration pneumonia).

The majority of the adverse events recorded for idasanutlin treatment are transient in nature and reversible. Clinical experience to date suggests that there is a dose-relationship for idasanutlin and GI adverse events, with an increased incidence of nausea, vomiting, and diarrhea at higher dose levels. Cytopenias, manifesting as thrombocytopenia and neutropenia, are expected to occur at higher dose/exposure levels and appears to be related to toxicity on normal early hematopoietic progenitors. Frequent monitoring of hematologic values (count of blood cells, including differential) is therefore required. The doses of idasanutlin that are planned to be administered in this study (150 mg and 200 mg) are lower than the maximum tolerated dose (MTD) in solid tumor patients (250 mg) (See Section A11–3.2).

Regarding clinical activity, the best overall response to idasanutlin monotherapy in solid tumors was stable disease (SD), with SD rates ranging from 30.6% (Study NP27872) to 41.1% (Study NP28902). The median duration of stable disease was 72.5 days, ranging from 8 days to 696 days (Study NP27872). The observed clinical activity is consistent with idasanutlin monotherapy acting mostly as a cytostatic agent in solid tumors.

Safety data are available for single-agent atezolizumab in patients with solid tumors, including CRC. Potential overlapping toxicities with idasanutlin may occur within the system organ class of GI disorders, respiratory, blood and lymphatic system and hepatobiliary disorders. The relevant corresponding overlapping toxicities of atezolizumab include colitis, pneumonitis, autoimmune hemolytic anemia, thrombocytopenia and hepatitis, all of which are considered to be immune related. Given the distinct mechanisms of action of atezolizumab and idasanutlin, it is anticipated that adverse reactions observed with either agent will not result in additive and/or synergistic toxic effects.

In summary, the investigation of the safety of each molecule as a single agent in patients with solid tumors has not revealed findings that would prohibit the investigation of the idasanutlin and atezolizumab combination in the setting of a Phase Ib/II study. Given the high unmet medical need in third line CRC for well tolerated and effective treatments, the rationale for the combination of atezolizumab and idasanutlin, and the anticipated safety profile of the combination, the benefit–risk profile is considered positive.

For the evaluation of the impact of the *coronavirus disease 2019 (*COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.4.

A11–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+IDASA ARM

A11–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 840 mg every 2 weeks (Q2W) (840 mg on Days 1 and 15 of each 28-day cycle). The average concentration following the 840 mg Q2W dosage is expected to be equivalent to that of 1200 mg every 3 weeks (Q3W), an approved dosage for atezolizumab, as outlined in the prescribing information. Anti-tumor activity has been observed across doses ranging from 1 to 20 mg/kg Q3W. In Study PCD4989g, the MTD of atezolizumab was not reached and no dose-limiting toxicities (DLTs) were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A11–3.2 RATIONALE FOR IDASANUTLIN DOSE AND SCHEDULE

During Phase I development, two different formulations of idasanutlin were tested: a microprecipitated bulk powder (MBP) formulation and a spray-dried powder (SDP) formulation. The choice of the idasanutlin dose regimen for this study is based on the experience with the initial MBP formulation in single-agent testing (Studies NP27872 and NP28902) in patients with solid tumors in the evaluation of the combination with 1 g/m^2 cytarabine in Study NP28679 in patients with AML and the bioequivalence study with the SDP formulation NP28902.

Serum levels of macrophage inhibitory cytokine (MIC-1), a secreted protein that is strongly induced by activated p53, were used to assess the pharmacodynamic effects of the idasanutlin MBP formulation in Studies NP27872 and NP28679. Analysis of patients treated with a tested dose range of 100 to 3200 mg/day of idasanutlin showed an exposure-related increase in MIC-1 response. A comparison of MIC-1 elevation between different idasanutlin dosing schedules (all administered in a 28-day cycle) showed that daily schedules were more effective at inducing MIC-1 than a weekly schedule. In contrast to the once daily for 5 days (QD $\times$ 5d) regimen, the once daily for 3 days regimen did not achieve steady-state exposure, did not alleviate thrombocytopenia, and patients did not achieve as long a duration of stable disease. Therefore, the QD $\times$ 5d regimen, followed by a 23-day drug-free interval (QD $\times$ 5d Q4W) was chosen for future clinical trials.

Clinical pharmacokinetic (PK) data showed approximate dose-proportionality in the exposure parameter of area under the concentration–time curve from 0 to 24 hours

($AUC_{0—24}$) on Day 5 of the QD × 5d schedule for the test range of 100 to 2400 mg/day with inter-patient variability of approximatively 40%–50%. The half-life ($T_{1/2}$) of idasanutlin is approximatively one day, and there were no major effects of high-fat or low-fat food on PK exposure.

In Study NP27872 of patients with solid tumors, the QD × 5d Q4W MTD for the MBP formulation was determined to be 500 mg. Thrombocytopenia, neutropenia, febrile neutropenia, and diarrhea were dose-limiting toxicities (DLTs). In Study NP28679, the lowest dose where responses were seen in AML was 400 mg of the MBP formulation in combination with cytarabine 1 g/m^2 and this dose proved to have an acceptable safety profile.

The alternative drug formulation SDP of idasanutlin was developed to improve drug substance stability and chosen for all future studies, including Study CO39612. PK data from a relative bioavailability study (NP28902, Part 2) demonstrated that the SDP formulation has an increase in the maximum concentration (C_{max}) and exposure (AUC) of 47% and 42%, respectively, compared with the MDP formulation. Therefore, the exposure achieved by the SDP formulation is considered to be approximatively twice the exposure achieved with the MDP formulation, and the resulting SDP equivalent of the MTD determined for the QD × 5d Q4W schedule in the solid tumor Study NP27872 is determined to be 250 mg.

Based on the above information, idasanutlin will be administered orally at a dose of 200-mg QD × 5d Q4W (SDP formulation), which is anticipated to be associated with an acceptable safety profile. However, to account for potential toxicities, special caution will be taken by starting idasanutlin at a lower dose of 150 mg QD × 5d during Cycle 1 and continuing idasanutlin at the 200-mg dose in all subsequent cycles in (at a minimum) the first 5 patients. If this regimen is determined to be safe and well tolerated (see Section A11–4.1.2.2), all subsequent patients will receive 200 mg QD × 5 Q4W in combination with atezolizumab during all cycles.

Note that due to the MTD at 250 mg in solid tumor patients, the idasanutlin dose increase will be limited to 200 mg to balance the potential for improving a patient's response with higher exposure with the potential for increased side effects.

A11–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+IDASA ARM

A11–4.1 TREATMENT IN ATEZO+ IDASA ARM

A11–4.1.1 Formulation, Packaging, and Handling

A11–4.1.1.1 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 and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A11–4.1.1.2 Idasanutlin

Idasanutlin will be supplied by the Sponsor as film-coated tablets (SDP formulation) at three dose strengths: 50 mg, 150 mg, and 200 mg.

For information on the formulation and handling of idasanutlin, see the Idasanutlin Investigator's Brochure.

A11–4.1.2 Dosage, Administration, and Compliance

Patients enrolled in the Atezo+Idasa arm will receive treatment as outlined in Tables A11–1 and A11–2 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease; see Section 3.1.1 in the protocol body for details). It is recommended that treatment be initiated no later than 7 days after randomization. Treatment with Atezo + Idasa when idasanutlin is administered at 150 mg or at 200 mg is described in Table 1 and 2, respectively.

Table 1 Initial Treatment Regimen for Atezo+Idasa Arm [a]

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Idasanutlin 150 mg orally once daily on Days 1–5 of each cycle [a] • Atezolizumab 840 mg IV on Days 1 and 15

Atezo + Idasa = atezolizumab plus idasanutlin.

[a] For details regarding intra-patient dose increase and dose increase after the safety evaluation phase, refer to Section A11–4.1.2.2.

Table 2 Treatment Regimen for Atezo+Idasa Arm after Dose Increase

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Idasanutlin 200 mg orally once daily on Days 1–5 of each cycle • Atezolizumab 840 mg IV on Days 1 and 15

Atezo + Idasa = atezolizumab plus idasanutlin.

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

Refer to Section A11–5.1.4 for information on treatment interruptions for patients who experience toxicities. Atezolizumab and idasanutlin treatment interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed. The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

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

No safety data related to atezolizumab or idasanutlin overdose are available.

A11–4.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-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 5. Atezolizumab infusions will be administered per the instructions outlined in Table 3.

Table 3 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, pulse oximetry, blood pressure, 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. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Guidelines for medical management of IRRs for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A11–5.1.4.

A11–4.1.2.2 Idasanutlin

Idasanutlin will be administered orally at a dose of 200 mg QD×5*d* Q4W; however initially, a minimum of 5 patients will receive idasanutlin tablets at a starting dose of 150 mg (either three 50-mg tablets or one 150-mg tablet) orally QD on Days 1 through 5 of the first 28-day cycle (QD×5d). If, based on the considerations listed below, treatment with idasanutlin 150 mg QD×5d plus atezolizumab 840 mg Q2W is determined to be safe and well tolerated, patients will receive idasanutlin at a dose of 200 mg (either as one 200-mg tablet, as one 150-mg tablet and one 50-mg table, or as four 50-mg tablets) on Days 1 through 5 of each 28-day cycle (QD×5d Q4W) in Cycle 2 and subsequent cycles.

Consideration for intra-patient dose increase to 200 mg will be based on a review of individual patient data collected from Day 1 of Cycle 1 to Day 1 of Cycle 2, including, but not limited to, laboratory and safety data. The dose increase to 200 mg will not be allowed if patients dosed at 150 mg develop any of the following toxicities during Cycle 1:

- Adverse event of any grade leading to a delay of more than 14 days in the start of next treatment cycle
- Increase in liver function tests meeting the criteria of Hy's Law
- Grade ≥ 3 non-hematologic adverse event, with the following exceptions:
  - Grade 3 diarrhea that responds to therapy within 48 hours
  - Grade 3 nausea or vomiting that occurs in the absence of premedication and responds to therapy within 72 hours
- Hematologic adverse event that meets any of the following criteria:
  - Grade ≥ 3 febrile neutropenia
  - Grade 3 or 4 neutropenia in the presence of sustained fever of $> 38^{\circ}$C (lasting > 5 days) or a documented infection
  - Grade 4 neutropenia lasting > 7 days
  - Grade 3 or 4 thrombocytopenia if associated with Grade ≥ 3 bleeding
  - Grade 4 thrombocytopenia lasting > 7 days
- Other toxicities that are considered clinically relevant and related to study treatment as determined by the investigator and the Medical Monitor

The decision to increase the dose of idasanutlin from 150 mg to 200 mg for an individual patient will be made in consultation with the Investigator and Sponsor, including the Medical Monitor and Safety Science Leader. During this evaluation period, patients who withdraw for any reason not related to an adverse event and who have completed ≤ 2 cycles of the treatment regimen will be replaced.

After approximately 6 patients have been dosed, a decision will be made as to whether idasanutlin should be dosed at 150 mg or 200 mg for all subsequent patients. If treatment with idasanutlin 150 mg for one cycle and subsequent intra-patient dose increase to 200 mg for at least one cycle is determined to be safe and well tolerated in a minimum of 5 out of 6 patients, the Sponsor may decide to administer idasanutlin at a starting dose of 200 mg in the next enrolled patients. Otherwise, the Sponsor may decide to maintain the idasanutlin dose at 150 mg in the next enrolled patients.

Each idasanutlin dose should be taken approximately 24 hours apart, once in the morning. On Day 1 of each cycle, patients should take their tablets in the clinic prior to the atezolizumab infusion, as directed by site personnel. Idasanutlin may be taken with or without food. Tablets should be swallowed intact with water and should not be

opened, broken, or chewed. Missed or vomited doses will not be made up. If vomiting occurs within 15 minutes and expelled tablets are intact, another dose may be given.

To assess patient compliance with self-administration of idasanutlin, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

To mitigate the risk of idasanutlin-related GI toxicities, all patients should receive the premedications outlined in Table 4.

Table 4 Premedication for Idasanutlin

Premedication/Indication	Timepoint	Administration
Mandatory Premedication		
5-HT3 receptor antagonist: To reduce the incidence and severity of nausea and vomiting	Day 1, 30–60 minutes prior to first administration of study medication (for long-acting anti-emetics, such as palonosetron); otherwise prior to each study medication administration (Days 1–5, for short acting anti-emetics, such as ondansetron or granisetron) [a]	Palonosetron IV 0.25 mg or PO 0.5 mg, or granisetron transdermal system, or oral ondansetron or granisetron [b] according to prescribing information
Recommended Premedication (at the discretion of the investigator)		
Loperamide: To reduce the incidence and severity of diarrhea	Day 1, 30 minutes prior first administration of study medication [a]	Loading dose of loperamide 4 mg orally

PO = by mouth

[a] Premedication to be repeated for every cycle.

[b] Palonosetron is the recommended option because of its efficacy against delayed nausea and lack of QT interval–prolonging effects.

Guidelines for idasanutlin dose modification, treatment interruption, or discontinuation because of toxicities are provided in Section A11–5.1.4.

A11–4.1.3 Stage 2 Treatment

Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1 in the protocol body) or unacceptable toxicity may be eligible to receive a different treatment combination during during Stage 2, provided a Stage 2 treatment is available for enrollment and they meet the eligibility criteria of that treatment regimen. Stage 2 treatment must begin within 3 months after

the patient has experienced loss of clinical benefit or unacceptable toxicity. However, it is recommended that patients begin Stage 2 treatment as soon as possible, but no earlier than 2 weeks after the last dose of treatment in Stage 1.

Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table 5 Stage 2 Treatment Regimens Available for the Atezo+Idasa Arm

Study Treatment	Appendix
No Stage 2 treatment currently available	—

A11–4.2 CONCOMITANT THERAPY FOR ATEZO+IDASA 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 patient 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.

A11–4.2.1 Permitted Therapy for Atezo+Idasa Arm

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

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic anticoagulation

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

  Prophylactic use of low molecular weight heparin (i.e., enoxaparin 40 mg/day) is allowed.
- Prophylactic antibiotic or anti viral treatment administered according to institutional standards
- *Vaccinations (such as influenza, COVID-19)*

  Live, attenuated vaccines are not permitted (see Section A11–4.2.3).
- Prophylactic standard anti-emetic therapy

- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin releasing–hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease).

  Treatment with atezolizumab and idasanutlin may be continued during palliative radiotherapy.

- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole brain radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.
  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

  – Anti-convulsant therapy, if required, is administered at a stable dose.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2 receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 adrenergic agonists).

A11–4.2.2 Cautionary Therapy for Atezo+Idasa Arm

Corticosteroids, *Immunosuppressive Medications,* and Tumor Necrosis Factor–α Inhibitors

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

Systemic corticosteroids *or immunosuppressive medications* are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 for details).

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 A11–4.2.3) may be used during the study at the discretion of the investigator.

A11–4.2.3 Prohibited Therapy for Atezo+Idasa 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, may be prohibited prior to starting study treatment, depending on the agent and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances outlined above in Section A11-4.2.1.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

- Strong/moderate inhibitors and strong/moderate inducers of CYP3A4 and CYP2C8, as well as CYP2C8 or OATP1B1/3 substrates, are prohibited within 14 days prior to initiation of idasanutlin and during treatment with idasanutlin (see Tables 6, 7, and 8).

Table 6 Prohibited CYP2C8 Substrates, Inhibitors, and Inducer

Substrates	Inhibitors	Inducer
Paclitaxel	Gemfibrozil	Rifampicin
Repaglinide	Pioglitazone	
Rosiglitazone		
Torasemide		

Note: Caution should be taken with the use of ibuprofen, monteleukast (CYP2C8 substrates), and trimethoprim (CYP2C8 inhibitor). These are only permitted outside of the 5-day treatment window with idasanutlin.

Table 7 Prohibited CYP3A4 Inducers

Inducers (Strong)
Carbamazepine
Cyproterone
Efavirenz
Etravirine
Modafinil
Nevirapine
Oxcarbazepine
Phenobarbital
Phenytoin
Rifampicin
St. John’s wort

Table 8 Prohibited OATP1B1/3 Substrates

OATP1B1/3 Substrates
Atorvastatin
Atrasentan
Bosentan
Ezetimibe
Fluvastatin
Glyburide
Irinotecan
Pitavastatin
Pravastatin
Repaglinide
Rifampin
Rosiglitazone
Rosuvastatin
Simvastatin Acid

OATP1B1/3 = organic anion-transporting polypeptide 1B1/3.

- In patients considered eligible for the study because they are able to tolerate anti-coagulant/anti-platelet treatment interruption, these agents must be discontinued 7 days (or 5 half-lives, whichever is shorter) prior to initiating study medication. After the study drug completion/discontinuation visit, treatment with anti-coagulant/anti-platelet agents may be re-initiated for patients with transfusion-independent adequate platelet levels as clinically indicated.
- In patients remaining transfusion-dependent or patients with an adverse event requiring anti-thrombotic therapy during the study treatment period, the clinical benefit of using anti-coagulation therapy (acute risk of thromboembolism/stroke) should be carefully weighed against its risks (acute risk of hemorrhage/uncontrolled bleeding) and only initiated if anti-coagulant/anti-platelet use is acutely required and use cannot be postponed until after the study drug completion/discontinuation visit. Close monitoring of platelet levels is recommended. Frequent measurement of peak anti-Xa levels and tight maintenance between 0.5 and 1.0 IU/ml are advised and may improve the risk/benefit ratio. The maintenance of anti-thrombotic treatment should be continuously re-assessed. Sustained use over time must be clinically warranted. Anti-thrombotic treatment should be reserved for those patients with established conditions, such as venous thromboembolism. Low molecular weight heparin (LMWH) preparations or unfractionated heparin (UFH) with doses adjusted to platelet levels are allowed and would be the preferred therapeutic

intervention. LMWH and UFH are recommended for patients who do not have contraindications to anticoagulant use.

A11–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO+IDASA ARM

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

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 5 months after the last dose of atezolizumab and for 6 weeks after the last dose of idasanutlin. Women must refrain from breastfeeding during this same period of time.

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

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

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

- 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 female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 90 days after the last dose of idasanutlin to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

A11–5 ASSESSMENT OF SAFETY FOR ATEZO + IDASA ARM

A11–5.1 SAFETY PLAN FOR ATEZO + IDASA ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and idasanutlin in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A11–5.1.1, A11–5.1.2, and A11–5.1.3). Guidelines for the management of patients who experience specific adverse events are provided in Section A11–5.1.4.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Because of the potential for overlapping toxicities identified for atezolizumab and idasanutlin, special caution will be taken by performing a planned safety evaluation for patients randomized to this arm. A minimum of 6 patients must complete at least one cycle of treatment (i.e., receive at least two doses of atezolizumab and 5 doses of idasanutlin) and complete at least 23 days of safety follow-up after the last dose of idasanutlin before additional patients can be enrolled. If the combination is determined sufficiently safe and well tolerated, randomization will be resumed.

If the intra-patient dose increase during Cycle 2 was allowed and determined to be safe and well tolerated in at least 5 out of 6 patients, the next enrolled patients will receive Idasanutlin at 200 mg from Cycle 1. If the intra-patient dose increase during Cycle 2 was not allowed or was determined not to be safe and well tolerated in at least 5 out of 6 patients, the idasanutlin dose will be maintained at 150 mg in the next enrolled patients (see Section A11–4.1.2.2).

Administration of atezolizumab 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 in the protocol body.

A11–5.1.1 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, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab. Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A11–5.1.2 Risks Associated with Idasanutlin

Diarrhea, nausea, vomiting, decreased appetite/anorexia, fatigue/asthenia, thrombocytopenia and increased hemorrhagic risk, neutropenia, febrile neutropenia, anaemia, pyrexia, sepsis, pneumonia, fungal infections, electrolyte disorders, and tumour lysis syndrome (TLS) are identified risks for idasanutlin. Some of these risks (i.e., sepsis, TLS) are more specific to hematological malignancies.

Across the solid tumor studies, 97% of patients had at least one adverse event; diarrhea, nausea, vomiting, decreased appetite, and fatigue were the most frequent (≥10% incidence). The most common treatment-related adverse events (>30% incidence) were diarrhea, nausea, and vomiting.

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

A11–5.1.3 Risks Associated with Combination Use of Atezolizumab and Idasanutlin

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and idasanutlin: diarrhea/colitis, electrolyte disorder, pneumonia/pneumonitis, thrombocytopenia, anemia, and hepatic toxicity.

A11–5.1.3.1 Gastrointestinal Toxicity

Gastrointestinal adverse events reported in Phase I idasanutlin studies were primarily diarrhea, nausea, vomiting, abdominal pain, constipation, and anorexia. Diarrhea was the most common adverse event. Nausea and vomiting were also frequently reported but to a lesser extent, and the majority of adverse events were Grade 1 and Grade 2.

Diarrhoea, nausea, and vomiting were very commonly observed in patients treated with atezolizumab (>10% patients). Colitis was less commonly observed in patients treated with atezolizumab (1%–10% of patients).

Please refer to Table A11–4 for additional information on mandatory premedication for idasanutlin. For detailed instructions for the management of gastrointestinal toxicities, please refer to Table A11–9.

A11–5.1.3.2 Pneumonia and Pneumonitis

Patients treated with idasanutlin are at increased risk for infections due to the effect on bone marrow progenitors and the related cytopenia. Severe, life threatening and sometimes fatal infections (i.e., pneumonia) have been reported. Pneumonia was more commonly observed in patients with acute myeloid leukemia (AML) treated with idasanutlin compared with solid cancer.

Pulmonary events, such as dyspnea, pneumonia, and pneumonitis have been associated with the use of atezolizumab. Pneumonia was more commonly observed in patients with non–small cell lung cancer.

For detailed instructions for the management of pulmonary events, please refer to Table A11–9.

A11–5.1.3.3 Hematologic Toxicities

Bone marrow toxicity induced by idasanutlin may manifest as cytopenias (i.e., pancytopenia, neutropenia, febrile neutropenia, thrombocytopenia, and anemia). In Study NP27872, which evaluated idasanutlin in patients with solid tumors, possible exposure-dependent neutropenia and thrombocytopenia were observed; these events were reversible and manageable. Blood counts must be monitored closely throughout study treatment; any Grade ≥3 decrease in neutrophil and thrombocyte counts must be followed until resolution.

For detailed instructions for the management of hematologic toxicities, please refer to Table A11–9.

A11–5.1.3.4 Hepatic Events

Hepatotoxicity is a potential risk for idasanutlin based on the results from nonclinical toxicology studies. In the clinical setting, the majority of hepatic events were non-serious, transient, and isolated elevations of bilirubin.

Cases of hepatitis, some leading to fatal outcomes, have been observed in clinical trials with atezolizumab. Most of the hepatic events identified were non-serious elevations of liver enzymes.

Liver function tests should be monitored during treatment. For detailed instructions for the management of hepatic events, please refer to Table A11–9.

A11–5.1.3.5 Electrolyte Disorders

Hypokalemia, hypophosphatemia, and hypomagnesemia were commonly observed in patients treated with idasanutlin. Electrolytes should be monitored during treatment, and electrolyte disorders should be treated according to institutional guidelines.

A11–5.1.4 Management of Patients Who Experience Adverse Events in Atezo+Idasa Arm

A11–5.1.4.1 Dose Modifications

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

The dose of idasanutlin can be reduced in 50-mg increments to 100 mg QD×5d Q4W. If further dose reduction below 100 mg for idasanutlin is indicated, the patient must discontinue idasanutlin. After dose reduction for idasanutlin, the dose should not be re-escalated during subsequent administrations. However, if the investigator believes the patient is likely to derive clinical benefit, the idasanutlin dose can be re-escalated after dose reduction. *The Medical Monitor is available to advise, as needed.*

A11–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for more than 12 weeks, the patient will be discontinued from the study. However, atezolizumab may be withheld for more than 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for more than 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

Idasanutlin treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment (see Table A11–9). All treatment-related toxicities should be resolved to Grade ≤1 or the baseline grade prior to beginning the next cycle, except for hematologic toxicities, which should be resolved to Grade ≤2. If idasanutlin has been withheld for more than 2 cycles (i.e., a maximum of 56 days) because of toxicity, the patient should be discontinued from idasanutlin. However, if the investigator believes the patient is likely to derive clinical benefit, idasanutlin can be resumed after being withheld for >56 days. *The Medical Monitor is available to advise as needed.*

If atezolizumab or idasanutlin is permanently discontinued, the other agent should also be discontinued unless the patient is likely to derive clinical benefit from single-agent use, as determined by the investigator. *The Medical Monitor is available to advise as needed.*

Refer to Section A11-4.1.2 for information on dose interruptions for reasons other than toxicity.

A11–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided below in Table A11–9 for events related to overlapping toxicities or idasanutlin treatment.

For cases in which management guidelines are not covered in Appendix 6 or Table A11–9, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table 9 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Idasa Arm

Event	Action to Be Taken
IRRs, *CRS,* anaphylaxis, and hypersensitivity reactions	• Guidelines for management of IRRs *and CRS* for atezolizumab are provided in Appendix 6. • For anaphylaxis precautions, see Appendix 5.
Hepatic Events	
Hepatic event, Grade 1 (including ALT or AST ≤ 3 × ULN or bilirubin > ULN to ≤ 1.5 × ULN)	• Continue atezolizumab and idasanutlin. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2 (including ALT or AST > 3.0–5.0 × ULN or bilirubin > 1.5–3.0 × ULN)	**All events:** • Withhold idasanutlin. • If event improves to Grade 1 or better, resume idasanutlin at full dose. • Monitor LFTs until values resolve to within normal limits. • **For suspected immune-mediated events that recur or persist > 5 days:** Withhold atezolizumab for up to 12 weeks after event onset. [a, b] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hepatic event, Grade 3 or 4 (including ALT or AST > 5.0 × ULN; and/or bilirubin > 3.0 × ULN)	• Permanently discontinue atezolizumab and idasanutlin and contact Medical Monitor. [c] • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over 1 month.

Table 9 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Idasa Arm (cont.)

Event	Action to Be Taken
Gastrointestinal Events	
Diarrhea or colitis, Grade 1	• Continue atezolizumab and idasanutlin. • Rule out other or concomitant causes, including, medications, malabsorption/lactose intolerance, fecal impaction, and dietary supplements high in fiber. • Dietary measures: Discontinue all lactose-containing products, alcohol, and high-osmolar supplements; instruct patients to eat frequent small meals (e.g., bananas, rice, apples, and toast). • Initiate loperamide treatment as per institutional practice - Suggested initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool up to a maximum dose of 16 mg/day - Recommend continuation of loperamide treatment until diarrhea free for 24 hours • If event persists for $>$24 hours, test for C. difficile infection. If patient has a confirmed infection, follow C. difficile infection guidelines below. • Endoscopy is recommended if symptoms persist for > 7 days. Monitor closely.

