Official Title: A Phase II, Single-Arm, Open-Label Study Evaluating the Safety and Pharmacokinetics of the Intravenous Fixed-Dose Combination (IV FDC) of Tiragolumab and Atezolizumab in Participants With Locally Advanced, Recurrent or Metastatic Solid Tumors

NCT Number: NCT05661578

Document Date: Protocol Amendment Version 4: 14-Dec-2023

PROTOCOL

PROTOCOL TITLE:	**A PHASE II, SINGLE-ARM, OPEN-LABEL STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS OF THE INTRAVENOUS FIXED-DOSE COMBINATION (IV FDC) OF TIRAGOLUMAB AND ATEZOLIZUMAB IN PARTICIPANTS WITH LOCALLY ADVANCED, RECURRENT OR METASTATIC SOLID TUMORS**
PROTOCOL NUMBER:	GO44096
STUDY NAME	SKYSCRAPER-11
VERSION NUMBER:	4
TEST COMPOUND:	Tiragolumab and atezolizumab IV FDC (RO7538483)
STUDY PHASE:	Phase II
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 157491 EudraCT Number: 2022-001157-23 EU CT Number: 2023-508489-14-00 PS ID: CIV-23-02-042474 NCT Number: NCT05661578
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Global Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
4	See electronic date stamp on final page of this document.	South Korea	4	To be determined
3	3 March 2023	South Korea	3	27 April 2023
2	14 December 2022	South Korea	2	22 December 2022
1	1 April 2022	South Korea	1	14 November 2022

PROTOCOL AMENDMENT, VERSION 4
RATIONALE

Protocol GO44096 has been amended to align with an update to the Atezolizumab Investigator's Brochure Version 20 and adverse event management guidelines, and to clarify inclusion criteria and procedures during the study. An inclusion criterion has also been modified to include patients with gastric cancer and TAP scores of at least 1% in the study.

Changes to the protocol, along with a rationale for each change, are summarized below:

- The requirement for temperatures to be taken tympanically has been removed to decrease burden on the sites (Sections 1.3 [Table 1] and 8.2.2).
- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma (Section 2.2.3).
- A requirement for the Internal Monitoring Committee (IMC) to review cumulative safety data after the last participant is enrolled has been removed to simplify the IMC process and leverage the ad hoc IMC reviews, which may take place if there are any safety concerns (Section 4.1.2).
- The "end of study" definition has been simplified to be the last visit of the last participant in the study or the date of the last data point for safety follow-up (Section 4.4).
- The cancer-specific inclusion criteria have been clarified as follows:
  - [redacted]
  - [redacted]
  - To require that participants must have histologic documentation of locally advanced, recurrent, or metastatic malignancy which is ineligible for definitive local therapy (Section 5.1.1)
  - [redacted]
- The additional inclusion criteria for indication-specific cancer have been updated:
  - [redacted]

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

- Cancer-specific exclusion criteria have been updated to include stereotactic radiotherapy, whole-brain radiotherapy, or neurosurgical resection for CNS metastases per the exclusion criteria for CNS metastases (Section 5.2.1).
- Safety reporting instructions related to in vitro diagnostics have been updated to align with study processes (Sections 8.3.1, 8.3.2, A3–5, A3–6, A3–8, A3–8.1, A3–8.2, and A3–8.3).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 8.3.4).
- The definitions and descriptions of pharmacokinetic-evaluable and anti-drug antibody-evaluable analysis sets have been updated to increase clarity (Section 9.3)
- [redacted]
- [redacted]
- [redacted]
- An overview of the administrative structure of the study was added to Appendix 1 (new Section A1–5).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 20 (Appendix 6).

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE II, SINGLE-ARM, OPEN-LABEL STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS OF THE INTRAVENOUS FIXED-DOSE COMBINATION (IV FDC) OF TIRAGOLUMAB AND ATEZOLIZUMAB IN PARTICIPANTS WITH LOCALLY ADVANCED, RECURRENT OR METASTATIC SOLID TUMORS**
PROTOCOL NUMBER:	GO44096
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TEST COMPOUND:	Tiragolumab and atezolizumab IV FDC (RO7538483)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE II, SINGLE-ARM, OPEN-LABEL STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS OF THE INTRAVENOUS FIXED-DOSE COMBINATION (IV FDC) OF TIRAGOLUMAB AND ATEZOLIZUMAB IN PARTICIPANTS WITH LOCALLY ADVANCED, RECURRENT OR METASTATIC SOLID TUMORS**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 157491 EudraCT Number: 2022-001157-23 EU CT Number: *2023-508489-14-00* *PS* ID: CIV-23-02-042474 NCT Number: NCT05661578

STUDY RATIONALE

The purpose of this study is to assess the safety, pharmacokinetics, and immunogenicity of tiragolumab and atezolizumab IV fixed-dose combination (FDC) in participants with locally advanced, recurrent, or metastatic solid tumors.