Table 9 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Idasa Arm (cont.)

Event	Action to Be Taken
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a, b] Continue idasanutlin. • Rule out other or concomitant causes, including, medications, malabsorption/lactose intolerance, fecal impaction, and dietary supplements high in fiber. • Dietary measures: Discontinue all lactose-containing products, alcohol, and high-osmolar supplements; instruct patients to eat frequent small meals (e.g., bananas, rice, apples, and toast). • Initiate loperamide treatment as per institutional practice - Suggested initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool up to a maximum dose of 16 mg/day - Recommend continuation of loperamide treatment until diarrhea free for 24 hours • If event persists for more than 24 hours, test for C. difficile infection. If patient has a confirmed infection, follow C. difficile infection guidelines below. • If event persists for more than 24 hours and patient experiences any additional symptoms (e.g., blood and/or mucus in stools, abdominal pain and cramps, dehydration), referral to a GI specialist is recommended for further evaluation, including biopsy. • If event persists after 48 hours of treatment with loperamide, consider second-line agents (e.g., diphenoxylate and atropine, octreotide, budesonide, or tincture of opium). • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

Table 9 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Idasa Arm (cont.)

Event	Action to Be Taken
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset.[a, b] Withhold idasanutlin until event has improved to Grade 1 or better. • Dietary measures: Discontinue all lactose-containing products, alcohol, and high-osmolar supplements; instruct patients to eat frequent small meals (e.g., bananas, rice, apples, and toast). • Monitor electrolytes daily (i.e., potassium, magnesium, calcium, and sodium). • Initiate loperamide treatment as per institutional practice - Suggested initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool up to a maximum dose of 16 mg/day - Recommend continuation of loperamide treatment until diarrhea free for 24 hours • Test for C. difficile infection. If patient has a confirmed C. difficile infection, follow guidelines below. • If colitis is suspected, or if event persists for more than 24 hours, refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab.[b] If event resolves to Grade 1 or better within 28 days, resume idasanutlin with a 50-mg dose reduction (lowest idasanutlin dose is 100 mg), with continued supportive care or prophylaxis. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.[c] • If event does not resolve to Grade 1 or better while withholding idasanutlin and with provision of maximal supportive care by 28 days, permanently discontinue idasanutlin and contact Medical Monitor.

Table 9 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Idasa Arm (cont.)

Event	Action to Be Taken
Diarrhea or colitis, Grade 3 (recurrent)	• If Grade 3 diarrhea recurs despite provision of supportive care and idasanutlin dose reduction, withhold idasanutlin until the diarrhea resolves to Grade 1 or better. Follow atezolizumab management guidelines for Grade 3 events. • If event resolves to Grade 1 or better within 28 days, then the idasanutlin dose will be re-introduced at the previously reduced dose (lowest idasanutlin dose is 100 mg). • If event does not resolve to Grade 1 or better within 28 days, idasanutlin should be permanently discontinued. • If the diarrhea recurs at Grade 3 after the second idasanutlin reintroduction, idasanutlin should be permanently discontinued.
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and idasanutlin and contact Medical Monitor. [c] • Test for C. difficile infection. If patient has a confirmed infection, follow C. difficile infection guidelines below. • Monitor electrolytes daily (i.e., potassium, magnesium, calcium, and sodium). • Administer IV fluids as clinically indicated and aim at all times for electrolyte correction. • If the patient is currently receiving loperamide at the maximum recommended daily dose (i.e., 16 mg/24 hours), consider second-line agents (i.e., diphenoxylate, atropine, octreotide, budesonide, or tincture of opium). • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Table 9 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Idasa Arm (cont.)

Event	Action to Be Taken
Clostridium difficile infection	• If loperamide at the maximum recommended daily dose (i.e., 16 mg/24 hours) does not improve the severity of diarrhea within 24 hours, test for C. difficile toxin and toxin-producing C. difficile in stool. • Consider clinically appropriate empirical therapy before microbiological evidence is found, such as the following: - Metronidazole: If the initial episode is mild CDI, administer 500 mg orally, three times daily for 10–14 days. - Vancomycin: If recurrent disease is suspected or moderate to severe CDI is present, administer 125 mg orally four times daily for 10–14 days. Once a C. difficile infection is confirmed, perform the following: • Discontinue unnecessary antimicrobial therapy. • Maintain adequate replacement of fluid and electrolytes. • Avoid any anti-motility medications/dietary supplements. • Use of proton pump inhibitors should be reviewed, as it has been shown to increase CDI susceptibility (Garey et al. 2008; Janarthanan et al. 2012). • Discontinue loperamide, if therapy is still ongoing. • Administer vancomycin as the preferred antibiotic of choice (125 mg orally four times daily for 10–14 days or 500 mg four times daily for 10 days). If CDI is severe or recurs, administer fidaxomicin (200 mg twice daily for 10 days) as an alternative to vancomycin.
Vomiting, Grade 1, 2, or 3	• Continue atezolizumab and idasanutlin. • If vomiting occurs within 15 minutes of taking idasanutlin and all expelled tablets are still intact, another dose may be given and the second dose should be noted in the medication diary. • Otherwise, no replacement dose is to be given.
Vomiting, Grade 4	• Permanently discontinue idasanutlin and atezolizumab and contact Medical Monitor. [c]
Pulmonary Events	
Pulmonary event, Grade 1	• Continue atezolizumab and idasanutlin and monitor closely.

Table 9 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Idasa Arm (cont.)

Event	Action to Be Taken
	• Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • *For Grade 1 pneumonitis, consider withholding atezolizumab.*
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks and idasanutlin for up to 56 days after event onset.[a, b] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent, if there is no suspicion of pulmonary infection. • If event resolves to Grade 1 or better, resume atezolizumab.[b] If event resolves to Grade 1 or better, resume idasanutlin with a 50-mg dose reduction (lowest idasanutlin dose is 100 mg). • If event does not resolve to Grade 1 or better while withholding atezolizumab and idasanutlin, permanently discontinue atezolizumab and idasanutlin and contact Medical Monitor.[c] • For recurrent events, *or events with no improvement after 48–72 hours of corticosteroids,* treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and idasanutlin and contact Medical Monitor.[c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day *IV methylprednisolone*, if there is no suspicion of pulmonary infection. • 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.
Hematologic Toxicity	
General guidance	• Due to the potential for myelosuppression with idasanutlin, standard precautions for neutropenia, thrombocytopenia, and anemia will be used for patients in this trial. Frequent blood monitoring is strongly recommended. Institutional guidelines for use of growth factor support, transfusions, and antibiotics should be followed with consideration for prohibited

Table 9 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Idasa Arm (cont.)

Event	Action to Be Taken
	medications.
Hematologic toxicity, Grade 1 and 2 Hb $\geq$ 8 g/dL [d] or Nadir WBC $\geq 2\times 10^9$/L (2000/μL) [d] or Nadir ANC $\geq 1 \times 10^9$/L (1000/μL) [d] or Nadir platelets $\geq 50\times 10^9$/L (50,000/μL) [d]	• Continue idasanutlin and atezolizumab.
Hematologic toxicity, Grade 3 and 4 Hb $<$ 8 g/dL [d] or Nadir WBC $< 2\times 10^9$/L (2000/μL) [d] or Nadir ANC $< 1 \times 10^9$/L (1000/μL) [d] or Nadir platelets $< 50\times 10^9$/L (50,000/μL) [d] or Febrile neutropenia	**First occurrence:** • Withhold idasanutlin and atezolizumab. [a] • Administer RBCs or platelets as required. • Idasanutlin: If event improves to Grade 1 or better within 56 days, and platelet count is $\geq 100\times 10^9$/L (100,000/mL), resume idasanutlin with a 50-mg dose reduction (lowest idasanutlin dose is 100 mg). If not, permanently discontinue idasanutlin. • Atezolizumab: If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. [a] If not, permanently discontinue atezolizumab. **Second occurrence:** • Follow guidelines for the first occurrence for atezolizumab. • Permanently discontinue idasanutlin.
Thrombocytopenia, Grade 3 or 4 of any duration if associated with Grade $\geq$ 3 bleeding	• Permanently discontinue idasanutlin.
Idasanutlin-related toxicities not described above	

Table 9 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Idasa Arm (cont.)

Event	Action to Be Taken
Grade 1 or 2	• Continue idasanutlin and atezolizumab.
Grade 3	**First occurrence:** • Withhold idasanutlin. Continue atezolizumab. • If event resolves to Grade 1 or better within 56 days, resume idasanutlin with a 50-mg dose reduction (lowest idasanutlin dose is 100 mg). If not, permanently discontinue idasanutlin [e]. **Second occurrence:** • Permanently discontinue idasanutlin. Atezolizumab may be continued at the discretion of the investigator per medical judgement.
Grade 4	• Permanently discontinue idasanutlin. Atezolizumab may be continued at the discretion of the investigator per medical judgement.
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue idasanutlin.
Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Withhold idasanutlin. • If event resolves to Grade 2 or better within 56 days, resume idasanutlin. If not, permanently discontinue idasanutlin.[e]
Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold idasanutlin. • If event resolves to Grade 2 or better within 56 days, and if Medical Monitor agrees, resume idasanutlin. If not, permanently discontinue idasanutlin.

BAL = bronchoscopic alveolar lavage; CDI = C.difficile infection; *CRS = cytokine release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; ULN = upper limit of normal.

Table 9 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Idasa Arm (cont.)

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

[d] Nadir of the prior cycle.

[e] If the investigator believes the patient is likely to derive clinical benefit, idasanutlin can be resumed after being withheld for > 56 days. *The Medical Monitor is available to advise as needed.*

A11–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO+IDASA 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 in the protocol body for reporting instructions). Adverse events of special interest for the Atezo+Idasa arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7 in the protocol body)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10 \times$ upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, and optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

- Grade ≥3 thrombocytopenia or Grade ≥2 thrombocytopenia if associated with bleeding
- Grade ≥3 neutropenia, including febrile neutropenia
- Grade ≥2 diarrhea
- Grade ≥2 C. difficile infection

A11–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+IDASA ARM

A11–5.3.1 Pregnancies in Female Patients

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

A11–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant two weeks before the first dose of idasanutlin treatment, during the study, or within 90 days after the last dose of idasanutlin. 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 patient exposed to idasanutlin. When permitted by the site, the pregnant partner will 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 patient or his pregnant partner may provide

information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A11–5.3.3 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 in the protocol body).

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.

A11–5.3.4 Congenital Anomalies/Birth Defects

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

A11–6. SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+IDASA ARM

Table 10: Schedule of Activities for Atezo+Idasa Arm

Assessment/ Procedure	Stage 1 Screen.	Treatment Cycles (28-Day Cycles) [a]										Stage 2 Screen. [c] or Treat. Discon. [d]	Follow-Up [d]
		Cycles 1 [b]				Cycle 2				Cycles ≥ 3			Every 3 Months (±7 days)
	D –28 to –1	D1	D5	D15 (±3d)	D22 (±3d)	D1 (±3d)	D5	D15 (±3d)	D22 (±3d)	D1 (±3d)	D15 (±3d)		
Molecular profile of CRC (if available)	See Appendix 15	Whenever updated information becomes available											
Vital signs [e]		x	x	x	x	x	x	x	x	x	x	x	
Weight		x [f]				x [f]				x [f]		x	
Complete physical examination [g]												x	
Limited physical examination [h]		x [f]	x [f]	x [f]	x [f]	x [f]	x [f]	x [f]	x [f]	x [f]	x [f]		
ECOG Performance Status		x [f]				x [f]				x [f]		x	
ECG [i]		x [f]	x [f]									x [j]	
Hematology [k]		x [l, m]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x	
Chemistry [n]		x [l, m]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x	
Coagulation (INR and aPTT)												x [j]	

Table 10: Schedule of Activities for Atezo+Idasa Arm (cont.)

Assessment/ Procedure	Stage 1 Screen.	Treatment Cycles (28-Day Cycles) [a]										Stage 2 Screen. [c] or Treat. Discon. [d]	Follow-Up [d]
		Cycles 1 [b]				Cycle 2				Cycles ≥ 3			Every 3 Months (±7 days)
	D –28 to –1	D1	D5	D15 (±3d)	D22 (±3d)	D1 (±3d)	D5	D15 (±3d)	D22 (±3d)	D1 (±3d)	D15 (±3d)		
TSH, free T3 (or total T3), and free T4 [o]	See Appendix 15	x [l]								x [l, o]			
Viral serology (if applicable)												x [j, p]	
C-reactive protein												x [j]	
Plasma CEA [q]		x [l]								x [l, q]			
LDH												x [j]	
Pregnancy test [r]		x [l,m]				x [l]				x [l]		x [s]	x [r]
Urinalysis [t]		Perform as clinically indicated										x [j, s]	
Serum autoantibody sample [u]		Perform if a patient experiences a suspected immune-mediated adverse event										x [j]	
Serum or plasma PK sample		Refer to Table 11 below											
Serum ADA sample		Refer to Table 11 below											

Table 10: Schedule of Activities for Atezo+Idasa Arm (cont.)

Assessment/ Procedure	Stage 1 Screen.	Treatment Cycles (28-Day Cycles) [a]										Stage 2 Screen. [c] or Treat. Discon. [d]	Follow-Up [d]
		Cycles 1 [b]				Cycle 2				Cycles ≥ 3			Every 3 Months (±7 days)
	D –28 to –1	D1	D5	D15 (±3d)	D22 (±3d)	D1 (±3d)	D5	D15 (±3d)	D22 (±3d)	D1 (±3d)	D15 (±3d)		
Plasma, serum, and PBMC biomarker samples	See Appendix 15	Refer to Table 11 below											
Blood sample for RBR (optional) [v]		x											
Tumor biopsy		x [w]											
Tumor biopsy (optional)		x [x]											
Tumor response assessments		x [y, z, aa]											
Concomitant medications [bb]		x	x	x	x	x	x	x	x	x	x	x	
Adverse events [cc]		x	x	x	x	x	x	x	x	x	x	x [cc]	x
Atezolizumab administration [dd, ee]		x		x		x		x		x	x		
Dispense idasanutlin [ee, ff]		x				x				x			

Table 10: Schedule of Activities for Atezo+Idasa Arm (cont.)

Assessment/ Procedure	Stage 1 Screen.	Treatment Cycles (28-Day Cycles) [a]										Stage 2 Screen. [c] or Treat. Discon. [d]	Follow-Up [d]
		Cycles 1 [b]				Cycle 2				Cycles ≥ 3			Every 3 Months (±7 days)
	D –28 to –1	D1	D5	D15 (±3d)	D22 (±3d)	D1 (±3d)	D5	D15 (±3d)	D22 (±3d)	D1 (±3d)	D15 (±3d)		
Study drug accountability [gg]			x				x				x		
Survival follow-up and anti-cancer treatment													x [hh]

ADA = anti-drug antibody; Atezo + Idasa = atezolizumab plus idasanutlin; CT = computed tomography; D, d = Day, day; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; Treat. = treatment; TSH = thyroid-stimulating hormone.

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 *may* occur outside of the specified window.

[b] It is recommended that treatment be initiated no later than 7 days after randomization.

[c] Patients who experience loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details) or unacceptable toxicity may be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.2 in the protocol body provided Stage 2 is open for enrollment) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will undergo follow-up assessments after completing the treatment discontinuation visit.

Table 10: Schedule of Activities for Atezo+Idasa Arm (cont.)

[e] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Refer to Section A11–4.1.2 for details related to vital signs monitoring during atezolizumab infusions.

[f] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[g] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.administered. The skin examination should be extended according to medical need.

[i] ECGs from Cycles 2 onward are mandatory only for patients with significant ECG abnormalities at prior timepoints or for patients who have QTc prolongation (>30 ms) at any timepoint during study or as clinically indicated. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[j] Assessments to be performed only for patients undergoing Stage 2 screening.

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

[l] Laboratory tests must be performed within 96 hours prior to *dosing* during the treatment period.

[m] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[n] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (per standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. CPK will be performed only on Day 1 of each cycle and at treatment discontinuation.

[o] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[p] At Stage 2, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[q] CEA will be assessed on Day 1 of Cycle 1 and every 2 cycles thereafter (i.e., Cycles 3, 5, 7, etc.) until disease progression.

[r] 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 and at 3 months and 6 months after treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

Table 10: Schedule of Activities for Atezo+Idasa Arm (cont.)

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

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

[u] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[v] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. RBR sample should be collected prior to study treatment.

[w] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial-biopsy arm (see Section 3.1.1.2 in the protocol body) will undergo tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible by the investigator). See Section 4.5.7 in the protocol body for tissue sample requirements.

[x] Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation, if deemed clinically feasible and may undergo additional on-treatment biopsies at any other time during Stage 1 or Stage 2 at the investigator's discretion.

[y] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[z] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head CT 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).

[aa] For patients who undergo screening for Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

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

Table 10: Schedule of Activities for Atezo+Idasa Arm (cont.)

treatment discontinuation visit.

[cc] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6 in the protocol body). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[dd] Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle. The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[ee] Treatment will continue until unacceptable toxicity or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details).

[ff] Premedication is required prior to idasanutlin administration (see Section A11–4.1.2.2 for details). Patients will receive idasanutlin orally once a day on Days 1–5 of each cycle. Each idasanutlin dose should be taken approximately 24 hours apart, once in the morning. On Day 1 of each cycle, patients should take their tablets in the clinic prior to the atezolizumab infusion, as directed by site personnel.

[gg] Medication diaries should be collected and reviewed, and unused medications should be collected for assessment of compliance.

[hh] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from 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 patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table 11 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Idasa Arm: Preliminary and Expansion Phases

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Idasanutlin PK (plasma) [a] • Biomarkers (plasma, serum, PBMC) • Biomarkers (PAXgene RNA)
	30 (±10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
	2 hours after idasanutlin dose	• Idasanutlin PK (plasma) [a]
	4 hours after idasanutlin dose	• Idasanutlin PK (plasma) [a]
Day 5 of Cycle 1	Prior to study treatment	• Idasanutlin PK (plasma) [a]
	2 hours after idasanutlin dose	• Idasanutlin PK (plasma) [a]
	6 hours after idasanutlin dose	• Idasanutlin PK (plasma) [a] • Biomarkers (PAXgene RNA)
Day 15 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Biomarkers (plasma, serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Idasanutlin PK (plasma) [a] • Biomarkers (plasma, serum, PBMC)
Day 5 of Cycle 2	6 hours after idasanutlin dose	• Biomarkers (PAXgene RNA)
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Idasanutlin PK (plasma) [a] • Biomarkers (plasma, serum)
Day 1 of Cycle 6	Prior to study treatment	• Idasanutlin PK (plasma) [a]
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Idasanutlin PK (plasma) [a] • Biomarkers (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Idasanutlin PK (plasma) [a]

Table 11 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Idasa Arm: Preliminary and Expansion Phases (cont.)

Visit	Time	Sample Type
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Idasanutlin PK (plasma) [a] • Biomarkers (plasma, serum)

ADA = anti-drug antibody; Atezo = atezolizumab; Idasa = idasanutlin; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: Based on emerging safety and efficacy data, the number of PK, ADA, and/or biomarker samples may be reduced/removed and/or the timing of samples may be modified.

[a] Idasanutlin and its metabolite(s) will be tested.

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Appendix 12
Study Details Specific to Atezo+Regorafenib Arm

TABLE OF CONTENTS

A12–1 BACKGROUND FOR ATEZO + REGORAFENIB 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 CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody mediated clearance of activated effector T cells.

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

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

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

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

A12–1.2 BACKGROUND ON REGORAFENIB

Regorafenib is an orally administered multikinase inhibitor, which targets signaling pathways implicated in multiple tumor-promoting processes. Its targets include the pro-angiogenic kinases, vascular endothelial growth factor receptor 1-3 (VEGFR 1-3) and tyrosine receptor kinase 2, and kinases promoting a pro-tumorigenic microenvironment, such as platelet-derived growth factor receptors and fibroblast growth factor. This agent also inhibits the mutant oncogenic kinases KIT, RET, and B-RAF, as well as the growth factor receptor for macrophages colony stimulating factor 1 receptor (CSF-1R) (Wilhelm et al. 2010; Uitdehaag et al. 2014). Regorafenib exhibited potent

tumor growth inhibition in nonclinical models, including colon tumor models (Wilhelm et al. 2010; Abou-Elkacem et al. 2013).

Regorafenib conferred a survival benefit over best supportive care in patients with refractory metastatic colorectal cancer (mCRC) in randomized, double-blind, placebo-controlled trials both in Western and Asian populations (Grothey et al. 2013; Li et al. 2015). The most common adverse events included hand–foot syndrome, fatigue, diarrhea, hypertension, voice changes, oral mucositis, and rash/desquamation.

Regorafenib is approved worldwide (under the tradename of Stivarga®) for the treatment of patients with mCRC who previously received fluoropyrimidine-based, oxaliplatin-based, and irinotecan-based chemotherapy; prior anti-VEGF therapy; and, if patients have a KRAS wild-type tumour, previous anti-EGFR therapy. It is also approved in Europe in unresectable or metastatic gastrointestinal (GI) tumours and in patients with hepatocellular carcinoma who were previously treated with sorafenib.

A12–2 RATIONALE FOR ATEZO + REGORAFENIB 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, urothelial carcinoma, renal cell carcinoma, melanoma, CRC, head and neck cancer,

gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

Early clinical data had shown encouraging results with the anti–PD-1 checkpoint inhibitor pembrolizumab as a single agent in patients with mCRC assessed as having high microsatellite instability (MSI-H) status but not with microsatellite stable (MSS) status (Le et al. 2015). These data resulted in the May 2017 approval of pembrolizumab in adult and pediatric patients with tumors characterized as MSI-H or deficient for mismatch repair genes based on objective response rate (ORR) and durability of the response. ORR was similar irrespective of whether patients were diagnosed with CRC (36%) or a different cancer type (46% across the 14 other MSI-H cancer types). Similar response rates were observed in patients with second line or later mCRC enrolled in a Phase Ia study investigating atezolizumab as single agent (Roche Study PCD4989g) and a Phase Ib study investigating the combination of atezolizumab plus bevacizumab (Roche Study GP28328, Arm A). In Study PCD4989g, there was 1 responder reported in 14 patients with MSS status per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). In the 10 patients with MSI-H status enrolled in Study GP28328, the investigator assessed confirmed ORR per RECIST v1.1 was 40% (95% CI: 12.2, 73.8), with all 4 responders having partial responses. No objective responses were seen in the 14 patients with MSS tumors.

A12–2.2 REGORAFENIB AS A MULTI-TARGETED ANTI-ANGIOGENIC AND IMMUNOMODULATORY AGENT

Consistent with its inhibitory activity on VEGFR 1-3, regorafenib demonstrated stronger anti-angiogenic activity compared with a selective anti-VEGFR2 antibody in a mouse colon tumor model (Abou-Elkacem et al. 2013). In addition to its inhibitory effect on angiogenesis, regorafenib also displayed immunomodulatory effects in nonclinical models (Abou-Elkacem et al. 2013; Hoff et al. 2017). Regorafenib treatment reduced tumor associated macrophage abundance in both MC38 and CTC26 colon tumors and also promoted their switch from the pro-tumorigenic M2 phenotype to the anti-tumorigenic M1 phenotype in colon tumor models (Abou-Elkacem et al. 2013; Hoff et al. 2017). These effects could result from the counteracting of the immune suppressive properties of VEGF signaling (Chen and Hurwitz 2018) or from the blockade CSF1-R–dependent signaling (Hoff et al. 2017), which positively regulates macrophage migration, differentiation, and survival (DeNardo and Ruffell 2019).

A12–2.3 RATIONALE FOR COMBINING REGORAFENIB WITH CHECKPOINT INHIBITION

The immune suppressive role of VEGF is now well established, and the combination of anti-VEGF therapies with blockade of the PD-L1/PD-1 axis has shown synergy in nonclinical models and has resulted in positive outcomes in Phase I to III clinical studies (Chen and Hurwitz 2018). In addition, M2-macrophages are considered a central driver

of the immunosuppressive tumor microenvironment through their ability to suppress DC differentiation and function and T-cell effector function. As a result, macrophage depletion can unleash CD8+ T-cell response and increase the efficacy of checkpoint blockade in nonclinical tumor models (DeNardo and Ruffell 2019). Therefore, among the multi-targeted mechanisms of action of regorafenib, blockade of VEGF and CSF-1R signaling is expected to show combinatorial efficacy with checkpoint inhibition (CPI). Accordingly, the combination of regorafenib with anti–PD-1 blockade showed superior anti-tumor activity compared with either individual agent in murine colon tumor models (Hoff et al. 2017).

Clinical data from the REGONIVO trial presented at ASCO 2019 (Fukuoka et al. 2019) showed promising results when combining the standard-of-care treatment regorafenib with the anti–PD-1 checkpoint inhibitor antibody nivolumab in patients with advanced, metastatic colorectal or gastric cancer (GC). An objective tumor response was observed in 19 patients (38%), including 11 patients with MSS GC, 7 patients with MSS CRC, and 1 patient with MSI-H CRC, with corresponding ORRs of 44% in GC and 29% in MSS CRC. At a median follow-up of 8.0 months, the median PFS time was 6.3 months. These outcomes outperform the clinical activity of regorafenib and anti-PD1 antibody when used as a single-agent therapy in MSS mCRC where ORRs of 2% and 0% were observed, respectively (Grothey et al. 2013; Le et al. 2015; Li et al. 2015; Eng et al. 2019). Taken together, these data suggest a synergy between PD-1 blockade and regorafenib. The regorafenib plus nivolumab combination is currently being investigated further in a randomized Phase III trial compared with single-agent regorafenib in patients with MSS mCRC.

These data provide a rationale to further investigate combination strategies of regorafenib with checkpoint inhibitors, such as atezolizumab, in patients with MSS CRC.

A12–2.4 BENEFIT–RISK ASSESSMENT

This study will enroll patients with mCRC who have become refractory to first- and second-line standard therapies. This patient population has a median OS of less than 9 months with currently available treatments. Treatment options have shown limited efficacy and are often poorly tolerated.

Despite the success of single-agent CPI in the MSI-H patient population, the vast majority of patients with CRC have MSS tumors and do not respond to single-agent CPI, highlighting the need for safe and effective combination treatments. In addition, the benefit of single-agent regorafenib over best supportive care is limited. Therefore, there remains a great need for investigating new cancer immunotherapy combinations to improve the outcome of this difficult-to-treat patient population.

The most frequently observed adverse drug reactions (≥30%) in patients receiving regorafenib are pain, hand–foot skin reaction, asthenia/fatigue, diarrhea, decreased appetite and food intake, hypertension, and infection. These toxicities occur early and may be dose-dependent (Grothey 2019). A randomized Phase II study (the ReDOS trial) showed that using a weekly dose-escalation strategy (from 80 mg/day to 160 mg/day) enabled patients to stay on treatment longer and decreased the incidence of Grade 3 and 4 toxicities when compared with using the approved starting dose of 160 mg/day (Bekaii-Saab et al. 2019).

In the dose-escalation cohort of the REGONIVO study, patients were treated with 80-mg, 120-mg, or 160-mg doses of regorafenib once per day for 21 days in a 28-day cycle plus 3 mg of nivolumab every 2 weeks. Treatment-related adverse events (all grades) were reported in 100% of patients across the 3 dose groups. The rate of Grade ≥3 treatment-related adverse events was 40%. The most common Grade ≥3 treatment-related adverse events were rash (12%), proteinuria (12%), palmar-plantar erythrodysesthesia (10%), and liver dysfunction (6%). In patients who received regorafenib at the 80-mg dose, the rate of Grade ≥3 treatment-related adverse events was 27% compared with 44% in those who received the 120-mg dose. These toxicities were considered to be manageable by the investigators and were balanced with the unprecedented efficacy signal in this heavily pre-treated patient population. The dose of regorafenib that is planned to be administered in this study is 120 mg/day, which is the maximum tolerated dose (MTD) that was identified in the REGONIVO study. Moreover, dose escalation from 80 mg/day to 120 mg/day during Cycle 1 will be allowed in order to improve the safety profile of regorafenib in combination with CPI.

Safety data are available for single-agent atezolizumab in patients with solid tumors, including CRC. Potential overlapping toxicities with regorafenib may occur within the system organ class of GI, hepatobiliary, cardiac, skin, nervous system and blood and lymphatic system disorders. The relevant corresponding overlapping toxicities of atezolizumab include immune-related colitis, hepatitis, myocarditis, skin rash, meningoencephalitis, and thrombocytopenia. Given the distinct mechanisms of action of atezolizumab and regorafenib, it is anticipated that adverse reactions observed with either agent will not result in synergistic toxic effects. In summary, the investigation of the safety of each single agent in patients with solid tumors and of the combination of regorafenib with the anti–PD-1 antibody nivolumab have not revealed findings that would prohibit the investigation of the regorafenib and atezolizumab combination in the setting of a Phase Ib/II study.

Considering the potentially synergistic mechanisms of action of regorafenib and atezolizumab, as well as the preliminary efficacy and manageable safety profile of the combination of regorafenib with nivolumab reported in the REGONIVO study, treatment

with atezolizumab and regorafenib appears to have promising therapeutic potential in solid tumors, such as MSS mCRC.

For the evaluation of the impact of the *coronavirus disease 2019 (*COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.4.

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

A12–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 840 mg every 2 weeks (Q2W) (840 mg on Days 1 and 15 of each 28-day cycle). The average concentration following the 840 mg Q2W dosage is expected to be equivalent to that of 1200 mg every 3 weeks (Q3W), an approved dosage for atezolizumab , as outlined in the prescribing information. Anti-tumor activity has been observed across doses ranging from 1 to 20 mg/kg Q3W. In Study PCD4989g, the MTD of atezolizumab was not reached and no dose-limiting toxicities (DLTs) were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A12–3.2 RATIONALE FOR REGORAFENIB DOSE AND SCHEDULE

The approved dose for regorafenib is 160 mg/day. In the REGONIVO study evaluating regorafenib in combination with nivolumab in Asian patients, DLTs were reported at the 160-mg/day dose and Grade 3 skin toxicities were reported in 20% of the patients treated with the 120-mg/day dose. This resulted in the use of the 80-mg/day dose of regorafenib in the expansion cohort. However, modeling and simulation analyses of data from the CORRECT and CONCUR trials showed that a starting dose of 80 mg/day might result in reduced efficacy if not escalated to doses of either 120 mg/day or 160 mg/day (Grothey 2019). Therefore, to ensure an efficacious dose is administered, as well as to account for the fact that this study will be conducted in a global population (inclusive of Caucasian patients with potential differences in body size, drug metabolism, and toxicities), regorafenib will be used at a dose of 120 mg/day on Days 1–21 of each 28-day cycle. Furthermore, to account for the results from the ReDOS trial (Bekaii-Saab et al. 2019) showing a lower incidence of adverse events, a starting dose of 80 mg/day of regorafenib will be allowed, followed by a dose escalation to 120 mg/day (as per institutional guidelines) during Cycle 1 if no significant drug-related toxicity is observed.

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

A12–4.1 TREATMENT IN ATEZO + REGORAFENIB ARM

A12–4.1.1 Formulation, Packaging, and Handling

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 and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A12–4.1.1.2 Regorafenib

For information on the formulation, packaging, and handling of regorafenib, refer to the local prescribing information.

A12–4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + Regorafenib arm will receive treatment as outlined in Table 1 until unacceptable toxicity or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator, after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 in the protocol body for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table 1 Treatment Regimen for Atezo + Regorafenib Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Atezolizumab 840 mg IV on Days 1 and 15 of each cycle • Regorafenib 120 mg by mouth once daily on Days 1–21 [a]

Atezo = atezolizumab.

[a] Regorafenib should be initiated at 80 mg, allowing sufficient time to monitor drug-related toxicities before considering dose escalation to 120 mg.

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

Guidelines for dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A12–5.1.4. Atezolizumab or regorafenib treatment interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed.

The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12. No safety data related to atezolizumab overdose are available. The highest dose of regorafenib studied clinically is 220 mg per day. The most frequently observed adverse drug reactions at this dose were dermatologic events, dysphonia, diarrhea, mucosal inflammation, dry mouth, decreased appetite, hypertension, and fatigue. There is no specific antidote for regorafenib overdose. In the event of suspected overdose, interrupt regorafenib, institute supportive care, and observe until clinical stabilization.

A12–4.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-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 5. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 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, pulse oximetry, blood pressure, 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. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A12–5.1.4.

A12–4.1.2.2 Regorafenib

Regorafenib will be used in the commercially available formulation.

Patients will receive regorafenib at a dose level of 120 mg (three tablets of 40 mg each) orally once daily on Days 1–21 of a 28-day cycle (see Table 1). This 4-week period is considered a treatment cycle. Regorafenib should be initiated at 80 mg, allowing sufficient time to monitor drug-related toxicities before considering dose escalation to 120 mg.

Regorafenib should be taken at the same time each day. On clinic visit days when PK samples are collected, patients should take their regorafenib dose in the clinic. The tablets should be swallowed whole with water after a light meal that contains <30% fat. An example of a light (low-fat) meal would include one portion of cereal (about 30 g),

one glass of skimmed milk, one slice of toast with jam, one glass of apple juice, and one cup of coffee or tea (520 calories, 2 g fat).

To assess patient compliance with self-administration of regorafenib, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

Guidelines for regorafenib dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A12–5.1.4.

A12–4.1.3 Stage 2 Treatment

Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1 in the protocol body) or unacceptable toxicity may be eligible to receive a different treatment combination during during Stage 2, provided a Stage 2 treatment is available for enrollment and they meet the eligibility criteria of that treatment regimen. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. However, it is recommended that patients begin Stage 2 treatment as soon as possible, but no earlier than 2 weeks after the last dose of treatment in Stage 1.

Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table 3 Stage 2 Treatment Regimens Available for the Atezo + Regorafenib Arm

Study Treatment	Appendix
No Stage 2 treatment currently available	—

A12–4.2 CONCOMITANT THERAPY FOR ATEZO + REGORAFENIB 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 patient 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.

For more detailed information on permitted, prohibited, or cautionary therapy; prohibited foods; and other restrictions (as applicable) for regorafenib, refer to the local prescribing information.

A12–4.2.1 Permitted Therapy for Atezo + Regorafenib Arm

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

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic anticoagulation

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

  Prophylactic use of low molecular weight heparin (i.e., enoxaparin 40 mg/day) is allowed.
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- *Vaccinations (such as influenza, COVID-19)*

  Live, attenuated vaccines are not permitted (see Section A12–4.2.3).
- Prophylactic standard anti-emetic therapy
- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin releasing–hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease).

Treatment with atezolizumab and regorafenib may be continued during palliative radiotherapy.

- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole brain radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.

  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

  – Anti-convulsant therapy, if required, is administered at a stable dose.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2 receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 adrenergic agonists).

A12–4.2.2 Cautionary Therapy for Atezo + Regorafenib Arm

Corticosteroids, *Immunosuppressive Medications,* and Tumor Necrosis Factor–α Inhibitors

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

Systemic corticosteroids *or immunosuppressive medications* are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 for details).

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 A12–4.2.3) may be used during the study at the discretion of the investigator.

UDP-Glucuronosyltransferase 1-1 and UDP-Glucuronosyltransferase 1-9

Regorafenib is metabolized by UDP-glucuronosyltransferase 1-1 (UGT1A1), and regorafenib and its metabolites are inhibitors of UGT1A1 and UDP-glucuronosyltransferase 1-9 (UGT1A9). Therefore, inhibitors of UGT1A1 (e.g., erlotinib, nilotinib, pazopanib, lapatinib, sorafenib) and substrates of UGT1A1 (e.g., irinotecan with its active metabolite SN-38, raltegravir, bazedoxifene, eltrombopag) and substrates of UGT1A9 (e.g., sorafenib, mycophenolic acid) should be used with caution.

Breast Cancer Resistance Protein

Patients receiving substrates of the breast cancer resistance protein (BCRP) transporter (e.g., methotrexate, fluvastatin, atorvastatin) should be monitored for signs and symptoms of increased exposure.

A12–4.2.3 Prohibited Therapy for Atezo + Regorafenib 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, may be prohibited prior to starting study treatment, depending on the agent and is prohibited during study treatment until disease progression is documented and the patient has

discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances outlined above in Section A12–4.2.1.

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin 2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort) and strong inhibitors of CYP3A4 activity (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) are prohibited.

A12–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + REGORAFENIB ARM

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

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 5 months after the last dose of atezolizumab and for 2 months after the last dose of regorafenib. Women must refrain from breastfeeding during this same period of time.

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

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

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

- 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 female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 2 months after the last dose of regorafenib to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

A12–5 ASSESSMENT OF SAFETY FOR ATEZO + REGORAFENIB ARM

A12–5.1 SAFETY PLAN FOR ATEZO + REGORAFENIB ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and regorafenib 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 the management of patients who experience specific adverse events are provided in Section A12–5.1.4.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Because of the potential for overlapping toxicities identified for atezolizumab and regorafenib, special caution will be taken by performing a planned safety evaluation for patients randomized to this arm (see Section 3.1.1.1).

Administration of atezolizumab 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 in the protocol body.

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, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab. Refer to Appendix 6 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 Regorafenib

The overall safety profile of regorafenib is based on data from more than 4800 treated patients in clinical trials, including placebo-controlled Phase III data for 636 patients with mCRC, 132 patients with GI stromal tumors, and 374 patients with hepatocellular carcinoma. The most serious adverse drug reactions in patients receiving regorafenib are severe liver injury, hemorrhage, GI perforation, and infection. The most frequently observed adverse drug reactions (≥ 30%) in patients receiving regorafenib are pain, hand-foot skin reaction, asthenia/fatigue, diarrhea, decreased appetite and food intake, hypertension, and infection.

Refer to the regorafenib local prescribing information for complete information regarding clinical safety.

A12–5.1.3 Risks Associated with Combination Use of Atezolizumab and Regorafenib

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and regorafenib: gastrointestinal toxicities (diarrhea/colitis), hepatic toxicity, cardiac toxicities (cardiac ischemia, myocardial infarction/myocarditis), dermatological toxicity/skin rash, Posterior Reversible Encephalopathy Syndrome (PRES)/meningoencephalitis, and hemorrhage/thrombocytopenia.

A12–5.1.4 Management of Patients Who Experience Adverse Events in Atezo+Regorafenib Arm

A12–5.1.4.1 Dose Modifications

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

For management of drug-related toxicities, the dose of regorafenib can be reduced by a decrement of 40 mg once a day (one dose level) from 120 mg to 80 mg. During the allowed dose escalation (Section A12–4.1.2.2), the continuation of a dose of 80 mg/day for as long as required for the management of drug-related toxicities is also allowed. If further dose reduction below 80 mg is indicated, the patient must discontinue regorafenib, unless the patient is likely to derive clinical benefit as determined by the investigator. *The Medical Monitor is available to advise as needed.* After dose reduction, the dose of regorafenib may be re-escalated at the investigator's discretion, provided there are no safety concerns.

A12–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or

equivalent before atezolizumab can be resumed. If atezolizumab is withheld for more than 12 weeks, the patient will be discontinued from the study. However, atezolizumab may be withheld for more than 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for more than 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

Regorafenib treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If regorafenib has been withheld for more than 42 days because of toxicity, the patient should be discontinued from regorafenib. However, regorafenib can be resumed after being withheld for more than 42 days if the patient is likely to derive clinical benefit. *The Medical Monitor is available to advise as needed.*

If atezolizumab or regorafenib is permanently discontinued, the other agent should also be discontinued unless the patient is likely to derive clinical benefit from single-agent use, as determined by the investigator. *The Medical Monitor is available to advise as needed.*

Refer to Section A12-4.1.2 for information on dose interruptions for reasons other than toxicity.

A12–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided below in Table 4 for events related to overlapping toxicities or regorafenib treatment.

For cases in which management guidelines are not covered in Appendix 6 or Table 4, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib Arm

Event	Action to Be Taken
IRRs, *CRS,* anaphylaxis, and hypersensitivity reactions	• Guidelines for management of IRRs *and CRS* for atezolizumab are provided in Appendix 6. • For anaphylaxis precautions, see Appendix 5.
Dermatologic toxicity (rash, hand–foot skin reaction/palmar–plantar erythrodysesthesia)	
General Guidance	• A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.
Dermatologic event, Grade 1	• Continue atezolizumab. Continue regorafenib at the same dose level. • Immediately institute supportive measures for symptomatic relief. • If rash is suspected to be related to atezolizumab, consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g. antihistamines).

Table 4: Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib Arm (cont.)

Event	Action to Be Taken
Dermatologic event, Grade 2	• Continue atezolizumab. Continue regorafenib and decrease dose by one level. [a] For suspected atezolizumab-related events: • Consider patient referral to dermatologist *for evaluation and, if indicated, biopsy.* • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • *If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.* For suspected regorafenib-related events: • Immediately institute supportive measures. <u>First occurrence:</u> • If event does not resolve to Grade 1 or better after dose reduction, withhold regorafenib for a minimum of 7 days. If event resolves to Grade 1 or better within 42 days, resume regorafenib at the reduced dose level. [a] If not, permanently discontinue regorafenib. [e] • A dose re-escalation is permitted at the investigator's discretion. <u>If event does not resolve within 7 days or at second or third occurrence:</u> • Withhold regorafenib for a minimum of 7 days. If event resolves to Grade 1 or better within 42 days, resume regorafenib with a one-level dose reduction. [a] If not, permanently discontinue regorafenib. [e] <u>Fourth occurrence:</u> • Permanently discontinue regorafenib. [e]

Table 4: Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib Arm (cont.)

Event	Action to Be Taken
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [b] Withhold regorafenib for a minimum of 7 days or until toxicity resolves to Grade 1 or better. For suspected atezolizumab-related events: • 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 within 12 weeks, resume atezolizumab. [b, c] If not, permanently discontinue atezolizumab and contact Medical Monitor. [d] • If event resolves to Grade 1 or better within 42 days, resume regorafenib with a one-level dose reduction.[a] If not, permanently discontinue regorafenib and contact Medical Monitor. For suspected regorafenib-related events: • Institute supportive measures immediately <u>First and second occurrence:</u> • If event resolves to Grade 1 or better within 42 days, resume regorafenib with a one-level dose reduction. [a, g] If not, permanently discontinue regorafenib. [e] • For first occurrence, a dose re-escalation is permitted at the investigator's discretion • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. [b] If not, permanently discontinue atezolizumab and contact Medical Monitor [d] <u>Third occurrence:</u> • Permanently discontinue regorafenib. [e]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and regorafenib and contact Medical Monitor. [d, e]
Suspected Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue regorafenib and contact Medical Monitor.

Table 4: Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib Arm (cont.)

Event	Action to Be Taken
Hepatic toxicity (elevations in ALT, AST, and/or bilirubin)	
≤ 5 × ULN elevations in ALT/AST (maximum Grade 2)	• Continue atezolizumab. Continue regorafenib at the same dose level. • Monitor LFTs more frequently until return to < 3 ULN (Grade 1) or baseline. For suspected immune-mediated events of > 5 days duration: • Withhold atezolizumab for up to 12 weeks after event onset. [b] Regorafenib can be continued at the same dose level at the investigator's discretion. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. [b, c] If not, permanently discontinue atezolizumab and contact Medical Monitor. [d]

Table 4: Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib Arm (cont.)

Event	Action to Be Taken
$>5\times$ ULN but $\leq 20\times$ ULN elevations in ALT/AST (Grade 3)	For suspected regorafenib-related/non–immune-mediated elevations in ALT/AST: • Withhold atezolizumab for up to 12 weeks after event onset. [b] Withhold regorafenib for up to 42 days. • Monitor LFTs at least weekly for at minimum of 4 weeks until transaminases return to <3 ULN (Grade 1) or baseline. • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. [b] If not, permanently discontinue atezolizumab and contact Medical Monitor. [d] <u>First occurrence:</u> • If event resolves to Grade 1 or better within 42 days, resume regorafenib with a one-level dose reduction. [a, g] If not, permanently discontinue regorafenib. [e] <u>Second occurrence:</u> • Permanently discontinue regorafenib. [g] For suspected immune-mediated events: • Permanently discontinue atezolizumab and contact Medical Monitor. [d] Withhold regorafenib. • 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 Grade 1 or better within 12 weeks, taper corticosteroids over $\geq$ 1 month. [b] • If event resolves to Grade 1 or better within 42 days, resume regorafenib with a one-level dose reduction. [a] If not, permanently discontinue regorafenib. [e]

Table 4: Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib Arm (cont.)

Event	Action to Be Taken
$>20\times$ ULN elevations in ALT/AST (Grade 4)	• Permanently discontinue atezolizumab and regorafenib and contact Medical Monitor. [d, e] • Follow Grade 3 management guidelines for suspected immune-mediated events.
$>3\times$ ULN elevations in ALT/AST (Grade 2 or higher) with concurrent bilirubin $>2\times$ ULN	• Permanently discontinue atezolizumab and regorafenib and contact Medical Monitor. [d, e] • Monitor liver function at least weekly until values return to baseline. • Investigate causes for elevated bilirubin and initiate treatment per institutional guidelines. • Exception: Patients with Gilbert syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.
GI toxicities	
Any GI perforation or fistula	• Permanently discontinue regorafenib. [e]
Diarrhea or colitis, Grade 1	• Continue atezolizumab. Continue regorafenib at the same dose level. • 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 [b]. Regorafenib may be continued at the same dose level at the investigator's discretion. • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. [b, c] If not, permanently discontinue atezolizumab and contact Medical Monitor. [d] • If regorafenib was withheld and event resolves to Grade 1 or better within 42 days after event onset, decrease by one dose level when resuming treatment. [a, g]

Table 4: Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib Arm (cont.)

Event	Action to Be Taken
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [b] Withhold regorafenib for up to 42 days. For suspected immune-mediated events (including colitis): • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. [b, c] If not, permanently discontinue atezolizumab and contact Medical Monitor. [d] For regorafenib-related events: <u>First and second occurrence:</u> • If event resolves to Grade 1 or better within 42 days, resume regorafenib with a one-level dose reduction. [a] If not, consider permanent discontinuation of regorafenib. [e] • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab.[b] If not, consider permanent discontinuation of atezolizumab and contact medical monitor[d]. <u>Third occurrence:</u> • Consider permanent discontinuation of regorafenib. [e]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and regorafenib and contact Medical Monitor. [d, e] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Table 4: Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib Arm (cont.)

Event	Action to Be Taken
Cardiac Toxicities	
General guidance	• Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. • 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.
Immune-mediated myocarditis, Grade 1	• Atezolizumab may be continued at the investigator's discretion. Regorafenib may be continued at the same dose level, at the investigator's discretion. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myocarditis, Grade 2	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [d] Regorafenib may be continued at the same dose level, at the investigator's discretion. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • 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 event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. [b, c] If not, permanently discontinue atezolizumab and contact Medical Monitor. [d]

Table 4: Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib Arm (cont.)

Event	Action to Be Taken
Immune-mediated myocarditis, Grade 3	• Permanently discontinue atezolizumab and contact Medical Monitor.[d] Withhold regorafenib for up to 42 days. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better within 12 weeks, taper corticosteroids over ≥ 1 month.[b] • If event resolves to Grade 1 or better within 42 days, consider resuming regorafenib.[g]
Immune-mediated myocarditis, Grade 4	• Permanently discontinue atezolizumab and regorafenib contact Medical Monitor.[d, e] • Manage as per Grade 3 guidelines.
New or acute onset cardiac ischemia or infarction	• Withhold atezolizumab. Withhold regorafenib. • If the acute cardiac ischemic events resolve and if the potential benefits outweigh the risks of further cardiac ischemia, resume atezolizumab and resume regorafenib. If not, permanently discontinue atezolizumab and regorafenib and contact Medical Monitor.[d, e]
Infection	
Infections, Grade 3 or 4 or a worsening infection of any grade	• Withhold regorafenib. Atezolizumab may be continued at the investigator's discretion. • If infection resolves within 42 days, resume regorafenib at the same dose level. If not permanently discontinue regorafenib.[e]
Hemorrhage	

Table 4: Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib Arm (cont.)

Event	Action to Be Taken
Hemorrhage, Grade 3 or 4	• Permanently discontinue regorafenib and contact Medical Monitor. [e, f] • Monitor INR levels more frequently in patients receiving warfarin.
Hypertension	
General guidance	• Grade 2 or above, start anti-hypertensive therapy.
Hypertension, Grade 2	• Withhold regorafenib. Continue atezolizumab. • If blood pressure is < 150/100 mmHg within 42 days, resume regorafenib with the decision to maintain the current dose level or to reduce by one dose level at the discretion of the investigator. [a]
Hypertension, Grade 3	• Withhold regorafenib. Atezolizumab may be continued at the investigator's discretion. • If blood pressure is < 150/100 mmHg within 42 days, resume regorafenib with the decision to maintain the current dose level or to reduce by one dose level at the discretion of the investigator. [a] • If blood pressure is not controlled to < 150/100 mmHg with anti-hypertensive therapy, permanently discontinue regorafenib and contact Medical Monitor. [e]
Hypertension, Grade 4 (includes hypertensive crisis and hypertensive encephalopathy)	• Permanently discontinue atezolizumab and regorafenib and contact Medical Monitor. [d, e]
Reversible posterior leukoencephalopathy syndrome	
Reversible posterior leukoencephalopathy syndrome	• Permanently discontinue regorafenib and contact Medical Monitor. [e]

Table 4: Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib Arm (cont.)

Event	Action to Be Taken
Wound dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	• Permanently discontinue regorafenib and contact Medical Monitor. [e]
Regorafenib-related toxicities not described above	
Grade 1 or Grade 2 (tolerable)	• Continue atezolizumab. Continue regorafenib at the same dose level.
Grade 2 (intolerable) or Grade 3	• Atezolizumab may be continued at the investigator's discretion. First and second occurrence: • Withhold regorafenib until event resolves to Grade 1 or better within 42 days, then resume regorafenib with a one-level dose reduction. [a, g] If event does not resolve to Grade 1 or better, permanently discontinue regorafenib. [e] Third occurrence: • Consider permanent discontinuation of regorafenib. [e]
Grade 4	• Permanently discontinue atezolizumab and regorafenib and contact Medical Monitor. [d, e]
Atezolizumab-related toxcities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue regorafenib at the same dose level.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold regorafenib. [f] • If event improves within 42 days, resume regorafenib.[g] If not, permanently discontinue regorafenib. [e]

Table 4: Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib Arm (cont.)

CRS = cytokine release syndrome; ECMO = extracorporeal membrane oxygenation; GI = gastrointestinal; IRR = infusion-related reaction; ULN = upper limit of normal; VAD = ventricular assist device.

[a] The dose of regorafenib can be reduced by a decrement of 40 mg, once a day, from 120 mg to 80 mg (i.e., one dose level) for management of drug-related toxicities. Additional dose reductions are not allowed. If a dose reduction is indicated for a patient receiving the 80-mg dose of regorafenib, then that patient should discontinue regorafenib, unless the patient is likely to derive clinical benefit as determined by the investigator. *The Medical Monitor is available to advise as needed.* Upon adverse event resolution, a dose re-escalation of regorafenib from 80 mg to 120 mg is allowed at the investigator's discretion.

[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 ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

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

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

[e] Resumption of regorafenib may be considered in patients who are deriving benefit and and have fully recovered from the toxicity. *The decision to* re-challenge *patients* with regorafenib *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *The* Medical Monitor *is available to advise as needed.*

[f] For Grade 3 events not related to regorafenib, regorafenib may be continued at the discretion of the investigator per medical judgement.

[g] Regorafenib may be withheld for a longer period of time (i.e. >42 days after event onset). The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

A12–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO+REGORAFENIB 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 in the protocol body for reporting instructions). Adverse events of special interest for the Atezo+Regorafenib arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7 in the protocol body)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10 \times$ upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, and optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

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

A12–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab or 2 months after the last dose of regorafenib. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A12–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 2 months after the last dose of regorafenib. 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 patient exposed to study treatment. When permitted by the site, the pregnant partner will 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 patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator 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 in the protocol body).

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 patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 in the protocol body).

A12–6. SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+REGORAFENIB ARM

Table 5 Schedule of Activities for Atezo + Regorafenib Arm

Assessment/Procedure	Screening Days –28 to –1	Treatment Cycles (28-Day Cycles) [a]									Stage 2 Screen. [c] or Treat. Discon. [d]	Follow-Up Every 3 Months (±7 days)
		Cycle 1 [b]				Cycle 2			Cycles ≥3			
		Days				Days			Days			
		1	8 (±1 d)	15 (±1 d)	22 (±1 d)	1	8 (±1 d)	15 (±1 d)	1 (+2d)	15 (±2 d)		
Molecular profile of CRC (if available)	See Appendix 15	Whenever updated information becomes available										
Vital signs [e]		x	x	x	x	x	x	x	x	x	x	
Weight		x [f]				x [f]			x [f]		x	
Complete physical examination [g]											x	
Limited physical examination [h]		x [f]	x [f]	x [f]	x [f]	x [f]	x [f]	x [f]	x [f]	x [f]		
ECOG Performance Status		x [f]				x [f]			x [f]		x	
ECG [i]		Perform as clinically indicated [f]									x [o]	
Hematology [j]		x [k, l]		x [k]		x [k]		x [k]	x [k]	x [k]	x	
Chemistry [m]		x [k, l]		x [k]		x [k]		x [k]	x [k]	x [k]	x	
Coagulation (INR and aPTT) [n]		x [k, l]				x [k]			x [k]		x [o]	
TSH, free T3 (or total T3), and free T4 [p]		x [k, l, p]									x	
Viral serology [q]											x [o, q]	
C-reactive protein											x [o]	
Plasma CEA [r]		x [k]							x [k, r]			

Table 5 Schedule of Activities for Atezo + Regorafenib Arm (cont.)