The treatment options of sequential IV infusions of tiragolumab and atezolizumab (with separate IV bags for dilution and observation after each drug administration) every 3 or 4 weeks (Q3W or Q4W) are currently being evaluated in several Phase III studies. However, there continues to be a need to streamline and simplify the administration of the combination therapy for both patients and healthcare providers. The IV FDC formulation affords the ability to prepare and administer both drugs from one vial and one IV bag, respectively, decreasing the number of infusions and administration time. [redacted].

OBJECTIVES AND ENDPOINTS

Primary Objective	Corresponding Endpoint
• To evaluate the safety and tolerability of tiragolumab and atezolizumab IV FDC	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 – The severity of CRS will also be determined according to the ASTCT CRS Consensus Grading Scale.
Secondary Objectives	**Corresponding Endpoints**
• To characterize the pharmacokinetics of tiragolumab and atezolizumab following administration of IV FDC	• Serum concentrations of tiragolumab and atezolizumab at specified timepoints for the following parameters: – Area under the concentration–time curve at Cycle 1 – C_{max} at Cycle 1 – Additional PK parameters such as C_{min} at Cycle 1 and CL will be reported as appropriate.

Secondary Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate the immune response to tiragolumab and atezolizumab following IV FDC administration by measuring anti-tiragolumab and anti-atezolizumab antibodies.	• Prevalence of ADAs to tiragolumab at baseline and the incidence of treatment emergent ADAs to tiragolumab during the study • Prevalence of ADAs to atezolizumab at baseline and the incidence of treatment emergent ADAs to atezolizumab during the study

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CL = clearance; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CRS = cytokine release syndrome; FDC = fixed dose combination; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PK = pharmacokinetic.

OVERALL DESIGN

This Phase II, single-arm, open-label, multicenter study is designed to evaluate the safety, pharmacokinetics, and immunogenicity of tiragolumab and atezolizumab IV FDC administered in participants with histologically-confirmed PD-L1–selected solid tumors whose disease is locally advanced, recurrent, or metastatic and for whom an investigational agent in combination with an anti–PD-L1 antibody is considered an acceptable treatment option. Participants must not have received prior checkpoint inhibitor treatment for their cancer.

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

Phase:	II	Population Type:	Adult patients
Control Method:	Open-label	Population Diagnosis or Condition:	Histologically confirmed PD-L1–selected solid tumors
Interventional Model:	Single group	Population Age:	≥ 18 years
Test Compound:	Tiragolumab and atezolizumab IV FDC (RO7538483)	Site Distribution:	Multicenter
Active Comparator:	Not applicable	Study Intervention Assignment Method:	Non-randomized
Number of Arms:	1	Number of Participants to Be Enrolled:	40–60

STUDY TREATMENT

The investigational medicinal product for this study is tiragolumab 600 mg and atezolizumab 1200 mg IV FDC. The IMP will be administered intravenously on Day 1 of each 21-day cycle (every 3 weeks).

Modification of the tiragolumab and atezolizumab IV FDC dose is not permitted.

DURATION OF PARTICIPATION

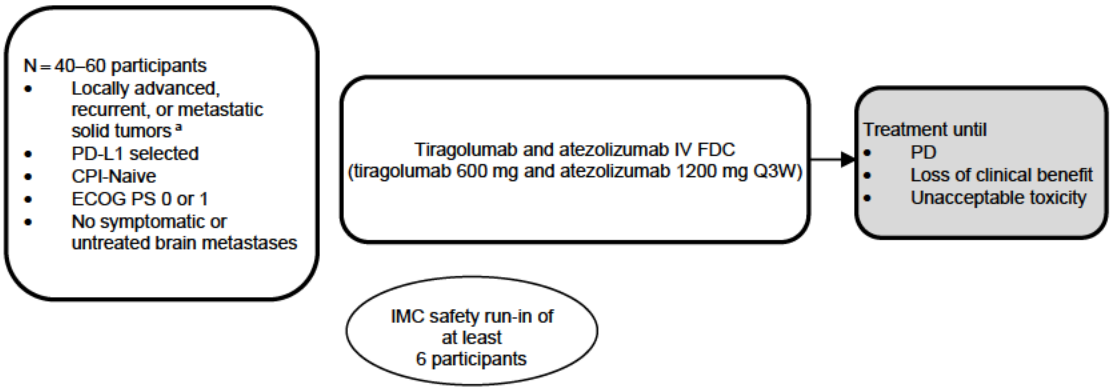
The total duration of study participation for each individual is expected to range from 1 day to more than 4 months.