Assessment/Procedure	Screening Days –28 to –1	Treatment Cycles (28-Day Cycles) [a]									Stage 2 Screen. [c] or Treat. Discon. [d]	Follow-Up Every 3 Months (±7 days)
		Cycle 1 [b]				Cycle 2			Cycles ≥ 3			
		Days				Days			Days			
		1	8 (±1 d)	15 (±1 d)	22 (±1 d)	1	8 (±1 d)	15 (±1 d)	1 (+2d)	15 (±2 d)		
LDH	See Appendix 15										x [o]	
Pregnancy test [s]		x [k, l]				x [k]			x [k]		x [t]	x [s]
Urinalysis [u]		x				x			x		x [o, t]	
Serum autoantibody sample [v]		Perform if patients experience suspected immune-mediated adverse event									x [o]	
Blood sample for RBR (optional) [w]		x										
Biomarker samples		Refer to Table 6 below										
Serum ADA sample		Refer to Table 6 below										
Serum and plasma PK sample		Refer to Table 6 below										
Tumor biopsy		x [x]										
Tumor biopsy (optional)		x [y]										
Tumor response assessments		x [z, aa, bb]										
Concomitant medications [cc]		x	x	x	x	x	x	x	x	x	x	
Adverse events [dd]		x	x	x	x	x	x	x	x	x	x [dd]	x [dd]
Administer atezolizumab [ee, ff]		x		x		x		x	x	x		
Dispense regorafenib [ff, gg]		x				x			x			
Study drug accountability [hh]				x		x		x	x	x		
Survival follow-up and anti-cancer treatment												x [ii]

Table 5 Schedule of Activities for Atezo + Regorafenib Arm (cont.)

ADA = anti-drug antibody; CT = computed tomography; d = day; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; Treat. = treatment; TSH = thyroid-stimulating hormone.

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 *may* occur outside of the specified window.

[b] It is recommended that treatment be initiated no later than 7 days after randomization.

[c] Patients who experience loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details) or unacceptable toxicity may be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.2 in the protocol body provided Stage 2 is open for enrollment) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will undergo follow-up assessments after completing the treatment discontinuation visit.

[e] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Refer to Section A12-4.1.2 for details related to vital signs monitoring during atezolizumab infusions.

[f] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[g] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.administered. The skin examination should be extended according to medical need.

[i] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

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

[k] Laboratory tests must be performed within 96 hours prior to *dosing* during the treatment period.

[l] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

Table 5 Schedule of Activities for Atezo + Regorafenib Arm (cont.)

[m] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (per standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. CPK will be performed only on Day 1 of each cycle and at treatment discontinuation.

[n] Monitoring of INR/aPTT should be performed more frequently if clinically indicated.

[o] Assessments to be performed only for patients undergoing Stage 2 screening.

[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[q] At Stage 2, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[r] CEA will be assessed on Day 1 of Cycle 1 and every 2 cycles thereafter (i.e., Cycles 3, 5, 7, etc.) until disease progression.

[s] 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 and at 3 months and 6 months after treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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

[u] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. Patients with ≥2+protein on dipstick urinalysis must undergo a 24-hour urine collection and demonstrate <3.5 g of protein in 24 hours. *Urinalysis may be performed up to 72 hours prior to Day 1 of each cycle, as results must be available prior to treatment administration.*

[v] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[w] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. RBR sample should be collected prior to study treatment.

[x] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial-biopsy arm (see Section 3.1.1.2 in the protocol body) will undergo tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible by the investigator). See Section 4.5.7 in the protocol body for tissue sample requirements.

[y] Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation, if deemed clinically feasible and may undergo additional on-treatment biopsies at any other time during Stage 1 or Stage 2 at the investigator's discretion.

Table 5 Schedule of Activities for Atezo + Regorafenib Arm (cont.)

[z] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[aa] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head CT 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).

[bb] For patients who undergo screening for Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

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

[dd] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6 in the protocol body). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[ee] Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle. The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[ff] Treatment will continue until unacceptable toxicity or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details).

Table 5 Schedule of Activities for Atezo + Regorafenib Arm (cont.)

[gg] Patients will receive regorafenib orally on Days 1–21 of each cycle. At least 7 days off regorafenib are required prior to starting a new treatment cycle (See Section A12–4.1.2.2 for more details). On clinic visit days when PK samples are collected, patients should take their regorafenib dose in the clinic.

[hh] Medication diaries should be collected and reviewed, and unused medications should be collected for assessment of compliance.

[ii] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from 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 patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table 6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Regorafenib Arm: Preliminary and Expansion Phases

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Regorafenib PK (plasma) [a] • Biomarkers (plasma, serum, PBMC)
	30 (±10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 8 of Cycle 1	Prior to study treatment	• Regorafenib PK (plasma) [a]
Day 15 of Cycle 1	Prior to study treatment	• Regorafenib PK (plasma) [a] • Biomarkers (plasma, serum)
Day 22 of Cycle 1	24 hours after regorafenib dose	• Regorafenib PK (plasma) [a]
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycles 4 and 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)

Atezo = atezolizumab; ADA = anti-drug antibody; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: Based on emerging safety/efficacy data the number of PK/ADA and/or biomarker samples may be reduced/removed and/or the timing of samples may be modified. Samples may be banked in the preliminary phase and ungated at expansion as appropriate.

[a] Regorafenib PK includes regorafenib, regorafenib M-2, and regorafenib M-5.

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Appendix 13
Study Details Specific to Atezo+Regorafenib+AB928 Arm

TABLE OF CONTENTS

A13–1 BACKGROUND FOR ATEZO + REGORAFENIB + AB928 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 CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody mediated clearance of activated effector T cells.

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

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

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

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

A13–1.2 BACKGROUND ON REGORAFENIB

Regorafenib is an orally administered multikinase inhibitor, which targets signaling pathways implicated in multiple tumor-promoting processes. Its targets include the pro-angiogenic kinases, vascular endothelial growth factor receptor 1-3 (VEGFR 1-3) and tyrosine receptor kinase 2, and kinases promoting a pro-tumorigenic microenvironment, such as platelet-derived growth factor receptors and fibroblast growth factor. This agent also inhibits the mutant oncogenic kinases KIT, RET, and B-RAF, as well as the growth factor receptor for macrophages colony stimulating factor 1 receptor (CSF-1R) (Wilhelm et al. 2010; Uitdehaag et al. 2014). Regorafenib exhibited potent tumor growth inhibition in nonclinical models, including colon tumor models (Wilhelm et al. 2010; Abou-Elkacem et al. 2013).

Regorafenib conferred a survival benefit over best supportive care in patients with refractory metastatic colorectal cancer (mCRC) in randomized, double-blind, placebo-controlled trials both in Western and Asian populations (Grothey et al. 2013; Li et al. 2015). The most common adverse events included hand–foot syndrome, fatigue, diarrhea, hypertension, voice changes, oral mucositis, and rash/desquamation.

Regorafenib is approved worldwide (under the tradename of Stivarga®) for the treatment of patients with mCRC who previously received fluoropyrimidine-based, oxaliplatin-based, and irinotecan-based chemotherapy; prior anti-VEGF therapy; and, if patients have a KRAS wild-type tumour, previous anti-EGFR therapy. It is also approved in Europe in unresectable or metastatic gastrointestinal (GI) tumours and in patients with hepatocellular carcinoma who were previously treated with sorafenib.

A13–1.3 BACKGROUND ON AB928

AB928 is a low molecular weight, orally bioavailable, selective dual antagonist of the adenosine 2a receptor ($A_{2a}R$) and the adenosine 2b receptor ($A_{2b}R$). Adenosine, a cellular metabolite that can inhibit the activation of various immune cell types, is present at high concentrations in many tumors and may play a key role in creating an immune-suppressed tumor microenvironment (TME). Within the TME, adenosine can be generated from several extracellular sources (e.g., adenosine triphosphate [ATP]) and is present at higher concentrations compared with healthy tissue. The therapeutic rationale for the clinical development of AB928 derives from the observation that most tumors contain high extracellular levels of adenosine, which activates $A_{2a}R$ and $A_{2b}R$ on T cells and myeloid cells, respectively, resulting in impaired T-cell activation and proliferation. Through the use of biochemical and cell-based assays and nonclinical models, AB928 has been shown to selectively reverse the immunosuppressive effects caused by high concentrations of adenosine, without causing any immune activation effects on its own.

Refer to the AB928 Investigator's Brochure for details on nonclinical studies.

A13–2 RATIONALE FOR ATEZO+REGORAFENIB+AB928 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, urothelial carcinoma, renal cell carcinoma, melanoma, CRC, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

Early clinical data had shown encouraging results with the anti–PD-1 checkpoint inhibitor pembrolizumab as a single agent in patients with mCRC assessed as having high microsatellite instability (MSI-H) status, but not with microsatellite stable (MSS) status (Le et al. 2015). These data resulted in the May 2017 approval of pembrolizumab in adult and pediatric patients with tumors characterized as MSI-H or deficient for mismatch repair genes based on objective response rate (ORR) and durability of the response. ORR was similar irrespective of whether patients were diagnosed with CRC (36%) or a different cancer type (46% across the 14 other MSI-H cancer types). Similar response rates were observed in patients with second line or later mCRC enrolled in a Phase Ia study investigating atezolizumab as single agent (Roche Study PCD4989g) and a Phase Ib study investigating the combination of atezolizumab plus bevacizumab (Roche Study GP28328, Arm A). In Study PCD4989g, there was 1 responder reported in 14 patients with MSS status per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). In the 10 patients with MSI-H status enrolled in Study GP28328, the investigator assessed confirmed ORR per RECIST v1.1 was 40% (95% CI: 12.2, 73.8), with all 4 responders having partial responses. No objective responses were seen in the 14 patients with MSS tumors.

A13–2.2 REGORAFENIB AS A MULTI-TARGETED ANTI-ANGIOGENIC AND IMMUNOMODULATORY AGENT

Consistent with its inhibitory activity on VEGFR 1-3, regorafenib demonstrated stronger anti-angiogenic activity compared with a selective anti-VEGFR2 antibody in a mouse colon tumor model (Abou-Elkacem et al. 2013). In addition to its inhibitory effect on angiogenesis, regorafenib also displayed immunomodulatory effects in nonclinical models (Abou-Elkacem et al. 2013; Hoff et al. 2017). Regorafenib treatment reduced

tumor associated macrophage abundance in both MC38 and CTC26 colon tumors and also promoted their switch from the pro-tumorigenic M2 phenotype to the anti-tumorigenic M1 phenotype in colon tumor models (Abou-Elkacem et al. 2013; Hoff et al. 2017). These effects could result from the counteracting of the immune suppressive properties of VEGF signaling (Chen and Hurwitz 2018) or from the blockade CSF1-R–dependent signaling (Hoff et al. 2017), which positively regulates macrophage migration, differentiation, and survival (DeNardo and Ruffell 2019).

A13–2.3 THE ADENOSINE PATHWAY

Research over the past decade has led to the discovery of several new immunomodulatory pathways, including the CD39/CD73–adenosine axis, which has emerged as one of the most promising pathways to therapeutically target in immuno-oncology (Le Mercier et al. 2015; Marin-Acevedo et al. 2018).

One hallmark of immunogenic cell death is the release of ATP into the extracellular space within the TME, which contributes to T-cell activation and anti-tumor responses (Kroemer et al. 2013). However, this extracellular ATP undergoes rapid degradation by two ectonucleotidases: CD39 and CD73. CD39 converts ATP to adenosine monophosphate (AMP), and, subsequently, CD73 converts AMP to adenosine. Multiple cell types within the TME, including tumor cells, cancer-associated fibroblasts, endothelial cells, and immune cells, express CD39 and CD73. Adenosine is present at high concentrations in many tumors types and has been shown to have multiple pro-tumoral effects, including the promotion of tumor cell growth, survival and dissemination; angiogenesis; and tumor immune evasion (Vigano et al. 2019).

Adenosine is immunosuppressive for multiple immune cell types through signaling via $A_{2a}R$ and $A_{2b}R$. Downstream signaling through $A_{2a}R$ primarily impacts the biology of T-cells and NK cells by impairing their effector function (i.e., proliferation and inflammatory cytokine production). Downstream signaling through $A_{2b}R$ mostly acts on myeloid cells by increasing their immunosuppressive function. This includes the promotion of macrophage M2 polarization through the induction and upregulation of arginase-1, interleukin 10, and VEGF production. In addition, adenosine signaling inhibits the differentiation of monocytes to dendritic cells (DCs) through $A_{2b}R$ and interferes with their Th1–priming activity through both $A_{2a}R$ and $A_{2b}R$ (Vigano et al. 2019). Targeted blockade of the adenosine pathway was shown to effectively promote anti-tumor immunity and tumor control in various nonclinical models (Beavis et al. 2015; Dahan and Ravetch, 2016; Allard et al. 2017; Perrot et al. 2019). Therefore, targeting adenosine receptors to block the deleterious effects of high concentrations of extracellular adenosine has emerged as novel approach to stimulate antitumor immunity. AB928 was developed as a low molecular weight, orally bioavailable, selective dual antagonist of $A_{2a}R$ and $A_{2b}R$. Nonclinical data have shown that AB928 selectively reverses the immunosuppressive effects caused by high concentrations of adenosine,

without causing any immune activation effects of its own. Targeting the adenosine pathway by dual inhibition of $A_{2a}R$ and $A_{2b}R$ combines the advantages of (1) blockade of adenosine signaling downstream of the redundant pathways that generate adenosine and (2) broad interference with the multiple pro-tumorigenic and immunosuppressive activities of adenosine.

Recent evidence suggests a pro-tumorigenic role for the adenosine pathway in the biology of CRC. First, the immunosuppressive role of the adenosine pathway has been documented in nonclinical colon tumor models through apoptotic T-regulatory cells. Maj et al. reported the presence of apoptotic T-regulatory cells in the TME of human ovarian cancer samples, as well as in murine tumors, including the syngenic MC38 colon carcinoma. However, these T-regulatory cells retained strong immunosuppressive properties and abolished the anti-tumor effect of immunotherapy. The authors further showed that apoptotic T-regulatory cells suppressed effector T-cells through the release of large amounts of ATP and the conversion to adenosine via the CD39 and CD73 ectonucleotidases (Maj et al. 2017). Analyses of clinical samples further support a role of adenosine in T-regulatory cell–mediated suppression in CRC. Sundström et al showed that T-regulatory cells isolated from patients with CRC expressed high levels of CD39 and were able to prevent migration of CD8+ T cells, which could be rescued by blocking CD39 (Sundström et al. 2016). Another study also showed that CD39+ T-regulatory cells accumulate in tumors and peripheral blood of patients with CRC and that the peripheral CD39+ T-regulatory cells isolated from these patients suppress proliferation of T-cells, suggesting CD39 as a potential therapeutic target in CRC (Ahlmanner et al. 2018).

Furthermore, several correlative studies also suggest a prognostic role for the adenosine pathway in CRC. Data from the The Cancer Genome Analysis showed that, of the many tumor types that express high levels of CD73, CRC is among the highest across tumor types (Direnzo et al. 2019) and high expression of CD73 was correlated with decreased overall survival (OS) in CRC (Wu et al. 2012). Additionally, selected single nucleotide polymorphisms in the ENTPD1 gene encoding for CD39 may affect the clinical outcome of patients with mCRC treated with FOLFIRI and bevacizumab. Indeed, patients with any C allele in CD39 rs11188513 had a significantly shorter median PFS and OS compared with patients with the T/T variant (Tokunaga et al. 2019).

Taken together, nonclinical and clinical data suggest that targeting the adenosine pathway may improve outcomes for patients with CRC.

A13–2.4 RATIONALE FOR COMBINING AB928 WITH CHECKPOINT INHIBITION AND REGORAFENIB

The immune suppressive role of VEGF is now well established, and the combination of anti-VEGF therapies with blockade of the PD-L1/PD-1 axis has shown synergy in

nonclinical models and has resulted in positive outcomes in Phase I to III clinical studies (Chen and Hurwitz 2018). In addition, M2-macrophages are considered a central driver of the immunosuppressive TME through their ability to suppress DC differentiation and function and T-cell effector function. As a result, macrophage depletion can unleash CD8+ T-cell response and increase the efficacy of checkpoint blockade in nonclinical tumor models (DeNardo and Ruffell 2019). Therefore, among the multi-targeted mechanisms of action of regorafenib, blockade of VEGF and CSF-1R signaling is expected to show combinatorial efficacy with checkpoint inhibition (CPI). Accordingly, the combination of regorafenib with anti–PD-1 blockade showed superior anti-tumor activity compared with either individual agent in murine colon tumor models (Hoff et al. 2017).

Clinical data from the REGONIVO trial presented at ASCO 2019 (Fukuoka et al. 2019) showed promising results when combining the standard-of-care treatment regorafenib with the anti–PD-1 checkpoint inhibitor antibody nivolumab in patients with advanced, metastatic colorectal or gastric cancer (GC). An objective tumor response was observed in 19 patients (38%), including 11 patients with MSS GC, 7 patients with MSS CRC, and 1 patient with MSI-H CRC, with corresponding ORRs of 44% in GC and 29% in MSS CRC. At a median follow-up of 8.0 months, the median PFS time was 6.3 months. These outcomes outperform the clinical activity of regorafenib and anti–PD-1 antibody when used as a single-agent in MSS mCRC where ORRs of 2% and 0%, respectively, were observed (Grothey et al. 2013; Le et al. 2015; Li et al. 2015; Eng et al. 2019). Taken together, these data suggest a synergy between PD-1 blockade and regorafenib and provide a rationale to further investigate combinatorial strategies building on the backone of regorafenib plus anti–PD-L1/PD-1 therapy in MSS CRC.

Elevated CD73 expression has the potential to increase extracellular levels of adenosine that render tumors more resistant to immunotherapies (Serra et al. 2011). Adenosine stimulates the adenosine receptors on T cells and NK cells, thereby increasing PD-L1 expression and suppressing anti-tumor immune responses (Vigano et al. 2019). These nonclinical findings appear to be corroborated by clinical correlative data in CRC that showed a positive correlation between $A_{2a}R$ expression and PD-L1 expression in primary tumor specimens and an independent association for the expression of both markers with shorter OS (Wu et al. 2012). Additionally, CD73 was shown to be upregulated in patients following anti–PD-1 treatment, pointing to the adenosine pathway as a potential mechanism of resistance to anti–PD-1 therapy (Fong et al. 2017). Accordingly, recent nonclinical studies have shown that blockade of the adenosine receptor with either anti-CD73 antibodies or adenosine receptor antagonists enhances the anti-tumor immune response induced by PD-L1/PD-1 inhibitors (Allard et al. 2013; Mittal et al. 2014; Beavis et al, 2015; Perrot et al. 2019). Furthermore, a preliminary signal of clinical activity has been reported for the combination of the anti-CD73 antibody

oleclumab with the anti–PD-L1 antibody durvalumab in pancreatic cancer and MSS CRC (Overman et al. 2018). These findings underscore the potential for synergy of $A_{2a}R$/$A_{2b}R$ antagonists plus PD-1/PD-L1 blockade.

Finally, additional mechanisms suggest the potential for combined efficacy of regorafenib with adenosine pathway inhibition. Adenosine has direct mitogenic effects on vascular cells that may contribute to angiogenesis, although the main pro-angiogenic actions of adenosine have been attributed to its ability to regulate the production of pro- and anti-angiogenic substances from vascular cells and immune cells within the microenvironment of hypoxic tissues, mediated by both $A_{2a}R$ and $A_{2b}R$ signaling (Feoktistov et al. 2002; Olah and Caldwell, 2003; Desai et al. 2015). In addition, data from the REGONIVO study showed a decrease in T-regulatory cell infiltration in post-treatment biopsies from patients who responded to the regorafenib plus nivolumab combination. As apoptotic T-regulatory cells can contribute to immunosuppression within the TME via the adenosine pathway (Maj et al. 2017), the finding from the REGONIVO study indicates that adding an inhibitor of the adenosine pathway to the combination of a checkpoint inhibitor plus regorafenib will enable a superior inhibition of intratumoral T-regulatory cells.

Therefore, the opportunity to evaluate the combination of an adenosine pathway inhibitior, such as AB928, an anti-angiogeneic agent, such as regorafenib, and an anti–PD-L1 therapy, such as atezolizumab, could bring together both additive and synergistic mechanisms of action, which could ultimately translate into clinical benefit in patients with mCRC who have become refractory to first- and second-line standard therapies.

A13–2.5 BENEFIT–RISK ASSESSMENT

This study will enroll patients with mCRC who have become refractory to first- and second-line standard therapies. This patient population has a median OS of less than 9 months with currently available treatments. Treatment options have shown limited efficacy and are often poorly tolerated.

Despite the success of single-agent CPI in the MSI-H patient population, the vast majority of patients with CRC have MSS tumors and do not respond to single-agent CPI, highlighting the need for safe and effective combination treatments. In addition, the benefit of single-agent regorafenib over best supportive care is limited. Therefore, there remains a great need for investigating new cancer immunotherapy combinations to improve the outcome of this difficult-to-treat patient population.

The most frequently observed adverse drug reactions (≥ 30%) in patients receiving regorafenib are pain, hand–foot skin reaction, asthenia/fatigue, diarrhea, decreased appetite and food intake, hypertension, and infection. These toxicities occur early and

may be dose-dependent (Grothey 2019). A randomized Phase II study (the ReDOS trial) showed that using a weekly dose-escalation strategy (from 80 mg/day to 160 mg/day) enabled patients to stay on treatment longer and decreased the incidence of Grade 3 and 4 toxicities when compared with using the approved starting dose of 160 mg/day (Bekaii-Saab et al. 2019).

In the dose-escalation cohort of the REGONIVO study, patients were treated with 80-mg, 120-mg, or 160-mg doses of regorafenib once per day for 21 days in a 28-day cycle plus 3 mg of nivolumab every 2 weeks (Q2W). Treatment-related adverse events (all grades) were reported in 100% of patients across the 3 dose groups. The rate of Grade ≥ 3 treatment-related adverse events was 40%. The most common Grade ≥ 3 treatment-related adverse events were rash (12%), proteinuria (12%), palmar-plantar erythrodysesthesia (10%), and liver dysfunction (6%). In patients who received regorafenib at the 80-mg dose, the rate of Grade ≥ 3 treatment-related adverse events was 27% compared with 44% in those who received the 120-mg dose. These toxicities were considered to be manageable by the investigators and were balanced with the unprecedented efficacy signal in this heavily pre-treated patient population.

The dose of regorafenib that is planned to be administered in this study is 120 mg/day, which is the maximum tolerated dose (MTD) that was identified in the REGONIVO study. Moreover, based on the ReDOS study findings dose escalation from 80 mg/day to 120 mg/day during Cycle 1 will be allowed in order to improve the safety profile of regorafenib in combination with CPI.

Because AB928 is currently being evaluated in cancer patients and efficacy data are not yet available, its benefits are unknown at this time. However, based on its mechanism of action, nonclinical data demonstrated that AB928 selectively reverses the immunosuppressive effects caused by high concentrations of adenosine, without causing any immune activation effects of its own. Preliminary safety data from the first-in-human Phase I placebo-controlled, blinded study in healthy volunteers (Study AB928CSP0001) showed that the investigational product (blinded AB928 or matching placebo) was tolerable at all doses tested (i.e., no early stopping rules were met) and did not affect any physiologic parameters potentially sensitive to adenosine inhibition at a dose of 75 mg. All reported adverse events were of mild or moderate severity, and there was no clear pattern of toxicity observed at the dose levels tested, other than mild-to-moderate GI symptoms. No clinically significant laboratory findings (with the exception of an increase in C-reactive protein in 1 patient who received a single 10-mg dose of blinded investigational product) or signs of general, cardiac, or neurologic toxicity were observed, and no patients discontinued from the study.

Safety data are also available for the combination of AB928 with the anti–PD-1 antibody AB122, which is currently undergoing evaluation in an ongoing Phase I, open-label,

multicenter, dose-escalation and dose-expansion study (Study AB928CSP0005). In the dose-escalation phase, patients received doses of 75 mg, 150 mg, and 200 mg once daily (QD) in combination with AB122 at a dose and schedule of 240 mg Q2W. As of 03 July 2019, 9 of 12 patients (75%) with previously treated advanced solid tumors reported at least one treatment-emergent adverse event. The most commonly reported adverse events (in more than 1 patient) regardless of AB928 dose, severity, or relationship to investigational treatment were fatigue (4 patients); nausea and rash (3 patients each); and, abdominal pain, headache, pruritus, sinusitis, upper respiratory tract infection, and vomiting (2 patients each). Most adverse events were mild to moderate in intensity. All 4 cases of fatigue were considered related to either AB928 and/or AB122, which was the most common treatment-related adverse event. All cases of fatigue were Grade 1. Three patients reported Grade 3 adverse events; none were related to AB928. No Grade 4 or 5 events were observed. Five serious adverse events were reported by 3 patients; no serious event was considered related to either AB928 or AB122. One patient who received AB928 at 150 mg QD experienced Grade 2 maculopapular rash that was considered dose-limiting according to the protocol definition as the participant missed >20% of AB928 doses during the dose-limiting toxicity (DLT) evaluation period as a result of the event. No other DLTs were reported.

Safety data are available for single-agent atezolizumab in patients with solid tumors, including CRC. Potential overlapping toxicities for the combination of atezolizumab, regorafenib, and AB928 may occur within the system organ classes of GI, hepatobiliary, cardiac, skin, nervous system, and blood and lymphatic system disorders. The relevant corresponding overlapping toxicities of atezolizumab include immune-related colitis, hepatitis, myocarditis, skin rash, meningoencephalitis and thrombocytopenia.

Exposures to AB928, regorafenib, and regorafenib active metabolites M-2 and M-5 may be affected by coadministration of AB928 and regorafenib. As AB928 is a substrate of breast cancer resistance protein (BCRP), regorafenib has potential to increase AB928 exposure through inhibition of BCRP. AB928, a CYP3A4 inducer in vitro, may reduce regorafenib exposure but increase exposures to active metabolites M-2 and M-5. AB928, regorafenib, M-2, and M-5 exposures in patients will be determined to monitor the potential DDI risk. Additionally, the concomitant use of known strong CYP3A4 inducers as well as known BCRP substrates with a narrow therapeutic window that are orally administered will be prohibited during study participation.

In summary, the investigation of the safety of each molecule as a single agent in patients with solid tumors has not revealed findings that would prohibit the investigation of the atezolizumab, regorafenib, and AB928 combination in the setting of a Phase Ib/II study. Considering the different but potentially synergistic mechanisms of action of atezolizumab, regorafenib, and AB928, as well as the preliminary efficacy and

manageable safety profile of the above described combinations, it is hypothesized that treatment with atezolizumab, regorafenib, and AB928 has promising therapeutic potential in solid tumors such as MSS mCRC.

For the evaluation of the impact of the COVID-19 pandemic on the benefit–risk assessment, please refer to Section 1.4.

A13–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + REGORAFENIB + AB928 ARM

A13–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 840 mg Q2W (840 mg on Days 1 and 15 of each 28-day cycle). The average concentration following the 840 mg Q2W dosage is expected to be equivalent to that of 1200 mg every 3 weeks (Q3W), an approved dosage for atezolizumab , as outlined in the prescribing information. Anti-tumor activity has been observed across doses ranging from 1 to 20 mg/kg Q3W. In Study PCD4989g, the MTD of atezolizumab was not reached and no DLTs were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A13–3.2 RATIONALE FOR REGORAFENIB DOSE AND SCHEDULE

The approved dose for regorafenib is 160 mg/day. In the REGONIVO study evaluating regorafenib in combination with nivolumab in Asian patients, DLTs were reported at the 160-mg/day dose and Grade 3 skin toxicities were reported in 20% of the patients treated with the 120-mg/day dose. This resulted in the use of the 80-mg/day dose of regorafenib in the expansion cohort. However, modeling and simulation analyses of data from the CORRECT and CONCUR trials showed that a starting dose of 80 mg/day might result in reduced efficacy if not escalated to doses of either 120 mg/day or 160 mg/day (Grothey 2019). Therefore, to ensure an efficacious dose is administered, as well as to account for the fact that this study will be conducted in a global population (inclusive of Caucasian patients with potential differences in body size, drug metabolism, and toxicities), regorafenib will be used at a dose of 120 mg/day on Days 1–21 of each 28-day cycle. Furthermore, to account for the results from the ReDOS trial (Bekaii-Saab et al. 2019) showing a lower incidence of adverse events, a starting dose of 80 mg/day of regorafenib will be allowed, followed by a dose escalation to 120 mg/day (as per institutional guidelines) during Cycle 1 if no significant drug-related toxicity is observed.

A13–3.3 RATIONALE FOR AB928 DOSE AND SCHEDULE

Preliminary data from Study AB928CSP0001 in healthy volunteers demonstrated that the investigational product (blinded AB928 or matching placebo) was tolerable at the doses tested (10–200 mg) and exhibited a predictable, linear, dose-proportional,

pharmacokinetic profile. To date, all reported adverse events in participants receiving single or multiple doses of AB928 were mild or moderate in severity, and no participants have discontinued from the study. There was no impact on any physiologic parameters that are potentially sensitive to adenosine inhibition at a dose of 200 mg QD.

As of 6 September 2019, AB928 at doses of 75–200 mg QD has been assessed in combination with multiple backbones in over 40 patients in oncology studies. The recommended dose for expansion of AB928 across all studies in the AB928 program is 150 mg QD. This dose regimen was selected based on the available pharmacokinetic (PK) data, correlation between PK and pharmacodynamic data, and the well-tolerated safety profile of AB928 in combination with either a chemotherapy or a PD-1 inhibitor (AB122).

A13–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + REGORAFENIB + AB928 ARM

A13–4.1 TREATMENT IN ATEZO + REGORAFENIB + AB928 ARM

A13–4.1.1 Formulation, Packaging, and Handling

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 and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A13–4.1.1.2 Regorafenib

For information on the formulation, packaging, and handling of regorafenib, refer to the local prescribing information.

A13–4.1.1.3 AB928

The AB928 drug product will be supplied by the Sponsor as gelatin capsules at a dose strength of 25 mg.

For information on the formulation and handling of AB928, see the pharmacy manual and the AB928 Investigator's Brochure.

A13–4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + Regorafenib + AB928 arm will receive treatment as outlined in Table 1 until unacceptable toxicity or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator, after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain

secondary to disease) (see Section 3.1.1 in the protocol body for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table 1 Treatment Regimen for Atezo + Regorafenib + AB928 Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• AB928 150 mg by mouth once daily on Days 1–28 of each cycle • Atezolizumab 840 mg IV on Days 1 and 15 of each cycle • Regorafenib 120 mg by mouth once daily on Days 1–21 of each cycle [a]

Atezo = atezolizumab.

[a] Regorafenib should be initiated at 80 mg, allowing sufficient time to monitor drug-related toxicities before considering dose escalation to 120 mg.

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

Guidelines for dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A13–5.1.5. Atezolizumab, regorafenib, or AB928 treatment interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed. The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12. No safety data related to atezolizumab or AB928 overdose are available. The highest dose of regorafenib studied clinically is 220 mg per day. The most frequently observed adverse drug reactions at this dose were dermatologic events, dysphonia, diarrhea, mucosal inflammation, dry mouth, decreased appetite, hypertension, and fatigue. There is no specific antidote for regorafenib overdose. In the event of suspected overdose, interrupt regorafenib, institute supportive care, and observe until clinical stabilization.

A13–4.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-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 5. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 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, pulse oximetry, blood pressure, 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. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A13–5.1.5.

A13–4.1.2.2 Regorafenib

Regorafenib will be used in the commercially available formulation.

Patients will receive regorafenib at a dose level of 120 mg (three tablets of 40 mg each) orally once daily on Days 1–21 of a 28-day cycle (see Table 1). This 4-week period is considered a treatment cycle. Regorafenib should be initiated at 80 mg, allowing sufficient time to monitor drug-related toxicities before considering dose escalation to 120 mg.

Regorafenib should be taken at the same time each day. On clinic visit days when PK samples are collected, patients should take their regorafenib dose in the clinic. The tablets should be swallowed whole with water after a light meal that contains < 30% fat. An example of a light (low-fat) meal would include one portion of cereal (about 30 g), one glass of skimmed milk, one slice of toast with jam, one glass of apple juice, and one cup of coffee or tea (520 calories, 2 g fat).

To assess patient compliance with self-administration of regorafenib, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

Guidelines for regorafenib dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A13–5.1.5.

A13–4.1.2.3 AB928

Patients will receive AB928 at a dose of 150 mg (six capsules of 25 mg each) orally once daily on Days 1-28 of a 28-day cycle (see Table 1).

AB928 should be taken at approximately the same time each day. On clinic visit days when PK samples are collected, patients should take their AB928 dose in the clinic. AB928 capsules should be swallowed whole with a glass of non-carbonated, room-temperature water (additional water is permitted) and should not be chewed, cut, or opened. If a dose of AB928 is missed (i.e., not taken within 12 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

To assess patient compliance with self-administration of AB928, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance

Guidelines for AB928 dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A13–5.1.5.

A13–4.1.3 Stage 2 Treatment

Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1 in the protocol body) or unacceptable toxicity may be eligible to receive a different treatment combination during during Stage 2,

provided a Stage 2 treatment is available for enrollment and they meet the eligibility criteria of that treatment regimen. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. However, it is recommended that patients begin Stage 2 treatment as soon as possible, but no earlier than 2 weeks after the last dose of treatment in Stage 1.

Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table 3 Stage 2 Treatment Regimens Available for the Atezo + Regorafenib + AB928 Arm

Study Treatment	Appendix
No Stage 2 treatment currently available	—

A13–4.2 CONCOMITANT THERAPY FOR ATEZO + REGORAFENIB + AB928 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 patient 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 + Regorafenib + AB928 Arm

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

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic anticoagulation

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

  Prophylactic use of low molecular weight heparin (i.e., enoxaparin 40 mg/day) is allowed.
- Prophylactic antibiotic or anti viral treatment administered according to institutional standards

- *Vaccinations (such as influenza, COVID-19)*

  Live, attenuated vaccines are not permitted (see Section A13–4.2.3).
- Prophylactic standard anti-emetic therapy
- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin releasing–hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease).

  Treatment with atezolizumab, regorafenib, and AB928 may be continued during palliative radiotherapy.
- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole brain radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.
  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.
  – Anti-convulsant therapy, if required, is administered at a stable dose.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2 receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious

infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 adrenergic agonists).

A13–4.2.2 Cautionary Therapy for Atezo+Regorafenib+AB928 Arm

Corticosteroids, *Immunosuppressive Medications,* and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, *immunosuppressive medications,* and tumor necrosis factor–α (TNF–α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and AB928. Therefore, in situations in which systemic corticosteroids, *immunosuppressive medications,* or TNF–α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, *immunosuppressive medications,* and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids *or immunosuppressive medications* are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 for details).

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.

UDP-Glucuronosyltransferase 1-1 and UDP-Glucuronosyltransferase 1-9

Regorafenib is metabolized by UDP-glucuronosyltransferase 1-1 (UGT1A1), andregorafenib and its metabolites are inhibitors of UGT1A1 and UDP-glucuronosyltransferase 1-9 (UGT1A9). Therefore, inhibitors of UGT1A1 (e.g., erlotinib, nilotinib, pazopanib, lapatinib, sorafenib) and substrates of UGT1A1 (e.g., irinotecan with its active metabolite SN-38, raltegravir, bazedoxifene, eltrombopag) and substrates of UGT1A9 (e.g., sorafenib, mycophenolic acid) should be used with caution.

Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

AB928 is a substrate of CYP2C8. Caution should be exercised when AB928 is concomitantly administered with known CYP2C8 strong inhibitors (e.g., gemfibrozil) and/or known strong CYP2C8 inducers.

Other Potential Drug–Drug Interactions with AB928

In vitro nonclinical studies have identified AB928 as a substrate of P-gp, BCRP, CYP3A4, CYP2C8, and of multiple isoforms of UGT (UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 2B4, 2B7, and 2B15). AB928 is also a weak to moderate inhibitor of CYP2C8, CYP2C9, CYP2C19, and CYP3A4. AB928 is an inhibitor of P-gp, BCRP, BSEP, OAT3, OCT2, MATE1, and MATE2-K. Lastly, AB928 is a weak to moderate inducer of CYP3A4. Potential drug–drug interactions may occur with concomitant medications acting on these pathways.

A13–4.2.3 Prohibited Therapy for Atezo + Regorafenib + AB928 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, may be prohibited prior to starting study treatment, depending on the agent, and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances outlined above in Section A13–4.2.1.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab and AB928, for 5 months after the final dose of atezolizumab, and for 90 days after the final dose of AB928.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin 2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab and AB928.
- Known strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort) and strong CYP3A4 inhibitors (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole)
- Known breast cancer resistance protein (BCRP) strong inhibitors (e.g., cyclosporin A, eltrombopag) and/or BCRP substrates with a narrow therapeutic window administered orally (e.g., prazosin, rosuvastatin)
- Known P-glycoprotein (P-gp) strong inhibitors (eg, itraconazole, quinidine, verapamil, dronedarone ranolazine) and/or P-gp substrates with a narrow therapeutic window administered orally (e.g., digoxin)
- Strong UGT inhibitors (e.g., atazanavir)

- Sensitive BSEP substrates
- Sensitive OCT2 substrates
- Sensitive MATE-1 substrates

A13–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + REGORAFENIB + AB928 ARM

Contraception requirements for women and men in the Atezo + Regorafenib + AB928 arm are outlined below:

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 5 months after the last dose of atezolizumab, for 2 months after the last dose of regorafenib, and for 30 days after the last dose of AB928. Women must refrain from breastfeeding during this same period of time.

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

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

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

- 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 female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 2 months after the last dose of regorafenib and for 30 days after the last dose of AB928 to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

A13–5 ASSESSMENT OF SAFETY FOR ATEZO + REGORAFENIB + AB928 ARM

A13–5.1 SAFETY PLAN FOR ATEZO + REGORAFENIB + AB928 ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab, regorafenib, and AB928 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 the management of patients who experience specific adverse events are provided in Section A13–5.1.5.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Because of the potential for overlapping toxicities identified for atezolizumab, regorafenib, and AB928, special caution will be taken by performing a planned safety evaluation for patients randomized to this arm (see Section 3.1.1.1).

Administration of atezolizumab 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 in the protocol body.

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, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab. Refer to Appendix 6 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 Regorafenib

The overall safety profile of regorafenib is based on data from more than 4800 treated patients in clinical trials, including placebo-controlled Phase III data for 636 patients with mCRC, 132 patients with GI stromal tumors, and 374 patients with hepatocellular carcinoma. The most serious adverse drug reactions in patients receiving regorafenib are severe liver injury, hemorrhage, GI perforation, and infection. The most frequently observed adverse drug reactions (≥ 30%) in patients receiving regorafenib are pain, hand-foot skin reaction, asthenia/fatigue, diarrhea, decreased appetite and food intake,

hypertension, and infection. Refer to the regorafenib local prescribing information for complete information regarding clinical safety.

A13–5.1.3 Risks Associated with AB928

The safety profile for AB928 is limited and based on data from less than 40 patients with advanced cancer and 85 healthy volunteers (data cutoff July 2019). Patients with advanced cancer received AB928 at doses of 75 mg, 150 mg, or 200 mg once daily in combination with chemotherapy and/or immunotherapy. The most frequently observed AB928-related adverse events, regardless of dose and combination therapy, occurring in 2 or more patients, were fatigue, nausea, pruritus, and anemia. Grade 3 adverse events related to AB928 were limited to fatigue and anemia (2 patients each); and nausea, neutrophil count decreased, and white blood cell count decreased (1 patient each). No AB928-related Grade 4 or Grade 5 events were reported. No serious adverse events were considered related to AB928. Based on limited human safety information, no adverse drug reactions have been identified for AB928. Refer to the AB928 Investigator's Brochure for detailed safety information from the ongoing clinical program of AB928.

A13–5.1.4 Risks Associated with Combination Use of Atezolizumab, Regorafenib, and AB928

Potential overlapping toxicities for the combination of atezolizumab, regorafenib, and AB928 may occur within the system organ classes of GI, hepatobiliary, cardiac, skin, nervous system, and blood and lymphatic system disorders and include gastrointestinal toxicities (diarrhea/colitis), hepatic toxicity, cardiac toxicities (cardiac ischemia, myocardial infarction/myocarditis), dermatological toxicity/skin rash, Posterior Reversible Encephalopathy Syndrome (PRES)/meningoencephalitis, and hemorrhage/thrombocytopenia.

A13–5.1.5 Management of Patients Who Experience Adverse Events in Atezo+Regorafenib+AB928 Arm

A13–5.1.5.1 Dose Modifications

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

For management of drug-related toxicities, the dose of regorafenib can be reduced by a decrement of 40 mg once a day (one dose level) from 120 mg to 80 mg. During the allowed dose escalation (Section A13–4.1.2.2), the continuation of a dose of 80 mg/day for as long as required for the management of drug-related toxicities is also allowed. If further dose reduction below 80 mg is indicated, the patient must discontinue regorafenib, unless the patient is likely to derive clinical benefit as determined by the investigator. *The Medical Monitor is available to advise as needed.* After dose reduction,

the dose of regorafenib may be re-escalated at the investigator's discretion, provided there are no safety concerns.

For management of drug-related toxicities, the dose of AB928 may be reduced up to two times as outlined in Table 4. If further dose reduction below 75 mg is indicated, AB928 should be discontinued. After dose reduction, the dose may be escalated during subsequent administrations at the investigator's discretion.

Table 4 Recommended Dose Reductions for AB928

	Initial Dose	First Dose Reduction	Second Dose Reduction
AB928	150 mg	100 mg	75 mg

A13–5.1.5.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for more than 12 weeks, the patient will be discontinued from the study. However, atezolizumab may be withheld for more than 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for more than 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

Regorafenib treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If regorafenib has been withheld for more than 42 days because of toxicity, the patient should be discontinued from regorafenib. However, regorafenib can be resumed after being withheld for more than 42 days if the patient is likely to derive clinical benefit. *The Medical Monitor is available to advise as needed.*

AB928 treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If AB928 has been withheld for more than 42 days because of toxicity, the patient should be discontinued from AB928. However, AB928 can be resumed after being withheld for more than 42 days if the patient is likely to derive clinical benefit. *The Medical Monitor is available to advise as needed.*

If atezolizumab, regorafenib, or AB928 is permanently discontinued, the other agent or agents should also be discontinued unless the patient is likely to derive clinical benefit from single-agent use, as determined by the investigator. *The Medical Monitor is available to advise as needed.*

Refer to 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 the management of patients who experience specific adverse events are provided below in Table 5 for events related to overlapping toxicities or regorafenib and AB928 treatment.

For cases in which management guidelines are not covered in Appendix 6 or Table 5, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib+AB928 Arm

Event	Action to Be Taken
IRRs, *CRS,* anaphylaxis, and hypersensitivity reactions	• Guidelines for management of IRRs *and CRS* for atezolizumab are provided in Appendix 6. • For anaphylaxis precautions, see Appendix 5.
Dermatologic toxicity (rash, hand–foot skin reaction/palmar–plantar erythrodysesthesia)	
General Guidance	• A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.
Dermatologic event, Grade 1	• Continue atezolizumab. Continue regorafenib and AB928 at the same dose level. • Immediately institute supportive measures for symptomatic relief. • If rash is suspected to be related to atezolizumab, consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g. antihistamines).

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib+AB928 (cont.)

Event	Action to Be Taken
Dermatologic event, Grade 2	• Continue atezolizumab. Consider AB928 dose modification as clinically indicated; otherwise continue AB928 at the same dose. Continue regorafenib and decrease dose by one level. [a] For suspected atezolizumab-related events: • Consider patient referral to dermatologist *for evaluation and, if indicated, biopsy.* • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • *If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.* For suspected regorafenib-related events: • Immediately institute supportive measures. <u>First occurrence:</u> • If event does not resolve to Grade 1 or better after dose reduction, withhold regorafenib for a minimum of 7 days. If event resolves to Grade 1 or better within 42 days, resume regorafenib at the reduced dose level. [a] If not, permanently discontinue regorafenib. [g] • A dose re-escalation is permitted at the investigator's discretion. <u>If event does not resolve within 7 days or at second or third occurrence:</u> • Withhold regorafenib for a minimum of 7 days. If event resolves to Grade 1 or better within 42 days, resume regorafenib with a one-level dose reduction. [a] If not, permanently discontinue regorafenib. [g] <u>Fourth occurrence:</u> • Permanently discontinue regorafenib. [g] For suspected AB928-related events: • Immediately institute supportive measures. • If the event does not resolve to Grade 1 or better within 7 days, consider dose interruption. If event resolves to Grade 1 or better, resume AB928 at the same dose or with a one-level dose reduction. • A dose re-escalation is permitted at the investigator's discretion.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib+AB928 (cont.)

Event	Action to Be Taken
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [b] Withhold regorafenib and AB928 for a minimum of 7 days or until toxicity resolves to Grade 1 or better. . For suspected atezolizumab-related events: • 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 within 12 weeks, resume atezolizumab. [b, c] If not, permanently discontinue atezolizumab and contact Medical Monitor. [d] • If event resolves to Grade 1 or better within 42 days, resume regorafenib and AB928 with a one-level dose reduction. [a, j, k] If not, permanently discontinue regorafenib and AB928 and contact Medical Monitor. [g, i] For suspected regorafenib-related events: • Institute supportive measures immediately <u>First and second occurrence:</u> • If event resolves to Grade 1 or better within 42 days, resume regorafenib with a one-level dose reduction. [a] If not, permanently discontinue regorafenib. [g] • For first occurrence, a dose re-escalation of regorafenib is permitted at the investigator's discretion. • If event resolves to Grade 1 or better within 12 weeks for atezolizumab and within 42 days for AB928, resume study treatment. [b, k] If not, permanently discontinue atezolizumab and AB928 and contact Medical Monitor [d, i] <u>Third occurrence:</u> • Permanently discontinue regorafenib.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib+AB928 (cont.)

Event	Action to Be Taken
Dermatologic event, Grade 3 (continued)	For suspected AB928-related events: • Immediately institute supportive measures. • Refer patient to dermatologist. • If event resolves to Grade 1 or better within 42 days, resume AB928 with a one-level dose reduction. [k, h] If not, permanently discontinue AB928 and contact Medical Monitor. [i] • A dose re-escalation of AB928 is permitted at the investigator's discretion. • If event resolves to Grade 1 or better within 12 weeks for atezolizumab and within 42 days for regorafenib, resume study treatment. [b, j] If not, permanently discontinue atezolizumab and regorafenib and contact Medical Monitor [d, g]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab, regorafenib, and AB928 and contact Medical Monitor. [d, g, i]
Suspected Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue regorafenib and contact Medical Monitor. • Withhold AB928. If the event resolves to Grade 1 or better, resume AB928 after consultation with the Medical Monitor. • Permanently discontinue AB928 if withheld for >42 days or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, and contact Medical Monitor.
Hepatic toxicity (elevations in ALT, AST, and/or bilirubin)	
$\leq 5 \times$ ULN elevations in ALT/AST (maximum Grade 2)	• Continue atezolizumab. Continue regorafenib and AB928 at the same dose level. • Monitor LFTs more frequently until return to <3 ULN (Grade 1) or baseline. For suspected immune-mediated events of >5 days duration: • Withhold atezolizumab for up to 12 weeks after event onset. [b] Regorafenib and AB928 can be continued at the same dose level at the investigator's discretion. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. [b, c] If not, permanently discontinue atezolizumab and contact Medical Monitor. [d]

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib+AB928 (cont.)

Event	Action to Be Taken
$>5\times$ ULN but $\leq 20\times$ ULN elevations in ALT/AST (Grade 3)	For suspected regorafenib-related/non–immune-mediated elevations in ALT/AST: • Withhold atezolizumab for up to 12 weeks after event onset. [b] Withhold regorafenib and AB928 for up to 42 days. • Monitor LFTs at least weekly for at minimum of 4 weeks until transaminases return to <3 ULN (Grade 1) or baseline. • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • If event resolves to Grade 1 or better within 12 weeks for, atezolizumab and within 42 days for AB928, resume study treament[b, k]. If not, permanently discontinue atezolizumab and AB928 and contact Medical Monitor. [d, i] <u>First occurrence:</u> • If event resolves to Grade 1 or better within 42 days, resume regorafenib with a one-level dose reduction. [a, j] If not, permanently discontinue regorafenib [g]. <u>Second occurrence:</u> • Permanently discontinue regorafenib. [g] For suspected immune-mediated events: • Permanently discontinue atezolizumab and contact Medical Monitor. [d] Withhold regorafenib and AB928 for up to 42 days. [j, k] • 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 Grade 1 or better within 12 weeks, taper corticosteroids over $\geq$ 1 month. [b] • If event resolves to Grade 1 or better within 42 days, resume regorafenib and AB928 with a one-level dose reduction. [a, h, j, k] If not, permanently discontinue regorafenib and AB928 and contact Medical Monitor. [g, i]

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib+AB928 (cont.)

Event	Action to Be Taken
$>20\times$ ULN elevations in ALT/AST (Grade 4)	• Permanently discontinue atezolizumab, regorafenib, and AB928 and contact Medical Monitor. [d, g, i] • Follow Grade 3 management guidelines for suspected immune-mediated events.
$>3\times$ ULN elevations in ALT/AST (Grade 2 or higher) with concurrent bilirubin $>2\times$ ULN	• Permanently discontinue atezolizumab, regorafenib, and AB928 and contact Medical Monitor. [d, g, i] • Monitor liver function at least weekly until values return to baseline. • Investigate causes for elevated bilirubin and initiate treatment per institutional guidelines. • Exception: Patients with Gilbert syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.
GI toxicities	
Any GI perforation or fistula	• Permanently discontinue regorafenib. [g]
Diarrhea or colitis, Grade 1	• Continue atezolizumab. Continue regorafenib and AB928 at the same dose level. • 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 [b]. Regorafenib and AB928 may be continued at the same dose level at the investigator's discretion. • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. [b, c] If not, permanently discontinue atezolizumab and contact Medical Monitor. [d] • If regorafenib was withheld and event resolves to Grade 1 or better within 42 days decrease by one dose level when resuming treatment. [j] • If AB928 was withheld and event resolves to Grade 1 or better within 42 days, resume AB928 at the same dose level. [k]

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib+AB928 (cont.)

Event	Action to Be Taken
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [b] Withhold regorafenib and AB928 for up to 42 days after event onset. For suspected immune-mediated events (including colitis): • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. [b, c] If not, permanently discontinue atezolizumab and contact Medical Monitor. [d] • If event resolves to Grade 1 or better within 42 days resume regorafenib and AB928 with a one-level dose reduction. [a, h, j, k] If not, permanently discontinue regorafenib and AB928 and contact Medical Monitor. [g, i] For regorafenib-related events: <u>First and second occurrence:</u> • If event resolves to Grade 1 or better within 42 days, resume regorafenib with a one-level dose reduction. [a] If not, consider permanent discontinuation of regorafenib. • If event resolves to Grade 1 or better within 12 weeks for, atezolizumab and within 42 days for AB928, resume study treatement and decrease AB928 by one dose level. [b, h, k] For AB928, a dose re-escalation is permitted at the investigator's discretion. If not, consider permanent discontinuation of atezolizumab and AB928 and contact medical monitor. [d, i] <u>Third occurrence:</u> • Consider permanent discontinuation of regorafenib. [g] Atezolizumab and AB928 may be continued at the investigator's discretion.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib+AB928 (cont.)

Event	Action to Be Taken
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab, regorafenib, and AB928 and contact Medical Monitor. [d, g, i] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Cardiac Toxicities	
General guidance	• Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. • 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.
Immune-mediated myocarditis, Grade 1	• Atezolizumab may be continued at the investigator's discretion. Regorafenib and AB928 may be continued at the same dose level, at the investigator's discretion. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib+AB928 (cont.)

Event	Action to Be Taken
Immune-mediated myocarditis, Grade 2	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [d] Regorafenib and AB928 may be continued at the same dose level, at the investigator's discretion. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • 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 event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. [b, c] If not, permanently discontinue atezolizumab and contact Medical Monitor. [d]
Immune-mediated myocarditis, Grade 3	• Permanently discontinue atezolizumab and contact Medical Monitor. [d] Withhold regorafenib and AB928 for up to 42 days. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better within 12 weeks, taper corticosteroids over ≥ 1 month. [b] • If event resolves to Grade 1 or better within 42 days, consider resuming regorafenib and AB928 with one dose level reduction. [a, h, j, k]
Immune-mediated myocarditis, Grade 4	• Permanently discontinue atezolizumab, regorafenib, and AB928 contact Medical Monitor. [d, g, i] • Manage as per Grade 3 guidelines
New or acute onset cardiac ischemia or infarction	• Withhold atezolizumab, regorafenib, and AB928. • If the acute cardiac ischemic events resolve and if the potential benefits outweigh the risks of further cardiac ischemia, resume atezolizumab, regorafenib, and AB928. If not, permanently discontinue atezolizumab, regorafenib, and AB928 and contact Medical Monitor. [d, g, i]

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib+AB928 (cont.)