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Internal Monitoring Committee

1.2 STUDY SCHEMA

Figure 1 Study Schema



CPI = checkpoint inhibitor; ECOG PS = Eastern Cooperative Oncology Group Performance Status; *FDC = fixed dose combination;* IMC = Internal Monitoring Committee; PD = progressive disease; Q3W = every 3 weeks.

[a] Enrollment will focus on participants who have esophageal adenocarcinoma, esophageal squamous cell carcinoma, *gastric cancer,* gastroesophageal junction cancer, hepatocellular carcinoma, melanoma, non–small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, and urothelial bladder cancer. Additional tumor types may be added as the PD-L1 cutoffs become available.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities

	Screening [a]	Treatment	Treatment Discontinuation [b]	Post-treatment Follow-Up
Day(s) (Window)	Days –28 to –1	Day 1 of Each 21-Day Cycle (±3 days)	≤30 Days after Final Dose	Every 3 Months (±1 month)
Informed consent • Optional Prescreening ICF for PD-L1 testing • Main ICF for study participation	x [c]			
[redacted]	x			
Demographics	x			
Medical history, including cancer history, and baseline conditions	x			
Vital signs [e]	x	x	x	
Weight	x		x	
Height	x			
Complete physical examination [f]	x			
Limited physical examination [g]		x	x	
ECOG Performance Status [h]	x	x [h]	x [h]	
Single 12-lead ECG [i]	x		x	
Hematology [j]	x [k]	x [l]	x	
Chemistry panel [m]	x [k]	x [l]	x	

Table 1 Schedule of Activities (cont.)

Day(s) (Window)	Screening [a]	Treatment	Treatment Discontinuation [b]	Post-treatment Follow-Up
	Days –28 to –1	Day 1 of Each 21-Day Cycle (±3 days)	≤30 Days after Final Dose	Every 3 Months (±1 month)
Pregnancy test [n]	x [k]	x [l]	x	
Urinalysis [o]	x			
TSH, free T3, and T4	x	x [p]	x	
[redacted] [q]	x			
Coagulation (aPTT and INR)	x		x	
Serum ferritin and CRP	x			
Auto-antibody tests		x [r]		
Tiragolumab and atezolizumab IV FDC administration		x		
Tumor assessment	x [s]	x [t]		x [t]
Brain scan	x [u]			
Serum PK sample		See Table 2.		
Serum ADA sample		See Table 2.		
Serum and plasma sample for biomarkers		See Table 2.		

Table 1 Schedule of Activities (cont.)

Day(s) (Window)	Screening [a]	Treatment	Treatment Discontinuation [b]	Post-treatment Follow-Up
	Days –28 to –1	Day 1 of Each 21-Day Cycle (±3 days)	≤30 Days after Final Dose	Every 3 Months (±1 month)
[redacted]		At the time of disease progression if clinically feasible [v]		
Concomitant medications [w]	x [w]	x [w]	x [w]	
Adverse events [x]	x [x]	x [x]	x [x]	x [x]
Survival and anti-cancer therapy follow-up [y]				x

ADA=anti-drug antibody; CT=computed tomography; [redacted] ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; FDC=fixed dose combination; FFPE=formalin-fixed, paraffin-embedded; [redacted]

ICF=Informed Consent Form; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; NA=not applicable; PET=positron emission tomography; PK=pharmacokinetic; RBR=Research Biosample Repository; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; RTD=Roche Tissue Diagnostics; TIGIT=T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains; [redacted]

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. For non-PK/ADA samples, assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

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

[a] Results of standard-of-care assessments performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such assessments do not need to be repeated for screening. Individuals who do not meet the criteria for participation in this study may qualify for one re-screening opportunities (for a total of two screenings per individual) at the investigator's discretion, as described in Section 5.4.

[b] The treatment discontinuation visit is to be performed within 30 days after the last study treatment administration or within 30 days after the date the decision was made to permanently discontinue study treatment.

[c] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment. Participants have the option to sign the prescreening ICF to consent to PD-L1 testing during prescreening, prior to signing the main ICF for all screening procedures and study participation.

Table 1 Schedule of Activities (cont.)

[d] If archival tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a participant's archival tissue test results do not meet eligibility criteria. See Section 8.7 for tissue sample requirements. All tissue submission must be accompanied with pathology report.

[e] Vital signs include temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure. See Section 8.2.2 for detailed information on vital signs measurements.

[f] A complete physical examination includes, at a minimum, assessments of the participant's head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[g] Symptom-directed physical examinations; see Section 8.2.1 for details.

[h] ECOG Performance Status (see Appendix 10) may be assessed ≤4 days before Day 1 of each cycle. If screening assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated for Day 1 of Cycle 1.