Event	Action to Be Taken
Infection	
Infections, Grade 3 or 4 or a worsening infection of any grade	• Withhold regorafenib. Atezolizumab and AB928 may be continued at the investigator's discretion. • If infection resolves within 42 days, resume regorafenib at the same dose level. If not permanently discontinue regorafenib. [g]
Hemorrhage	
Hemorrhage, Grade 3 or 4	• Permanently discontinue regorafenib and contact Medical Monitor. [f, g] Monitor INR levels more frequently in patients receiving warfarin.
Hypertension	
General guidance	• Grade 2 or above, start anti-hypertensive therapy.
Hypertension, Grade 2	• Withhold regorafenib. Continue atezolizumab and AB928. • If blood pressure is $<$150/100 mmHg within 42 days, resume regorafenib with the decision to maintain the current dose level or to reduce by one dose level at the discretion of the investigator. [a]
Hypertension, Grade 3	• Withhold regorafenib. Atezolizumab and AB928 may be continued at the investigator's discretion. • If blood pressure is $<$150/100 mmHg within 42 days, resume regorafenib with the decision to maintain the current dose level or to reduce by one dose level at the discretion of the investigator. [a] • If blood pressure is not controlled to $<$150/100 mmHg with anti-hypertensive therapy, permanently discontinue regorafenib and contact Medical Monitor. [g]
Hypertension, Grade 4 (includes hypertensive crisis and hypertensive encephalopathy)	• Permanently discontinue atezolizumab, regorafenib, and AB928 and contact Medical Monitor. [d, g, i]
Reversible posterior leukoencephalopathy syndrome	
Reversible posterior leukoencephalopathy syndrome	• Permanently discontinue regorafenib and contact Medical Monitor. [g]

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib+AB928 (cont.)

Event	Action to Be Taken
Wound dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	• Permanently discontinue regorafenib and contact Medical Monitor. [g]
Regorafenib-related toxicities not described above	
Grade 1 or Grade 2 (tolerable)	• Continue atezolizumab. Continue regorafenib and AB928 at the same dose level.
Grade 2 (intolerable) or Grade 3	• Atezolizumab and AB928 may be continued at the investigator's discretion. First and second occurrence: • Withhold regorafenib until event resolves to Grade 1 or better within 42 days, then resume regorafenib with a one-level dose reduction. [a] If event does not resolve to Grade 1 or better, permanently discontinue regorafenib. [g] Third occurrence: • Consider permanent discontinuation of regorafenib. [g]
Grade 4	• Permanently discontinue atezolizumab, regorafenib, and AB928 and contact Medical Monitor. [d, g, i]
Atezolizumab-related toxcities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue regorafenib and AB928 at the same dose level.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold regorafenib and AB928. • If event improves, resume regorafenib and AB928. If not, permanently discontinue regorafenib and AB928. [g, i]

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib+AB928 (cont.)

Event	Action to Be Taken
AB928-related toxicities not described above	
Grade 1 or 2	• Initiate symptom-directed supportive care. • Continue atezolizumab and regorafenib. • Consider AB928 dose modification as clinically indicated; otherwise continue AB928 at the same dose.
Grade 3	• Withhold AB928. Atezolizumab and regorafenib may be continued at the investigator's discretion. • If event resolves to Grade 1 or better within 42 days, resume AB928 with a one-level dose reduction. If not, or if AB928 is held for >42 days, permanently discontinue AB928. [k] • Dose re-escalation of AB928 is permitted at the investigator's discretion.
Grade 4	• Permanently discontinue AB928. Withhold atezolizumab and regorafenib. • If event improves, resume atezolizumab and regorafenib. If not, permanently discontinue atezolizumab and regorafenib. [d, g]

CRS = cytokine release syndrome; ECMO = extracorporeal membrane oxygenation; GI = gastrointestinal; IRR = infusion-related reaction; ULN = upper limit of normal; VAD = ventricular assist device.

[a] The dose of regorafenib can be reduced by a decrement of 40 mg, once a day, from 120 mg to 80 mg (i.e., one dose level) for management of drug-related toxicities. Additional dose reductions are not allowed. If a dose reduction is indicated for a patient receiving the 80-mg dose of regorafenib, then that patient should discontinue regorafenib, unless the patient is likely to derive clinical benefit as determined by the investigator. *The Medical Monitor is available to advise as needed.* Upon adverse event resolution, a dose re-escalation of regorafenib from 80 mg to 120 mg is allowed at the investigator's discretion.

[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 ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

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

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

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Regorafenib+AB928 (cont.)

[e] Atezolizumab may be continued at the discretion of the investigator in consultation with the Medical Monitor, and both atezolizumab and regorafenib treatment may resume if the patient is thought to be deriving benefit.

[f] For Grade 3 events, regorafenib may be continued at the discretion of the investigator per medical judgment.

[g] Resumption of regorafenib may be considered in patients who are deriving benefit and have fully recovered from the toxicity. *The decision to* re-challenge *patients* with regorafenib *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *The* Medical Monitor *is available to advise as needed.*

[h] The dose of AB928 can be reduced from 150 mg to 100 mg (i.e., one dose level), and then from 100 mg to 75 mg for management of drug-related toxicities. Additional dose reductions are not allowed. If a dose reduction is indicated for a patient receiving the 75-mg dose of AB928, then that patient should discontinue AB928. Upon adverse event resolution, a dose re-escalation of AB928 is allowed at the investigator's discretion. *The Medical Monitor is available to advise as needed.*

[i] Resumption of AB928 may be considered in patients who are deriving benefit and have fully recovered from the toxicity. *The decision to* re-challenge *patients* with AB928 *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *The* Medical Monitor *is available to advise as needed.*

[j] Regorafenib may be withheld for a longer period of time (i.e. >42 days after event onset). The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

[k] AB928 may be withheld for a longer period of time (i.e. >42 days after event onset). The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

A13–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + REGORAFENIB + AB928 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 in the protocol body for reporting instructions). Adverse events of special interest for the Atezo+Regorafenib+AB928 arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7 in the protocol body)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10 \times$ upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, and optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

A13–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + REGORAFENIB + AB928 ARM

A13–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab, 2 months after the last dose of regorafenib, or 30 days after the last dose of AB928. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A13–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 2 months after the last dose of regorafenib or 30 days after the last dose of AB928. 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 patient exposed to study treatment. When permitted by the site, the pregnant partner will 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 patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator 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 in the protocol body).

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 patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 in the protocol body).

A13–6. SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+REGORAFENIB+AB928 ARM

Table 6: Schedule of Activities for Atezo + Regorafenib + AB928 Arm

Assessment/Procedure	Screening Days –28 to –1	Treatment Cycles (28-Day Cycles) [a]										Stage 2 Screen. [c] or Treat. Discon. [d]	Follow-Up Every 3 Months (±7 days)
		Cycle 1 [b]					Cycle 2			Cycles ≥3			
		Days					Days			Days			
		1	2	8 (±1 d)	15 (±1 d)	22 (±1 d)	1	8 (±1 d)	15 (±1 d)	1 (+2 d)	15 (±2 d)		
Molecular profile of CRC (if available)	See Appendix 15	Whenever updated information becomes available											
Vital signs [e]		x	x	x	x	x	x	x	x	x	x	x	
Weight		x [f]					x [f]			x [f]		x	
Complete physical examination [g]												x	
Limited physical examination [h]		x [f]		x [f]	x [f]	x [f]	x [f]	x [f]	x [f]	x [f]	x [f]		
ECOG Performance Status		x [f]					x [f]			x [f]		x	
ECG [i]		As clinically indicated [f]										x [o]	
Hematology [j]		x [k, l]		x [k]	x [k]		x [k]	x [k]	x [k]	x [k]	x [k]	x	
Chemistry [m]		x [k, l]		x [k]	x [k]		x [k]	x [k]	x [k]	x [k]	x [k]	x	
Coagulation (INR and aPTT) [n]		x [k, l]					x [k]			x [k]		x [o]	
TSH, free T3 (or total T3), and free T4 [p]		x [k, l, p]										x	
Viral serology [q]												x [o, q]	
C-reactive protein												x [o]	
Plasma CEA [r]		x [k]								x [k, r]			

Table 6: Schedule of Activities for Atezo+Regorafenib+AB928 Arm (cont.)

Assessment/Procedure	Screening Days –28 to –1	Treatment Cycles (28-Day Cycles) [a]										Stage 2 Screen. [c] or Treat. Discon. [d]	Follow-Up Every 3 Months (±7 days)
		Cycle 1 [b]					Cycle 2			Cycles ≥3			
		Days					Days			Days			
		1	2	8 (±1 d)	15 (±1 d)	22 (±1 d)	1	8 (±1 d)	15 (±1 d)	1 (+2 d)	15 (±2 d)		
LDH	See Appendix 15											x [o]	
Pregnancy test [s]		x [k, l]					x [k]			x [k]		x [t]	x [s]
Urinalysis [u]		x					x			x		x [o, t]	
Serum autoantibody sample [v]		Perform if patients experience suspected immune-mediated adverse event										x [o]	
Blood sample for RBR (optional) [w]		x											
Biomarker samples		Refer to Table 7 below											
Serum ADA sample		Refer to Table 7 below											
Serum and plasma PK sample		Refer to Table 7 below											
Tumor biopsy		x [x]											
Tumor biopsy (optional)		x [y]											
Tumor response assessments		x [z, aa, bb]											
Concomitant medications [cc]		x	x	x	x	x	x	x	x	x	x	x	
Adverse events [dd]		x	x	x	x	x	x	x	x	x	x	x [dd]	x [dd]
Administer atezolizumab [ee, ff]		x			x		x		x	x	x		
Dispense regorafenib [ff, gg]		x					x			x			
Dispense AB928 [ff, hh]		x					x			x			
Study drug accountability [ii]					x		x		x	x	x		
Survival follow-up and anti-cancer treatment													x [jj]

Table 6: Schedule of Activities for Atezo+Regorafenib+AB928 Arm (cont.)

ADA = anti-drug antibody; CT = computed tomography; d = day; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; Treat. = treatment; TSH = thyroid-stimulating hormone.

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 *may* occur outside of the specified window.

[b] It is recommended that treatment be initiated no later than 7 days after randomization; however the first dose of study treatment should not occur within 7 days after a core biopsy or other surgical procedure.

[c] Patients who experience loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details) or unacceptable toxicity may be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.2 in the protocol body provided Stage 2 is open for enrollment) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will undergo follow-up assessments after completing the treatment discontinuation visit.

[e] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Refer to Section A13–4.1.2 for details related to vital signs monitoring during atezolizumab infusions.

[f] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[g] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.administered. The skin examination should be extended according to medical need.

[i] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

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

[k] Laboratory tests must be performed within 96 hours prior to *dosing* during the treatment period.

[l] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[m] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (per standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. CPK will be

Table 6: Schedule of Activities for Atezo+Regorafenib+AB928 Arm (cont.)

performed only on Day 1 of each cycle and at treatment discontinuation.

[n] Monitoring of INR/aPTT should be performed more frequently if clinically indicated.

[o] Assessments to be performed only for patients undergoing Stage 2 screening.

[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[q] At Stage 2, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[r] CEA will be assessed on Day 1 of Cycle 1 and every 2 cycles thereafter (i.e., Cycles 3, 5, 7, etc.) until disease progression.

[s] 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 and at 3 months and 6 months after treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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

[u] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. Patients with ≥2+ protein on dipstick urinalysis must undergo a 24-hour urine collection and demonstrate <3.5 g of protein in 24 hours. *Urinalysis may be performed up to 72 hours prior to Day 1 of each cycle, as results must be available prior to treatment administration.*

[v] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[w] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. RBR sample should be collected prior to study treatment.

[x] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial-biopsy arm (see Section 3.1.1.2 in the protocol body) will undergo tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible by the investigator). See Section 4.5.7 in the protocol body for tissue sample requirements.

[y] Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation, if deemed clinically feasible and may undergo additional on-treatment biopsies at any other time during Stage 1 or Stage 2 at the investigator's discretion.

[z] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

Table 6: Schedule of Activities for Atezo+Regorafenib+AB928 Arm (cont.)

[aa] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head CT 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).

[bb] For patients who undergo screening for Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

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

[dd] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6 in the protocol body). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[ee] Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle. The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[ff] Treatment will continue until unacceptable toxicity or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details).

[gg] Patients will receive regorafenib orally on Days 1–21 of each cycle. At least 7 days off regorafenib are required prior to starting a new treatment cycle (see Section A13–4.1.2.2 for details). On clinic visit days when PK samples are collected, patients should take their regorafenib dose in the clinic.

[hh] Patients will receive AB928 orally on Days 1–28 of each cycle (see Section A13–4.1.2.3 for details). On clinic visit days when PK samples are collected, patients should take their AB928 dose in the clinic.

[ii] Medication diaries should be collected and reviewed, and unused medications should be collected for assessment of compliance

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

Table 6: Schedule of Activities for Atezo+Regorafenib+AB928 Arm (cont.)

records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table 7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Regorafenib+AB928 Arm: Preliminary and Expansion Phases

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Regorafenib PK (plasma) [a] • AB928 PK (plasma) [b] • Biomarkers (plasma, serum, PBMC)
	30 (±10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
	30 (±5) minutes after AB928 dose	• AB928 PK (plasma) [b]
	1 hour (±5 minutes) after AB928 dose	• AB928 PK (plasma) [b]
	2 hours (±10 minutes) after AB928 dose	• AB928 PK (plasma) [b]
	4 hours (±10 minutes) after AB928 dose	• AB928 PK (plasma) [b]
	6 hours (±10 minutes) after AB928 dose	• AB928 PK (plasma) [b]
Day 2 of Cycle 1	24 hours (±1 hour) after AB928 dose on Cycle 1 Day 1	• AB928 PK (plasma) [b]
Day 8 of Cycle 1	Prior to study treatment	• Regorafenib PK (plasma) [a] • AB928 PK (plasma) [b]
Day 15 of Cycle 1	Prior to study treatment	• Regorafenib PK (plasma) [a] • AB928 PK (plasma) [b] • Biomarkers (plasma, serum)
Day 22 of Cycle 1	Prior to study treatment	• Regorafenib PK (plasma) [a] • AB928 PK (plasma) [b]

Atezo = atezolizumab; ADA = anti-drug antibody; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: Based on emerging safety/efficacy data the number of PK/ADA and/or biomarker samples may be reduced/removed and/or the timing of samples may be modified.

[a] Regorafenib PK includes regorafenib, regorafenib M-2, and regorafenib M-5.

[b] AB928 PK includes AB928, AB928 glucuronide, and AB928 N-dealkylated.

Table 7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Regorafenib+AB928 Arm: Preliminary and Expansion Phases (cont.)

Visit	Time	Sample Type
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • AB928 PK (plasma) [b] • Biomarkers (plasma, serum, PBMC)
	30 (±5) minutes after AB928 dose	• AB928 PK (plasma) [b]
	1 hour (±5 minutes) after AB928 dose	• AB928 PK (plasma) [b]
	3 hours (±10 minutes) after AB928 dose	• AB928 PK (plasma) [b]
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • AB928 PK (plasma) [b]
Day 1 of Cycles 4 and 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • AB928 PK (plasma) [b] • Biomarkers (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • AB928 PK (plasma) [b]
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)

Atezo = atezolizumab; ADA = anti-drug antibody; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: Based on emerging safety/efficacy data the number of PK/ADA and/or biomarker samples may be reduced/removed and/or the timing of samples may be modified.

[a] Regorafenib PK includes regorafenib, regorafenib M-2, and regorafenib M-5.

[b] AB928 PK includes AB928, AB928 glucuronide, and AB928 N-dealkylated.

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Appendix 14
Study Details Specific to Atezo+ LOAd703 Arm

TABLE OF CONTENTS

A14–1 BACKGROUND ON ATEZO + LOAD703 ARM

A14–1.1 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 CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody mediated clearance of activated effector T cells.

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

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

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

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

A14–1.2 BACKGROUND ON LOAD703

LOAd703 is an oncolytic virus (OV) administered by intratumoral injection that is currently being evaluated in clinical trials for the treatment of melanoma and pancreatic, biliary, colorectal, and ovarian cancer. LOAd703 is armed with two immunostimulatory transgenes (TMZ-CD40L and 4-1BBL) that can activate dendritic cells (DCs) and stimulate anti-tumor T cells. Because of specific deletions in the viral genome, the replication of oncolysis by LOAd703 is restricted to malignant cells with a dysfunctional retinoblastoma pathway, a common mutation found in a wide spectrum of tumors. LOAd703 does not replicate in, and is not toxic to, healthy cells. However, transgene expression can occur in all cells infected with LOAd703, regardless of the cell's ability to replicate, including cells in the tumor microenvironment (Eriksson et al. 2017a). In

murine models, LOAd703 treatment has been shown to improve infiltration of T cells, natural killer (NK) cells, and DCs, in both tumors injected with OVs and tumors not injected with OVs.

Refer to the LOAd703 Investigator's Brochure for details on nonclinical and clinical studies.

A14–2 RATIONALE FOR ATEZO + LOAD703 ARM

A14–2.1 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, urothelial carcinoma, renal cell carcinoma, melanoma, CRC, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

Early clinical data had shown encouraging results with the anti–PD-1 checkpoint inhibitor pembrolizumab as a single agent in patients with metastatic CRC (mCRC) assessed as having high microsatellite instability (MSI-H) status, but not with microsatellite-stable (MSS) status (Le et al. 2015). These data resulted in the May 2017 approval of pembrolizumab in adult and pediatric patients with tumors characterized as MSI-H or deficient for mismatch repair genes based on objective response rate (ORR) and

durability of the response. ORR was similar irrespective of whether patients were diagnosed with CRC (36%) or a different cancer type (46% across the 14 other MSI-H cancer types). Similar response rates were observed in patients with second-line or later mCRC enrolled in a Phase Ia study investigating atezolizumab as single agent (Roche Study PCD4989g) and a Phase Ib study investigating the combination of atezolizumab plus bevacizumab (Roche Study GP28328, Arm A). In Study PCD4989g, there was 1 responder reported in 14 patients with MSS status per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). In the 10 patients with MSI-H status enrolled in Study GP28328, the investigator assessed confirmed ORR per RECIST v1.1 was 40% (95% CI: 12.2, 73.8), with all 4 responders having partial responses. No objective responses were seen in the 14 patients with MSS tumors.

A14–2.2 LOAD703 MECHANISM OF ACTION

OVs have the ability to infect and kill cancer cells through excessive viral replication. As such, many different OVs are currently being evaluated in both the nonclinical and clinical setting (Vacchelli et al. 2013). Some OVs are armed with immunostimulatory transgenes that can induce a systemic anti-tumor response. In addition, some OVs encode granulocyte macrophage–colony stimulating factor (GM-CSF), which can stimulate DCs. However, GM-CSF may also lead to induction of immunosuppressive cells (Tähtinen et al. 2015).

LOAd703 is an OV armed with the immunostimulatory transgenes TMZ-CD40L and 4-1BBL and is engineered to target the human receptor CD46, which is expressed by most tumors. LOAd703 has several modes of action that support anti-tumor activity. Induction of cell death by oncolysis is expected to enhance anti-tumor T-cell responses by releasing tumor antigens, which can be phagocytosed and processed by DCs. These antigen-presenting cells are activated by viral danger signals (such as TLR9) and can effectively cross-prime effector and memory $CD8^+$ T cells that migrate to the tumor and exert specific lytic activity towards cancer cells. Additionally, all infected cells, including tumor, stromal, and immune cells, can express TMZ-CD40L and 4-1BBL on their cell membrane. In addition to viral-mediated oncolysis, the translated TMZ-CD40L itself can bind to CD40 expressed on tumor cells to induce apoptosis.

Following the death of tumor cells via these two different pathways, tumor antigens are released into the surrounding tumor microenvironment, where tumor-residing DCs can engulf the released tumor antigens. Maturation, differentiation, and activation of DCs is induced following ligation of CD40 and 4-1BB, leading to priming and expansion of cytotoxic tumor-specific T and NK cells. Stimulation of 4-1BB further promotes T- and NK-cell proliferation and prolonged survival. Moreover, engagement of CD40 on tumor-associated macrophages stimulates their polarization towards M1 phenotype, whereas CD40 ligation on endothelial cells induces upregulation of adhesion molecules to facilitate lymphocyte transmigration into the tissue (Eriksson 2017b). LOAd703-encoded

transgenes TMZ-CD40L and 4-1BBL, together with oncolysis and activation of antigen-presenting cells by viral danger signals, can induce and sustain Th1-type of immunity while favorably altering the tumor microenvironment to support T-cell activity.

A14–2.3 RATIONALE FOR COMBINING LOAD703 WITH IMMUNE CHECKPOINT INHIBITION

Recently, single-agent immune checkpoint inhibitors have demonstrated clinical efficacy and long term disease control for some patients (typically 15%-30%) in a select set of tumor types (e.g., NSCLC, bladder cancer, MSI-H CRC). However, the majority of patients are either refractory to treatment or become resistant after an initial response. Resistance is likely due to the patient's immune status, (e.g., having an immunosuppressive tumor microenvironment with very few activated anti–tumor reactive T cells).

Treatment with intratumoral OVs not only induces tumor cell-restricted lysis but can prime the tumor microenvironment by influx of a variety of immune cells and cytokines. These modifications to the tumor microenvironment can set the stage for subsequent treatment with an immune checkpoint inhibitor, which is more effective in the presence of high lymphocytic infiltration. Tumors with low lymphocytic infiltration commonly do not respond at all to immune checkpoint inhibition. Since this type of treatment is dependent on preexisting tumor-reactive T cells, an appealing way to enhance the effect of immune checkpoint inhibitors is to sensitize patients' tumors with immune-activating therapy such as an immunostimulatory OV. Indeed, in a study combining the first approved OV, talimogene laherparepvec, with pembrolizumab (anti-PD1), preliminary efficacy data on 21 patients with melanoma demonstrated a 62% response rate, with 33% complete responders, which is almost double the response rate with PD-L1 blockade monotherapy (Ribas et al. 2017). An increase in $CD8^+$ T-cell infiltration, PD-L1 protein expression, and IFN-γ gene expression was observed in tumors of patients who responded to this combination therapy. Interestingly, responses were seen in patients whose baseline biopsies had very low $CD8^+$ T-cell infiltrate or negative IFNγ signature. Overall, the study suggests that oncolytic virotherapy can improve the efficacy of immune checkpoint inhibitors.

LOAd703 is engineered to target the human receptor CD46, which can be a major advantage, especially in the treatment of CRC, in which the prevalence of CD46 expression has been shown to be up to 80%. Because only negligible activity has been reported with single-agent immune checkpoint inhibitors in patients with mCRC who have MSS tumors, there is a strong rationale for combining anti–PD-L1 therapy with LOAd703 for the treatment of mCRC.

Combination therapy with LOAd703 and anti–PD-L1 has not been evaluated in nonclinical animal models of CRC, because of a lack of appropriate models that would

support both viral entry and replication in mouse tissues. However, the effect of the immunostimulatory transgenes has been evaluated in immunocompetent mice implanted with murine melanoma tumors expressing human CD46. This tumor model enables viral uptake but is non-permissive for viral replication and oncolysis, thus allowing simple assessment of the immunostimulatory capacity of LOAd703. Following intratumoral treatment with LOAd703 and systemic treatment with anti-PD-L1, robust stimulation of DCs, T cells, and NK cells was observed. While LOAd703 was able to control tumor growth as monotherapy, superior anti-tumor efficacy was observed when LOAd703 was combined with immune checkpoint inhibitors targeting either PD1 or PD-L1. Furthermore, biopsies demonstrated that combination therapy with LOAd703 and anti−PD-L1 increased tumor infiltration of cytotoxic T lymphocytes, NK cells, and $CD103^+$ DCs over single-agent therapies. Similarly, the combination of LOAd703 and anti−PD-L1 was found to control tumor growth and increase the frequency of tumor-infiltrating T cells in both injected and non-injected lesions, suggesting that combination therapy was able to induce systemic anti-tumor immunity.

In summary, additive and synergistic mechanisms of action of an armed oncolytic adenovirus such as LOAd703 and an anti−PD-L1 therapy such as atezolizumab could ultimately translate into clinical benefit when this treatment combination is administered to patients with mCRC.

A14−2.4 BENEFIT−RISK ASSESSMENT

This study will enroll patients with mCRC who have become refractory to first- and second-line standard therapies. The patient population for this study has a median overall survival (OS) of less than 9 months with currently available treatments. In addition, available standard of care treatments are often poorly tolerated. Despite the success of single-agent immune checkpoint inhibitors in the MSI-H patient population, the vast majority of patients with CRC have MSS tumors and do not respond to single-agent immune checkpoint inhibitors, highlighting the need for safe and effective combination treatments. Therefore, there remains a great need for investigating new cancer immunotherapy combinations to improve the outcome for this difficult-to-treat patient population.

Preliminary data from Phase I and II trials of other oncolytic adenoviruses have demonstrated the feasibility and the potential to combine them with immune checkpoint inhibitors.

In a Phase I dose-escalation study of DNX-2401, an unarmed intratumorally administered OV, in 37 patients with recurrent glioma, no dose-limiting toxicities (DLTs) occurred, and only 2 patients experienced adverse events related to DNX-2401, including Grade 1 to 2 headache, nausea, confusion, vomiting, and pyrexia (Lang, JCO 2018). In a Phase II study of DNX-2401 combined with pembrolizumab in 48 patients

with recurrent glioblastoma, no DLTs or unexpected safety issues were reported. The majority of adverse events were mild to moderate and unrelated to DNX-2401. The combination showed promising activity, with a median OS of 12 months and a 6-month OS rate of 91% (Aiken et al. 2019).

In the SPICE study (ColoAd1-1003), the combination of enadenotucirev (EnAd), an unarmed OV administered intravenously, was investigated in combination with nivoloumab in patients with solid tumors who had primary or secondary resistance to checkpoint inhibitors (n=40, Fakih et al. 2019). The combination had a manageable safety profile with the majority of patients reporting flu-like symptoms. Adverse events of infusion reactions and hypoxia met DLT criteria on Day 1 of Cycle 2 of EnAd, requiring increased prophylaxis. Cases of renal injury and lung injury led to the addition of mitigation measures in the ongoing protocol. Among the 34 mCRC patients enrolled in the study, 4 patients (21%) achieved stable disease for ≥4 months. One confirmed partial response (PR) of >15 weeks was seen in a patient who had mCRC with low-MSI status, low tumor mutation burden, and a BRAF mutation, a feature typically associated with a poor prognosis. Remarkably, a median OS of 14 months was reported, which is greater than the OS observed with regorafenib or TAS-102 treatment in this patient population.

In the Phase I portion of a study of ONCOS-10, an armed intraperitoneally administered OV encoding for GM-CSF, combined with the anti−PD-L1 antibody durvalumab in patients with refractory ovarian cancer or mCRC with intraperitoneal disease (n=17), 1 patient had durable confirmed PR and remains on treatment (for >1 year) and 4 patients had stable disease as best overall response (Zamarin 2020). No DLTs were reported.

Safety data are available for single-agent atezolizumab in patients with advanced solid tumors including CRC. Atezolizumab was generally well tolerated among the 14 patients with MSS mCRC who received single-agent atezolizumab in Study PCD4989g. Grade 3 or 4 adverse events, treatment-related adverse events, and serious adverse events were reported at a similar rate as for patients with other solid tumors. The most commonly reported treatment-related adverse events in this population (≥25%, 4 patients) were constipation, nausea, fatigue, diarrhea, dyspnea, pruritus, night sweats, and chills. Three patients (21.4%) reported Grade 3 or 4 adverse events related to atezolizumab: 2 cases of Grade 3 asthenia, which led to study drug withdrawal in one case, and 1 case of Grade 3 abnormal liver function tests.

Preliminary data from an ongoing Phase Ib trial in patients with metastatic triple-negative breast cancer (TNBC) or CRC with liver metastases (NCT03256344) suggest that atezolizumab can be safely combined with T-Vec, an OV administered by intrahepatic injection that expresses GM-CSF (Pascual et al 2020). The most common treatment-

related adverse events among the first 7 patients (all with TNBC) were pyrexia (85.7%) and chills (71.4%). No DLTs have been reported, and there was one confirmed PR.

Although LOAd703 has not been investigated as a single agent, it is being evaluated at doses of 5×10^{10} VP to 5×10^{11} VP, Q2W or Q3W, in combination with chemotherapy and/or atezolizumab in three ongoing Phase I/II studies. Study LOKON001 is evaluating LOAd703 in combination with gemcitabine plus nab-paclitaxel (Arm 1) and in combination with gemcitabine, nab-paclitaxel and atezolizumab (Arm 2) in pancreatic ductal adenocarcinoma. Study LOKON002 is evaluating LOAd703 in combination with chemotherapy in different solid tumor indications. Study LOKON003 is evaluating LOAd703 in combination with atezolizumab in patients with advanced melanoma.

As of the Development Safety Update Report cutoff date (31 May 2020), among the 21 patients treated in Arm 1 of Study LOKON001, 1 patient (5%) dosed at 5×10^{11} VP experienced a transient Grade 3 ALT elevation post- virus injection that led to a dose reduction to 1×10^{11} VP (this has been the only DLT reported to date). In the same study, 2 patients (9.5%) experienced LOAd703-related serious adverse events of Grade 1 fever. Among the 16 patients treated in Study LOKON002, 4 patients (25%) experienced a total of eight LOAd703-related serious adverse events that were Grade 1 or 2 fever (in 3 patients dosed at 5×10^{11} VP) and Grade 1 or 2 cytokine-release syndrome (CRS) (in 1 patient dosed at 1×10^{11} VP and 1 patient dosed at 5×10^{11} VP). For all reported serious adverse event cases, the criterion for seriousness was the requirement for a brief hospitalization.

In Arm 2 of Study LOKON001, 3 patients have been treated with LOAd703 at a dose of 1×10^{11} and 4 patients at 5×10^{11} VP in combination with gemcitabine, nab-paclitaxel and atezolizumab. In Study LOKON003, 2 patients have been treated with LOAd703 at a dose of 1×10^{11} VP in combination with atezolizumab. As of the data cutoff date of 9 November 2020, no DLT or LOAd703-related serious adverse events were reported across these two atezolizumab combination studies (Lokon data on file).

Across the three studies and range of dose levels, the most common adverse events have been fever, nausea, vomiting, chills, and ALT increase, with most events being mild or moderate. There have been no fatal adverse events related to LOAd703 or LOAd703-related adverse events leading to discontinuation of study treatment (Lokon data on file).

There is a theoretical risk of a non−targeted-organ expression of the immunostimulatory transgenes resulting from unintentional spreading of LOAd703 into adjacent normal tissue or blood vessels, which could lead to CRS. However, CRS would be expected to be transient, because the virus will not replicate in normal cells, and the immune system

will rapidly clear both OV and OV-infected cells. This rapid immune response will also make late immune-mediated events unlikely.

Biodistribution and shedding was investigated for various types of oncolytic adenovirus (i.e., replication deficient, or replication competent with tumor cell selectivity) administered either systemically, locally or directly into the tumor. Shedding of viral DNA was detected in serum, urine, stool and saliva, as well as in physiologic components related to the route of administration, such as in the ascites fluid following intraperitoneal injections and in the bronchoalveolar lavage following intrabronchial injections. In these studies, viral shedding is largely dose dependent, with the highest frequency, concentrations and durations of shedding reported in patients receiving the highest doses of virus (Dummer et al. 2000, Griscelli et al.2003, Makower et al. 2003, Small et al. 2006, Kawahira et al. 2010, Kimball et al. 2010, Kim et al. 2012, Kim et al. 2013, Garcia et al. 2019, Machiels et al. 2019). Data on shedding of live oncolytic adenoviruses virus is more limited with a few studies that reported live virus mostly in sputum samples in a dose dependent manner after both intravenous or intra tumoral administration. However, virus detection was limited to the first few days after virus administration, suggesting that shedding of the live virus is short lasting (Griscelli et al. 2003, Makower et al. 2003, Small et al. 2006). Due to the differences in the type of adenovirus tested, route of administration and shedding assays across studies, it is not possible to draw conclusions on any potential differences in shedding activity between different types of adenoviruses and/or route of administration. Of note, none of these studies have reported any transmission of oncolytic adenovirus to household contacts or healthcare providers.

LOAd703 is administered intra-tumorally which is expected to limit systemic exposure. In addition, the pre-existing and induced anti-adenovirus immune response will likely result in a rapid clearance of LOAd703 from the patient's body. These factors are likely to reduce the duration and extend LOAd703 shedding as a viable virus. In addition, should the virus be transmitted to another person, LOAd703 is designed to selectively replicate within, and lyse the tumor cells and as such is expected to result in minimal pathogenicity to the host normal cells/tissues compared to the parental adenovirus strain.

Notwithstanding the low risk of infectivity of LOAd703, the protocol includes precautionary measures to minimize exposure of healthcare providers and close contacts, including contraception requirements for both females and male study subjects (Section A14–4.3), precautionary instructions to study staff during preparation and administration of LOAd703 and precautionary instructions to patients and close contacts (Section A14–4.1.2.2). In addition, shedding analyses will be performed to evaluate the biodistribution and shedding potential of LOAd703 (A14–Table 9).

Given the mechanism of action for atezolizumab and LOAd703, immune-mediated adverse events and CRS are potential overlapping toxicities associated with the combination use of these two agents. Therefore, there may be a potential for an increased risk of enhanced inflammatory response if a patient develops SARS-CoV-2 infection while receiving atezolizumab and LOAd703. If a patient develops severe CRS during the study, a differential diagnosis including COVID-19 testing should be considered.

Because LOAd703 is currently under evaluation in cancer patients and sufficient efficacy data are not yet available, its benefits are unknown at this time.

In summary, preliminary data of the combination of OVs with immune checkpoint inhibitors support further investigation of OVs with an anti-PD-L1 in patients with refractory mCRC.

Safety data from ongoing investigations of LOAd703 have not revealed findings that would prohibit the investigation of LOAd703 combined with atezolizumab in the setting of a Phase Ib/II study. The benefit-risk profile is considered positive, given the high unmet need for well tolerated and effective treatments for patients with refractory mCRC, the scientific rationale for the combination of atezolizumab and LOAd703, and the anticipated safety profile for this combination.

A14–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + LOAD703

A14–3.1 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, as outlined in the prescribing information. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached, and no DLTs were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A14–3.2 RATIONALE FOR LOAD703 DOSE AND SCHEDULE

The intended target dose and schedule for LOAd703 is 5×10^{11} VP Q3W. However, to account for potential overlapping toxicities, special caution will be taken by starting LOAd703 at the lower dose of 1×10^{11} VP. The safety and tolerability of LOAd703 at a dose level of 1×10^{11} VP in combination with atezolizumab will be evaluated in approximately 3 to 6 patients. If the dose of LOAd703 is determined to be safe and well tolerated, the Sponsor may decide to escalate the dose to 5×10^{11} VP in the subsequent patients according to the considerations described in Section A14-4.1.2.2.

The doses and schedule were selected on the basis of previous experience with the predecessor OV AdCD40L and results from the ongoing LOAd703 studies LOKON001 and LOKON002. AdCD40L has been safely injected repeatedly (4–8 weekly injections) at 2.5×10^{11} VP in a 500 µl suspension in combination with cyclophosphamide preconditioning (Loskog et al. 2016). Furthermore, another oncolytic adenovirus expressing CD40L has been safely tested at doses ranging from 3×10^{10} to 2×10^{12} VP/dose (3–5 injections) in patients with or without metronomic cyclophosphamide combination (Pesonen et al. 2012). In Studies LOKON001 and LOKON002, the tested LOAd703 dose ranged from 5×10^{10} VP to the highest target dose of 5×10^{11} VP. In these studies, LOAd703 administered at a dose of 5×10^{11} VP Q2W did not significantly increase the rate of severe toxicities induced by the chemotherapy regimen or the combination of chemotherapy plus atezolizumab. Based on these results, 5×10^{11} VP Q2W has been selected as the recommended Phase II dose and schedule in combination with chemotherapy. The 5×10^{11} VP dose will continue to be evaluated in combination with chemotherapy plus atezolizumab as a Q2W regimen in Arm 2 of Study LOKON001 and is planned to be investigated in combination with atezolizumab as a Q3W regimen in Study LOKON003. The Q3W schedule of administration for LoAD703 aligns with the approved atezolizumab dosing schedule (1200 mg Q3W) and is expected to result in an acceptable safety profile, while reducing the procedure and visit burden to patients as compared with a Q2W regimen. Refer to the LOAD703 Investigator's Brochure for additional details.

A14–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + LOAD703 ARM

A14–4.1 TREATMENT IN ATEZO + LOAD703 ARM

A14–4.1.1 Formulation, Packaging, and Handling

A14–4.1.1.1 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 and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A14–4.1.1.2 LOAd703

The LOAd703 drug product will be supplied by the Sponsor as sterile frozen liquid in a single-use vial. Each vial contains 650µl LOAd703 adenoviral particles in suspension at a concentration of 1×10^{12} virus particles (VP)/ml.

For information on the formulation and handling of LOAd703, see the pharmacy manual and the LOAd703 Investigator's Brochure.

A14–4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + LOAd703 arm will receive treatment as outlined in Table 1 until unacceptable toxicity or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator, after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 in the protocol body for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table 1 Treatment Regimen for Atezo + LOAd703 Arm

Cycle Length	Dose, Route, and Regimen (Drugs Listed in Order of Administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle [a] • LOAd703 1×10^{11} VP or 5×10^{11} VP [b] intratumoral injection on Day 1 of each cycle [c]

[a] Atezolizumab will be administered preferably prior to LOAd703 injection. If LOAd703 cannot be administered the day of atezolizumab infusion, LOAd703 can be given on another day during the treatment week, after prior consultation with the Medical Monitor. If atezolizumab is administered after LOAd703, it should not be administered until the LOAd703 observation period has ended.

[b] Initially, approximatively 3 to 6 patients will be treated at the dose of 1×10^{11} VP. If this dose is determined to be safe and well tolerated in these first 3–6 patients, the dose may be increased to 5×10^{11}VP in the next enrolled patients according to the considerations described in Section A14–4.1.2.2.

[c] After the initial six injections of LOAd703 (Cyles 1–6), there is an option to continue treatment with LOAd703 for an additional 6 administrations (Cycles 7–12) for a maximum total number of 12 injections for patients who are deriving clinical benefit as determined by the investigator. In the absence of confirmed PD, (as described in Section 3.1.1), atezolizumab treatment can continue after LOAd703 treatment has ended or has been discontinued for reasons other than toxicity, provided the patient is tolerating atezolizumab and is receiving clinical benefit in the opinion of the investigator. *The Medical Monitor is available to advise as needed.*

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

Guidelines for dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A14–5.1.4. Atezolizumab or LOAd703 treatment interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed. The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12. No safety data related to atezolizumab or LOAd703 overdose are available.

A14–4.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Atezolizumab will be administered preferably prior to LOAd703 injection. If, for any reason, the investigator judges that LOAd703 should not be administered the day of atezolizumab infusion, LOAd703 can be given on another day during the treatment week after prior consultation with the Medical Monitor. If atezolizumab is administered after LOAd703, it should not be administered until the LOAd703 observation period has ended.

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 5. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 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, pulse oximetry, blood pressure, 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. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A14–5.1.4.

A14–4.1.2.2 LOAd703

LOAd703 will be administered by intratumoral injection at a dose level of 1×10^{11} VP or 5×10^{11} VP on Day 1 of each 21-day cycle during Cycles 1–6.

Administration of LOAd703 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.

LOAd703 injections will be administered per the instructions outlined in Table 3.

Dose Selection for LOAd703

Consideration for dose-escalation to 5×10^{11} VP will be based on a review of data from individual patients that have received at least one dose of the study treatment combination (i.e., LOAd703 and atezolizumab) and completed at least one treatment cycle (21 days). The dose-escalation decision will be based on the occurrence (or absence) of Grade 3 or higher toxicity (per CTCAE Version 4.0) related to LOAd703 and/or atezolizumab in the safety-evaluable patients, with the following exceptions:

- Grade 3 increase in liver function tests that resolves to Grade ≤ 1 or to baseline within 3 weeks
- Grade 3 fever and/or chills that improves to Grade ≤ 2 within 48 hours or fully resolves within 1 week
- Grade 3 arthralgia and/or myalgia that can be adequately managed with supportive care or that resolves to Grade ≤ 2 within 1 week
- Grade 3 nausea or vomiting that resolves to Grade ≤ 1 within 72 hours with or without appropriate supportive therapy
- Grade 3 headache that can be adequately managed with supportive care or that resolves to Grade ≤ 2 within 1 week
- Grade ≥ 3 fatigue/asthenia that resolves to Grade ≤ 2 within 1 week
- Grade 3 tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor

Evaluation of the LOAd703 1×10^{11} VP dose level will proceed as follows:

- Initially, a minimum of 3 patients will be treated with the 1×10^{11} VP dose in combination with atezolizumab 1200 mg Q3W.

- If the 1×10^{11} VP dose is determined to be safe and well tolerated in all 3 patients, the Sponsor may proceed to evaluate the 5×10^{11} VP dose in the next enrolled patients.
- If the 1×10^{11} VP dose is determined to be safe and well tolerated in only 2 out of 3 patients, this dose will be evaluated in 3 additional patients.
- If the 1×10^{11} VP dose is determined to be safe and well tolerated in a minimum of 5 out of 6 patients, the Sponsor may proceed to evaluate the 5×10^{11} VP dose in the next enrolled patients. Otherwise, the Sponsor may decide to maintain the LOAd703 dose at 1×10^{11} VP.
- If 2 or more of the first 3–6 patients dosed at 5×10^{11} VP experience a Grade 3 or higher toxicity related to LOAd703, enrollment into the Atezo + LOAd703 arm will be halted. If enrollment of this arm is halted, the available safety data will be reviewed by the Internal Monitoring Committee (IMC; see Section 3.1.4). Enrollment may continue if the IMC determines there is a positive benefit-risk assessment for patients entering the arm and there is a high likelihood that the underlying rate of Grade 3 or higher toxicity related to LOAd703 is not $\geq 30\%$.

Evaluation of the LOAd703 5×10^{11} VP dose level will proceed as follows:

- Initially, a minimum of 3 patients will be treated with the 5×10^{11} VP dose in combination with atezolizumab 1200 mg Q3W.
- If the 5×10^{11} VP dose is determined to be safe and well tolerated in a minimum of 2 out of 3 patients, the Sponsor may proceed to evaluate the 5×10^{11} VP dose in 3 additional patients.
- If the 5×10^{11} VP dose is determined to be safe and well tolerated in a minimum of 5 out of 6 patients, this dose will be selected for evaluation in the remaining patients.
- If 2 or more of the first 3–6 patients dosed at 5×10^{11} VP experiences a Grade 3 or higher toxicity related to LOAd703, the dose of 1×10^{11} VP will be selected for evaluation in the remaining patients.

During the dose-escalation phase, patients who withdraw for any reason other than a high-grade toxicity and who have completed < 1 cycle of the treatment regimen will be replaced. Also, the patients treated at the selected dose during the dose-escalation phase will contribute to the overall safety and efficacy analysis of the preliminary phase of this arm (see Section 3.1.1).

The Sponsor may also decide to maintain or de-escalate the dose of LOAd703 to 1×10^{11} VP if warranted by the emerging safety, pharmacokinetic, pharmacodynamic, biomarker, or efficacy data from the current study as well as data from ongoing studies with LOAd703.

Additionally, enrollment in the Atezo + LOAd703 arm will be halted if Grade 3 or higher study treatment-related adverse events that are unmanageable and lead to discontinuation of all study drugs occur in at least one-third of patients in a given LOAd703 dose level during the dose-escalation phase. If enrollment of this arm is halted, the available safety data will be reviewed by the IMC (see Section 3.1.4). Enrollment may continue if the IMC determines there is a positive benefit–risk assessment for patients entering that arm and there is a high likelihood that the underlying discontinuation rate due to adverse events is not ≥ 30%.

No intra-patient dose escalation is allowed.

In patients who are deriving clinical benefit as determined by the investigator and the Medical Monitor, there is the option to continue LOAd703 administrations for up to 6 additional administrations Q3W for a maximum total number of 12 injections.

Guidelines for LOAd703 Administration

The investigator will assess which lesion is deemed clinically feasible for injection. In general, preference should be given to injectable and measurable lesions (as per RECIST v1.1) over injectable and non-measurable lesions. The following criteria should be considered when selecting injectable lesion(s).

- Lesions selected for injection should meet at least one of the following size criteria:
  - Non-nodal lesions should measure ≥ 1 cm in the longest diameter
  - Nodal lesions should measure ≥ 1.5 cm in the shortest diameter
  - For non-nodal lesions with necrosis, the longest diameter of the necrotic region subtracted from the longest diameter of the lesion should measure ≥ 1 cm
- Lesions with any of the following characteristics should not be injected:
  - Lung lesions
  - Tumor lesions encasing or invading major blood vessels
  - Lesions with risks to bowel penetration
  - Lesions that have received lesion-directed therapy (eg, radiation, ablation, embolization) within 4 weeks prior to the start of study treatment
  - Predominantly necrotic lesions (the LOAd703 virus requires viable cells for efficacy.
  - For liver lesions:
    - Lesions located where any potential tumor swelling after injection may lead to biliary tract obstruction (e.g., < 1 cm adjacent to the left main, right main, or common biliary ducts)

- Lesions that are at risk of bleeding, including, but not limited to, the following:
  - Lesions located < 1 cm from the hepatic capsule
  - Lesions with tumor infiltration into the main portal vein, hepatic vein or vena cava
- Approximately more than one-third of the liver is estimated to be involved with metastases

Five hundred microliters (500 µl) LOAd703 at a total dose level of 1×10^{11} VP or 5×10^{11} VP will be administered by image guided injection (either ultrasound or computed tomography) into one measurable (as per RECIST v1.1) and injectable lesion.

The same lesion should preferably be used for all injections. However, if over the course of treatment the injected lesion no longer fullfills the criteria for injection as outlined above, the injected lesion is not responding over time, or the patient may benefit from injection into another lesion as assessed by the investigator, a new lesion may be selected for further injections.

If any of the above occurs and another lesion is selected for injection, an explanation describing why the lesion was changed should be documented in the eCRF.

Tumor biopsy sample collection following treatment initiation

In consenting patients, and if deemed clinically feasible by the investigator, a tumor biopsy sample will be collected from the injected lesion immediately before the third LOAd703 administration on Day 1 of Cycle 3. Local anesthesia is commonly not needed prior to LOAd703 injection but is recommended when this biopsy is taken.

Instructions to study staff involved in the preparation and administration of LOAd703

The LOAd703 virus will be handled only by study staff trained to handle genetically modified microorganisms. All study staff involved in the viral administration and the collection of excretion samples should wear personal protective equipment that are disposed of immediately after use. Pregnant or severely immunocompromised (e.g., bone marrow transplant) healthcare providers should be prohibited from preparing and/or dosing LOAd703 or caring for LOAd703-treated patients. For details on precautions during preparation and administration of LOAd703, see the Pharmacy Manual.

<u>Action plan in case of accidental exposure</u>

- Always inform the Supervisor (the principal investigator at the clinical trial site) and the IRB, if applicable, according to local institutional policy, as well as the Sponsor

about accidental exposure/contamination with LOAd703. The accident form should be completed to document types of accident and actions taken.

- **Virus spillage**: vacate the spill area for approximately 30 minutes to allow any potential aerosols to settle. Inactivate the LOAd703 virus with Virkon® or equivalent disinfectant by gently pouring Virkon®/disinfectant on the contaminated area. Allow it to inactivate for at least 10 minutes before cleaning with absorbent paper using gloves. Dispose of the paper and gloves in a biohazard box.
- **Clothes contamination**: Place the clothing item(s) in a trashbag and pour Virkon® disinfectant over it. Close the trashbag properly and discard it in the hazardous waste.
- **Accidental needle stick injury**: Allow the puncture wound to bleed before thoroughly flushing it with water, cleaning with soap and water and/or disinfectant and covering the site with sterile gauze dressing that is discarded in an appropriate waste container when removed.
- **Exposure of intact or broken skin to virus**: Flush with running water. Next wash with soap and rinse with water. Repeat washing. Soak the skin in disinfectant and allow air-dry. Seek medical care if inflammation or irritation develops.
- **Accidental exposure of mucous area (eyes, nose or mouth)**: Irrigate these areas with clean water or physiological saline solution (NaCL 0.9%). Eyes can also be rinsed with eyewash. Seek medical care if inflammation or irritation develops.

Guidance to patients and close contacts

- Patients should avoid touching or scratching injection sites or the occlusive dressings.
- When the dressing is removed at home, dressing should be handled with gloves or hands should be washed with soap and warm water immediately after the handling of the dressing. Used dressing should be placed in sealed plastic bags before disposal in the household trash.
- Avoid kissing and common usage of cutlery, crockery, drinking vessels, and tooth brushes for the duration of LOAd703 treatment and until 30 days after the last dose of LOAd703.
- Caregivers and family members should observe personal hygiene (i.e., handwashing) after contact with treated participants.
- Close contacts that are pregnant, newborn or immunocompromised should avoid exposure to the injection site and the patient's body fluids.

Table 3 Administration of First Two and Subsequent LOAd703 Injections

First Two Injections [a]	Subsequent Injections
• Patients should be monitored overnight. • Premedication or post-dose prophylaxis with paracetamol (1 g, oral) or nonsteroidal anti-inflammatory drug (e.g., Ibuprofen, 400 mg, oral) is recommended to reduce the risk of systemic injection reactions and CRS. • If the patient experienced a CRS with any previous injection, premedication with low-dose corticosteroids may be administered for subsequent doses at the discretion of the investigator. • Patients receiving LOAd703 as a percutaneous injection may receive an anxiolytic drug such as a benzodiazepine prior to the procedure. • Prophylactic antibiotics such as IV-administered fluroquinolone is recommended if there is a risk of penetrating bowels or other circumstances that increase risk of infections, in the opinion of the investigator. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the injection. • LOAd703 should be administered by intratumoral injection as outlined in Section A14–4.1.2.2. • After the injection, vital signs should be recorded every 30 (± 5) minutes for the first 2 hours and at 3h, 4h, 5h, 6h, and 8h (± 10 minutes). • If clinically indicated, vital signs should be recorded every 4 hours (± 30 minutes) thereafter until discharge. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• Patients should be monitored for a minimum of 6 hours. • Premedication or post-dose prophylaxis with paracetamol (1 g, oral) or nonsteroidal anti-inflammatory drug (e.g., Ibuprofen, 400 mg, oral) is recommended to reduce the risk of systemic injection reactions and CRS. • If the patient experienced a CRS with any previous injection, premedication with low-dose corticosteroids may be administered for subsequent doses at the discretion of the investigator. • Patients receiving LOAd703 as a percutaneous injection may receive an anxiolytic drug such as a benzodiazepine prior to the procedure. • Prophylactic antibiotics such as IV-administered fluroquinolone is recommended if there is a risk of penetrating bowels or other circumstances that increase risk of infections, in the opinion of the investigator. • Vital signs should be recorded within 60 minutes prior to the injection. • LOAd703 should be administered by intratumoral injection as outlined in Section A14–4.1.2.2. • After the injection, vital signs should be recorded every 30 (± 5) minutes for the first 2 hours and hourly until the end of the 6-hour observation period if the previous injection was tolerated without an injection-related reaction • If the patient experienced any injection-related reaction with the previous injection or if clinically indicated, the patient should be monitored overnight. After the injection, vital signs should be recorded every 30 (± 5) minutes for the first 2 hours and hourly (± 10 minutes) until the end of the 6-hour observation period. If clinically indicated, vital signs should be recorded every 4 hours (± 30 minutes) thereafter until discharge.

[a] Day 1 of Cycles 1 and 2.

Note that provisions should be made for overnight monitoring; patients may be released early according to the requirements outlined in Table 3 above at the discretion of the investigator.

Guidelines for LOAd703 dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A14–5.1.4.

A14–4.1.3 Stage 2 Treatment

Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1 in the protocol body) or unacceptable toxicity may be eligible to receive a different treatment combination during during Stage 2, provided a Stage 2 treatment is available for enrollment and they meet the eligibility criteria of that treatment regimen. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. However, it is recommended that patients begin Stage 2 treatment as soon as possible, but no earlier than 2 weeks after the last dose of treatment in Stage 1.

Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table 4 Stage 2 Treatment Regimens Available for the Atezo + LOAd703 Arm

Study Treatment	Appendix
No Stage 2 treatment currently available	—

A14–4.2 CONCOMITANT THERAPY FOR ATEZO + LOAD703 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 patient 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.

A14–4.2.1 Permitted Therapy for Atezo+LOAd703 Arm

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

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic anticoagulation

  Prophylactic anticoagulation for the patency of venous access devices is allowed provided the activity of the agent results in an INR $< 1.5\times$ upper limit of normal (ULN) and aPTT is within normal limits within 14 days prior to Day 1.
- Prophylactic antibiotic or antiviral treatment administered according to institutional standards
- *Vaccinations (such as influenza, COVID-19; please see Section A14–4.2.3)*

  Live, attenuated vaccines are not permitted.
- Prophylactic standard anti-emetic therapy
- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin releasing–hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease).

  Treatment with atezolizumab and LOAd703 may be continued during palliative radiotherapy. It is recommended not to irradiate a lesion that has been injected or will be injected with LOAd703.

- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole brain radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.

  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

  – Anti-convulsant therapy, if required, is administered at a stable dose.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 adrenergic agonists).

A14–4.2.2 Cautionary Therapy for Atezo + LOAd703 Arm

A14–4.2.2.1 Corticosteroids, *Immunosuppressive Medications,* and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, *immunosuppressive medications,* and tumor necrosis factor–α (TNF–α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and LOAd703. Therefore, in situations in which systemic corticosteroids, *immunosuppressive medications,* or TNF–α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, *immunosuppressive medications,* and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids *or immunosuppressive medications* are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 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 Anti-Platelet Agents and Low Molecular Weight Heparin

The following guidelines should be followed for procedures with moderate or significant risk of bleeding (deep lesions and/or organs):

- Long-acting agents such as aspirin or clopidogrel should be discussed on a case-by-case basis with the Sponsor and may need to be discontinued before the start of study treatment.
- Use of preventive doses of low molecular weight heparin (LMWH) or direct anti-oral coagulant (DOAC) is allowed but should be withheld 24 hours for LMWH or 48 h for DOAC prior to intratumoral injection and resumed 24 hours after the injection.

A14–4.2.3 Prohibited Therapy for Atezo+LOAd703 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, may be prohibited prior to starting study treatment, depending on the agent, and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances outlined above in Section A14–4.2.1.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab and LOAd703, for 5 months after the final dose of atezolizumab, and for 90 days after the final administration of LOAd703.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin 2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab and LOAd703.
- For procedures with moderate or significant risk of bleeding (deep lesions and/or organs), use of therapeutic doses of anticoagulants is prohibited.
- Adenovirus-based vaccines (e.g., ChAdOx1 nCoV-19, Ad26.COV2.S) are prohibited for up to 6 months prior to initiation of study treatment, during treatment with

atezolizumab and LOAd703, and up to 6 months after the final administration of LOAd703.

A14–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + LOAD703 ARM

Contraception requirements for women and men in the Atezo + LOAd703 arm are outlined below:

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse), or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 5 months after the last dose of atezolizumab and for 6 months after the last dose of LOAd703. Women must refrain from breastfeeding during this same period of time. During treatment with LOAd703 and for 6 months after the last dose, women must refrain from egg donation.

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

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

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

- 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 female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of LOAd703 and to avoid exposing the embryo. Men must refrain from donating sperm during this same period. The female sexual partner must also agree to remain abstinent (refrain from heterosexual intercourse and from donating eggs) or use contraceptive methods with a failure rate of $< 1\%$ per year during treatment with LOAd703 and for 6 months after the last dose. Women must refrain from breastfeeding during this same period of time.

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

A14–5 ASSESSMENT OF SAFETY FOR ATEZO + LOAD703 ARM

A14–5.1 SAFETY PLAN FOR ATEZO + LOAD703 ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and LOAd703 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 the management of patients who experience specific adverse events are provided in Section A14–5.1.4.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria, close monitoring of patients during the study, and reporting serious adverse events and adverse events of special interest until 180 days after the last administration of LOAd703 (see Section 5.3.1). Because of the potential for overlapping toxicities identified for atezolizumab and LOAd703, special caution will be taken by performing a planned safety evaluation for patients randomized to this arm (see Section 3.1.1.1).

Administration of all agents 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 in the protocol body.

A14–5.1.1 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, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab. Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A14–5.1.2 Risks Associated with LOAd703

The overall safety profile of LOAd703 is based on data from 44 patients with advanced cancer. The most common adverse reactions include fever, chills, nausea, vomiting and transient increased ALT. These adverse events occur a few hours after LOAd703 injection, when virus particles leak from the tumor to the blood stream where anti-adenovirus antibodies react to and clear the virus particles. The symptoms are transient and manageable with symptomatic medication. Grades 1–2 fever and Grades 1–2 CRS have been reported as serious adverse events related to LOAd703.

Local inflammation and swelling of the injected tumor may occur at the injected tumor site as part of the mechanism of action of LOAd703. Tumor inflammation can be associated with pain at the tumor site or affect the function of the organ in which the lesion is injected (e.g., increased level of liver function enzymes and bilirubin). Pain and erythema at the injection site related to the injection procedure may be observed as well.

One patient in Study LOKON001 developed sepsis with splenic infection after completing 6 LOAd703 doses at 5×10^{10} VP. The sepsis was reported as unrelated to LOAd703 and likely due to penetration of the bowel by the tumor. However, it is possible that the route of drug administration, via endoscopic ultrasound-guided injection of pancreatic lesions, may have contributed to the event. Therefore, the Study LOKON001 protocol was amended to include prophylactic administration of IV antibiotics on the day of LOAd703 administration if the injections are performed via an endoscopic procedure or if the percutaneous injection is of risk to penetrate bowels, depending on the location of the tumor.

Refer to the LOAd703 Investigator's Brochure and Section A14-2.4 for detailed safety information from ongoing clinical studies of LOAd703.

A14–5.1.3 Risks Associated with Combination Use of Atezolizumab, and LOAd703

Potential overlapping toxicities for the combination of atezolizumab and LOAd703 include immune-mediated adverse events, injection-related reactions, IRRs, and CRS.

A14–5.1.4 Management of Patients Who Experience Adverse Events in Atezo+LOAd703 arm

A14–5.1.4.1 Dose Modifications

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

For management of drug-related toxicities, the dose of LOAd703 may be reduced up to two times as outlined in Table 5 and Table 6. If further dose reduction below 5×10^{10} is indicated, LOAd703 should be discontinued. After dose reduction, the dose may not be escalated during subsequent administrations.

Table 5 Recommended Dose Reductions for the LOAd703 1×10^{11} VP Dose Level

	Initial Dose	First Dose Reduction
LOAd703	1×10^{11}VP	5×10^{10}VP

Table 6 Recommended Dose Reductions for the LOAd703 5 × 1011 VP Dose Level

	Initial Dose	First Dose Reduction	Second Dose Reduction
LOAd703	5×10^{11}VP	1×10^{11}VP	5×10^{10}VP

A14–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for more than 12 weeks, the patient will be discontinued from the study. However, atezolizumab may be withheld for more than 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for more than 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

LOAd703 may be temporarily suspended in patients experiencing toxicity related to study treatment. If LOAd703 has been withheld for more than 12 weeks because of toxicity, the patient should be discontinued from LOAd703. However, LOAd703 can be resumed after being withheld for more than 12 weeks if the patient is likely to derive clinical benefit. *The Medical Monitor is available to advise as needed.*

If atezolizumab or LOAd703 are permanently discontinued, the other agent should also be discontinued unless the patient is likely to derive clinical benefit from single-agent use, as determined by the investigator. *The Medical Monitor is available to advise as needed.*

Refer to 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 the management of patients who experience specific adverse events are provided below in Table 7 for events related to overlapping toxicities or LOAd703 treatment.

For cases in which management guidelines are not covered in Appendix 6 or Table 7, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table 7 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+LOAd703 Arm

Event	Action to Be Taken
Anaphylaxis, and hypersensitivity reactions	• Guidelines for management for atezolizumab are provided in Appendix 6. • For anaphylaxis precautions, see Appendix 5.
Tumor inflammation and injection-site reaction	• Consider treatment with anti-inflammatory medication and symptomatic pain control as needed. NSAID should be preferred over corticosteroids.
Systemic injection-related reactions, IRR, CRS	
General guidance	• Because systemic injection reactions and CRS related to LOAd703 maybe indistinguishable from IRR and CRS related to atezolizumab, the same supportive care and treatment with corticosteroids and/or anti-cytokine therapy is recommended for both as described in the IRR/CRS management guidelines in Appendix 6.
Grade 1[a] Including fever [b] with or without constitutional symptoms	• Follow guidelines for atezolizumab in Appendix 6. • Administer next injection of LOAd703 at the same dose level.
Grade 2 Fever [b] with hypotension not requiring vasopressors and/or Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Follow guidelines for atezolizumab in Appendix 6. • Collect sample for cytokine measurements (e.g. IL-6) at time of event and before releasing patient from hospital. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of LOAd703 may be administered at the same dose level.

Table 7 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+LOAd703 (cont.)

Event	Action to Be Taken
Grade 3 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	• Follow guidelines for atezolizumab in Appendix 6. • Collect sample for cytokine measurements (e,g. IL-6) at time of event and before releasing patient from hospital • Permanently discontinue LOAd703 and contact Medical Monitor. [g]
Grade 4 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)	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue LOAd703 and contact Medical Monitor. [g] • Collect sample for cytokine measurements (e,g. IL-6) at time of event and before releasing patient from hospital

Table 7 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+LOAd703 (cont.)

Hepatic event (elevations in ALT, AST, and/or bilirubin)	
General guidance	• For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. • If elevated, LFTs should be monitored closely to determine whether this is a transient or persistent elevation. • Patients with right upper quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests performed immediately and reviewed before the next administration of study drug(s). • If immune-mediated hepatitis is suspected, refer to guidance in Appendix 6.
Grade 1: ≤3×ULN elevations in ALT or AST; ≤1.5×ULN total bilirubin elevation; ≤2.5×ULN elevation ALP.	• Continue atezolizumab and LOAd703 at the same dose level.

Table 7 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+LOAd703 (cont.)

Grade 2: ALT > 3 × ULN and ≤ 5 × ULN; AST > 3 × ULN and ≤ 5 × ULN; Total bilirubin > 1.5 × ULN and ≤ 3 × ULN; ALP > 2.5 × ULN and ≤ 5 × ULN OR For patients with documented liver metastases AND: Baseline AST/ALT is > ULN to ≤ 5 × ULN and increase to > 5 × ULN to ≤ 10 × ULN.	• Continue atezolizumab and LOAd703 at the same dose level. • Monitor LFTs at least weekly for a minimum of 4 weeks until transaminases return to < 3 × ULN (Grade 1), baseline, or ≤ 5 ULN for patients with liver metastases and elevated LFTs at baseline. Check LFTs prior to next dose. • If event does not improve within 5 days: – Withhold LOAd703 and atezolizumab for up to 12 weeks after event onset. [h] – Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. – If event resolves to Grade 1 or better within 12 weeks (or ≤ 2-fold increase in baseline values for patients with liver metastases and elevated LFTs at baseline), resume atezolizumab and LOAd703 at the same dose level. [i] – If event does not resolve to Grade 1 or better (or≤ 2 fold increase in baseline values for patients with liver metastases and elevated LFTs at baseline) while withholding LOAd703 and atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [f, j]

Table 7 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+LOAd703 (cont.)

Grade 3 or 4: ALT $>5\times$ ULN; AST $>5\times$ ULN; Total bilirubin $>3\times$ ULN; ALP $>5\times$ ULN. OR For patients with documented liver metastases AND Baseline AST/ALT is $>$ ULN to $\leq 5\times$ ULN and AST/ALT increases to $>10\times$ ULN or total bilirubin increases to $>3\times$ ULN.	• Permanently discontinue atezolizumab and LOAd703 and contact Medical Monitor. [f, j] • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Immune-mediated adverse events or atezolizumab-related toxicities not described above	
Grade 1	• Follow guidelines for atezolizumab in Appendix 6. • Continue LOAd703.
Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • LOAd703 may be continued at the investigator's discretion
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue LOAd703. [g]
LOAd703-related toxicities not described above	
Grade 1 or 2	• Initiate symptom-directed supportive care. • Continue atezolizumab. • Consider LOAd703 dose modification as clinically indicated; otherwise continue LOAd703 at the same dose.

Table 7 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+LOAd703 (cont.)

Grade 3	• Withhold LOAd703. Atezolizumab may be continued at the investigator's discretion. • If event resolves to Grade 1 or better within 8 weeks, resume LOAd703 with a one-level dose reduction. If not, permanently discontinue LOAd703. [g] • Dose re-escalation of LOAd703 is not permitted.
Grade 4	• Permanently discontinue LOAd703. [g] Withhold atezolizumab. • If event improves and Medical Monitor agrees that atezolizumab should be continued, resume atezolizumab. If not, permanently discontinue atezolizumab. [f]

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; GI = gastrointestinal; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; LFT = liver function test; MAS = macrophage activation syndrome; NCI = National Cancer Institute; NSAID = nonsteroidal anti-inflammatory drug; ULN = upper limit of normal;

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

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

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

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

[e] There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

[f] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *The* Medical Monitor *is available to advise as needed.*

Table 7 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+LOAd703 (cont.)

[g] Resumption of LOAd703 at a lower dose level may be considered in patients who are deriving benefit and have fully recovered from the toxicity. *The decision to* re-challenge *patients* with LOAd703 *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *The* Medical Monitor *is available to advise as needed.*

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

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

[j] Rechallenge with a lower dose level of LOAd703 may be considered if an alternative cause for impaired liver tests is discovered and/or the laboratory abnormalities resolve to normal/baseline within 7 days. If signs/symptoms recur with rechallenge, permanently discontinue LOAd703.

A14–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + LOAD703 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 in the protocol body for reporting instructions). Adverse events of special interest for the Atezo+LOAd703 arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7 in the protocol body)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, systemic injection-related reactions, CRS, influenza-like illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, and optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

A14–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+LOAD703 ARM

A14–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 months after the last dose of atezolizumab and LOAd703. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A14–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of LOAd703. 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 patient exposed to study treatment. When permitted by the site, the pregnant partner will 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 patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator 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 in the protocol body).

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 patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 in the protocol body).

A14–6. SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+LOAD703 ARM

Table 8: Schedule of Activities for Atezo + LOAd703 Arm

Assessment/Procedure	Screening Days –28 to –1	Treatment (21-Day Cycles) [a]							Stage 2 Screening [d] or Treatment Discon [e]	Follow-Up Every 3 Months (± 7 days)
		Cycle 1 [b]			Cycle 2			Cycles ≥ 3		
		Days			Days			Days		
		1	2 [jj]	8 (± 3 days)	1 (± 3 days)	2 [jj]	8 (± 3 days)	1 (± 3 days)		
Molecular profile of CRC (if available)	See Appendix 15	Whenever updated information becomes available								
Vital signs [f]		x [c]	x	x	x [c]	x	x	x	x	
Weight		x [g]			x [g]			x [g]	x	
Complete physical examination [h]									x	
Limited physical examination [i]		x [g]	x [g]	x [g]	x [g]	x [g]	x [g]	x [g]	x	
ECOG Performance Status		x [g]			x [g]			x [g]	x	
ECG [j]		As clinically indicated [g]							x [k]	
Hematology [l]		x [m, n]		x [m]	x [m]		x [m]	x [m]	x	
Chemistry [o]		x [m, n]		x [m]	x [m]		x [m]	x [m]	x	
Coagulation (INR and aPTT) [p]		x [m, n]			x [m]			x [m]	x [k]	
TSH, free T3 (or total T3), and free T4 [q]		x [m, n, q]							x	
Viral serology [r]									x [k, r]	
C-reactive protein									x [k]	
Plasma CEA [s]		x [m]						x [m, s]		

Table 8: Schedule of Activities for Atezo + LOAd703 Arm (cont.)

Assessment/Procedure	Screening Days –28 to –1	Treatment (21-Day Cycles) [a]							Stage 2 Screening [d] or Treatment Discon [e]	Follow-Up Every 3 Months (± 7 days)
		Cycle 1 [b]			Cycle 2			Cycles ≥ 3		
		Days			Days			Days		
		1	2 [jj]	8 (± 3 days)	1 (± 3 days)	2 [jj]	8 (± 3 days)	1 (± 3 days)		
LDH									x [k]	
Pregnancy test [t]		x [m, n]			x [m]			x [m]	x [u]	x [t]
Urinalysis [v]	See Appendix 15	*Perform as clinically indicated*							x [k, u]	
Serum autoantibody sample [w]		Perform if patients experience suspected immune-mediated adverse event							x [k]	
Blood sample for RBR (optional) [x]		x								
Biomarker samples		Refer to Table 9 below								
Virus shedding samples		Refer to Table 9 below								
Serum ADA sample		Refer to Table 9 below								
Serum PK sample		Refer to Table 9 below								
Serum anti-adenovirus antibody sample		Refer to Table 9 below								
Tumor biopsy		x [y]								
Tumor biopsy (optional)		x [z]								
Tumor response assessments		x [aa, bb, cc]								
Concomitant medications [dd]		x	x	x	x	x	x	x	x	
Adverse events [ee]		x	x	x	x	x	x	x	x [ee]	x [ee]

Table 8: Schedule of Activities for Atezo + LOAd703 Arm (cont.)

Assessment/Procedure	Screening Days –28 to –1	Treatment (21-Day Cycles) [a]							Stage 2 Screening [d] or Treatment Discon [e]	Follow-Up Every 3 Months (± 7 days)
		Cycle 1 [b]			Cycle 2			Cycles ≥ 3		
		Days			Days			Days		
		1	2 [jj]	8 (± 3 days)	1 (± 3 days)	2 [jj]	8 (± 3 days)	1 (± 3 days)		
Administer atezolizumab [ff, hh]		x			x			x		
Administer LOAd703 [gg, hh]		x			x			x		
Survival follow-up and anti-cancer treatment										x [ii]

ADA = anti-drug antibody; CEA = carcinoembryonic antigen; CRC = colorectal cancer; CT = computed tomography; d = day; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

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 *may* occur outside of the specified window.

[b] It is recommended that treatment be initiated no later than 7 days after randomization; however the first dose of study treatment should not occur within 7 days after a core biopsy or other surgical procedure.

[c] Vital signs will be recorded through 8 hours post-injection for the first two injections (Day 1 of Cycles 1 and 2) as outlined in Section A14–4.1.2.2, Table 3. Provisions should be made for overnight monitoring.

[d] Patients who experience loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 for details) or unacceptable toxicity may be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.2 provided Stage 2 is open for enrollment) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[e] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit.

Table 8: Schedule of Activities for Atezo + LOAd703 Arm (cont.)

Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will undergo follow-up assessments after completing the treatment discontinuation visit.

[f] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Refer to Section A14–4.1.2.2, Table 3 for details related to vital signs monitoring during study treatment administration.

[g] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[h] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. The skin examination should be extended according to medical need. *During visits when a patient will undergo a tumor assessment, the physical examination should include an evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.*

[j] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[k] Assessments to be performed only for patients undergoing Stage 2 screening.

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

[m] Laboratory tests must be performed within 96 hours prior to *dosing* during the treatment period.

[n] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[o] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (per standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.

[p] Monitoring of INR/aPTT should be performed more frequently if clinically indicated.

[q] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[r] At Stage 2, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[s] CEA will be assessed on Day 1 of Cycle 1 and every 2 cycles thereafter (i.e., Cycles 3, 5, 7, etc.) until disease progression.

Table 8: Schedule of Activities for Atezo + LOAd703 Arm (cont.)

[t] 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 and at 3 months and 6 months after treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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

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

[w] Autoantibody analysis includes anti-nuclear antibody, anti−double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[x] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. RBR sample should be collected prior to study treatment.

[y] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner.

Patients enrolled in the mandatory serial-biopsy arm (see Section 3.1.1.2) will undergo tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible by the investigator). See Section 4.5.7 for tissue sample requirements.

[z] Patients who consent to optional biopsies will undergo tumor biopsy sample collection immediately before the third LOAd703 administration on Day 1 of Cycle 3, if deemed clinically feasible and may undergo additional on-treatment biopsies at any other time during Stage 1 or Stage 2 at the investigator's discretion.

[aa] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than loss of clinical benefit, even if they start new non−protocol-specified anti-cancer therapy.

[bb] All measurable and/or evaluable lesions identified at baseline should be reassessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head CT 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).

[cc] For patients who undergo screening for Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

Table 8: Schedule of Activities for Atezo + LOAd703 Arm (cont.)

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

[ee] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 180 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6 in the protocol body). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent.

Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[ff] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Atezolizumab will be administered preferably prior to LOAd703 injection. The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[gg] LOAd703 will be administered by intratumoral injection at a dose level of 1×10^{11} VP or 5×10^{11} VP on Day 1 of each 21-day cycle (Q3W) during Cycles 1–6. LOAd703 will be administered preferably after atezolizumab. Premedication or postdose prophylaxis with paracetamol (1 g, oral) or nonsteroidal anti-inflammatory drug (e.g., ibuprofen, 400 mg, oral) is recommended. Refer to Section A14–4.1.2.2 and Table 3 for details.

[hh] Treatment will continue until unacceptable toxicity or loss of clinical benefit defined as (1) confirmed disease progression or (2) lack of continued benefit as determined by the investigator (see Section 3.1.1 for details). In the absence of confirmed disease progression, atezolizumab treatment can continue after LOAd703 treatment has ended provided patient is tolerating atezolizumab and receiving clinical benefit in the opinion of the investigator in consultation with the Medical Monitor.

[ii] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from 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 patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table 8: Schedule of Activities for Atezo + LOAd703 Arm (cont.)

[jj] If LOAd703 is administered on Day 2, assessments will be performed on Day 3.

Table 9 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+LOAd703 Arm: Preliminary and Expansion Phases

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • LOAd703 Shedding [a] • LOAd703 ADA (serum) • Biomarkers (plasma, serum, PBMC)
	30 (± 10) minutes after atezolizumab infusion [b]	• Atezolizumab PK (serum)
Day 2 of Cycle 1	24 hours (± 4 hours) after LOAd703 injection on Day 1 [c]	• LOAd703 Shedding [a]
Day 8 of Cycle 1	At visit	• LOAd703 Shedding [a] • LOAd703 ADA (serum) • Biomarkers (plasma and serum)
Day 1 of Cycle 2	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • LOAd703 Shedding [a] • LOAd703 ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 2 of Cycle 2	24 hours (± 4 hours) after LOAd703 injection on Day 1 [d]	• LOAd703 Shedding [a]
Day 8 of Cycle 2	At visit	• LOAd703 Shedding [a] • LOAd703 ADA (serum)
Day 1 of Cycle 3	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • LOAd703 Shedding [a] • LOAd703 ADA (serum)
Day 1 of Cycle 4	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • LOAd703 Shedding [a] • LOAd703 ADA (serum) • Biomarkers (plasma and serum)
Day 1 of Cycle 6	Prior to any study treatment	• LOAd703 Shedding [a] • LOAd703 ADA (serum)
≤ 30 days after last dose of LOAd703 [e]	At visit	• LOAd703 Shedding [a] • LOAd703 ADA (serum)
Day 1 of Cycle 8	Prior to any study treatment	• Biomarkers (plasma and serum) • Atezolizumab PK (serum) • Atezolizumab ADA (serum)
3 months± 14 days after last dose of LOAd703 [e, f]	At visit	• LOAd703 Shedding [a] • LOAd703 ADA (serum)
Day 1 of Cycle 12	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

Appendix 14: Study Details Specific to Atezo+LOAd703 Arm

Visit	Time	Sample Type
6 months± 14 days after last dose of LOAd703 [e, f]	At visit	• LOAd703 Shedding [a] • LOAd703 ADA (serum)
Day 1 of Cycle 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last study dose)	At visit	• Biomarkers (plasma and serum)

Atezo = atezolizumab; ADA = anti-drug antibody; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

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

LOAd703 Shedding and ADA sample collections may align with atezolizumab infusion visits as appropriate per protocol specifications.

Viral shedding will be assessed by PCR.

[a] Shedding collection for LOAd703 includes: blood (serum), urine sample, oral swab, and a rectal swab.

[b] If Atezolizumab is administered on Day 2 of Cycle 1, collection visit will be on Day 2 of Cycle 1.

[c] If LOAd703 is administered on Day 2 of Cycle 1, collection visit will be on Day 3 of Cycle 1.

[d] If LOAd703 is administered on Day 2 of Cycle 2, collection visit will be on Day 3 of Cycle 2.

[e] LOAd703 shedding and ADA sample collections will be obtained at ≤ 30 days after the last dose of LOAd703, and at 3 and 6 months± 14 days after the last dose of LOAd703, regardless of whether patients will have received 6 or 12 doses.

[f] LOAd703 shedding and ADA sample collections at 3 months and 6 months for patients who continue atezolizumab monotherapy for < 6 months after discontinuation of LOAd703 treatment are optional.

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Appendix 15
Schedules of Activities for Screening

Table 1 Schedule of Activities for Stage 1 Screening

Assessment/Procedure	Stage 1 Screening [a] (Day –28 to –1)
Informed consent	x [b]
Demographic data	x
Medical history and baseline conditions	x
Molecular profile of colorectal cancer (if available)	x
MSI and *BRAF* status	x
Vital signs [c]	x
Weight	x
Height	x
Complete physical examination [d]	x
ECOG Performance Status	x
ECG (12-Lead) [e]	x
Hematology [f]	x [g]
Chemistry [h]	x [g]
Coagulation (INR, aPTT)	x [g]
TSH, free T3 (or total T3), free T4 [i]	x [g]
Viral serology [j]	x [g]
Pregnancy test [k]	x [g]
Urinalysis [l, m]	x [g]
C-reactive protein	x [g]
LDH	x [g]
Serum autoantibody sample [n]	x [g]
Tumor biopsy [o]	x [g]
Baseline tumor assessments [p]	x
Concomitant medications [q]	x
Adverse events [r]	x
TP53 mutation status	x [s]

ECOG = Eastern Cooperative Oncology Group; ECHO=echocardiogram; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IV=intravenous; MSI = microsatellite instability; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Table 1 Schedule of Activities for Stage 1 Screening (cont.)

[a] Patients who fail their first screening for study eligibility may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the consent form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 (within 14 days prior to Day 1 for laboratory tests) may be used; such tests do not need to be repeated for screening or re-screening.

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

[c] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[d] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[e] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

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

[g] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment (Cycle 1, Day 1). Exception: Serum autoantibody samples must be collected within this window, but results will not be available before initiation of study treatment.

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (per standard of care for the region), CPK, sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.

[i] Total T3 may be performed for sites where free T3 is not performed.

[j] At screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[k] All women of childbearing potential will have a serum pregnancy test at screening.

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

[m] Patients with $\geq 2+$ protein on dipstick urinalysis at screening must undergo a 24-hour urine collection for protein, but only if a regorafenib-containing arm is open for enrollment.

[n] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[o] Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided that the tissue was obtained from a biopsy performed within 6 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy. Refer to Section 4.5.7 for tissue sample requirements.

Table 1 Schedule of Activities for Stage 1 Screening (cont.)

[p] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, pelvis, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast, if feasible) of the abdomen, pelvis, and head should be performed. A CT scan with contrast or MRI scan with contrast of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if contrast 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. Refer to Section 4.5.6 for further details on tumor assessments.

[q] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 7 days prior to initiation of study treatment.

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

[s] TP53 mutation status testing will only be required during screening for patients who did not undergo prescreen testing.