[i] Single 12-lead ECG recordings will be obtained at screening, at the treatment discontinuation visit, and when clinically indicated. Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. See Section 8.2.3 for details.

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

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

[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 (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH.

[n] All female participants of childbearing potential will have a serum pregnancy test performed at screening within 14 days prior to initiation of study treatment. Urine pregnancy tests will be performed on Day 1 of each 21-day cycle during the treatment period and at the treatment discontinuation visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[o] Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, and blood).

[p] TSH, free T3 (or total T3 at sites where free T3 is not performed), and free T4 will be collected at screening, on Day 1 of Cycle 1, and every fourth cycle thereafter (e.g., Cycles 1, 5, 9, 13, and so forth).

[q] 

Table 1 Schedule of Activities (cont.)

[r] Serum samples will be obtained for auto-antibody testing prior to first dose on Day 1 of Cycle 1 and will include but will not necessarily be limited to anti-nuclear antibody anti–double-stranded DNA, anti-neutrophil cytoplasmic antibodies, and thyroid peroxidase antibody, to be performed based on clinical events during the study, either in individual participants or across the study population. If inflammatory arthritis develops, cyclic citrullinated peptide and rheumatoid factor antibody titers will also be evaluated. Additional serum collection for auto-antibody testing should be performed as clinically indicated.

[s] Tumor assessments performed as standard-of-care prior to obtaining consent and within 28 days prior to Day 1 of Cycle 1 may be used rather than repeating tests. All known sites of disease, including measurable and/or non-measurable disease, must be documented at screening. Screening tumor assessments must include CT scans with contrast or MRI (if CT contrast is contraindicated) and per institutional standard operating procedures of the chest, abdomen, and pelvis. If a CT scan for tumor assessment is performed in a PET/CT scanner, the CT acquisition must be consistent with the standards for a full contrast diagnostic CT scan. Further investigations, such as bone scans and CT scans of the neck, should also be performed if clinically indicated. See Section 8.1.1.1 for further details.

[t] Participants will undergo tumor assessments every 6 weeks (±7 days) for the first 48 weeks following treatment initiation (Day 1 of Cycle 1) and every 9 weeks (±7 days) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for participants who continue treatment after radiographic disease progression), as determined by the investigator, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Participants who are treated beyond disease progression per investigator-assessed RECIST v1.1 will undergo tumor assessments at the frequency described above after initial documentation of progression, or more frequently, if clinically indicated, regardless of time in study until treatment is discontinued (see Section 4.1.1 for details). At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected. See Section 8.1.1.1 for further details on radiographic assessments. Participants who discontinue study treatment (for any reason, including but not limited to clinical decline or toxicity) in the absence of radiographic disease progression per investigator-assessed RECIST v1.1 will continue to undergo tumor response assessments at the same frequency until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments should continue regardless of whether a participant starts a new anti-cancer therapy.

[u] An MRI or CT scan (with contrast) of the brain at screening to evaluate CNS metastasis. A brain MRI scan is the preferred imaging method for evaluating CNS metastases as it is more sensitive than CT for identifying brain metastases; however, CT of the brain is acceptable if MRI is contraindicated. If a CT scan with contrast is performed and the presence of brain metastases is considered equivocal, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases.

[v] Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner.

[w] Includes any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by a participant in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit.

[x] [redacted]

Table 1 Schedule of Activities (cont.)

[redacted]

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

Table 2 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

[redacted]

[a] [redacted]

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to assess the safety, pharmacokinetics, and immunogenicity of tiragolumab and atezolizumab IV fixed-dose combination (FDC) in participants with locally advanced, recurrent, or metastatic solid tumors.

The combination of tiragolumab and atezolizumab is being studied in a wide range of solid tumors. The treatment options of sequential IV infusions of tiragolumab and atezolizumab (with separate IV bags for dilution and observation after each drug administration) every 3 or 4 weeks (Q3W or Q4W) are currently being evaluated in several Phase III studies. However, there continues to be a need to streamline and simplify the administration of the combination therapy for both patients and healthcare providers. The IV FDC formulation affords the ability to prepare and administer both drugs from one vial and one IV bag, respectively, decreasing the number of infusions and administration time. [redacted]

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

2.2 BACKGROUND

2.2.1 Background on Cancer

Cancer is a leading cause of death worldwide, with approximately 9,894,133 deaths globally in 2020. In North America, the number of new cases was estimated to be 2,556,860 (1,372,000 cases in men and 1,184,860 new cases in women), with 699,274 cancer deaths. Similar data are observed for all of Europe (central and eastern, western, southern, northern) in 2020; there were 4.04 million new cases (2.13 million in men; 1.91 million in women) and 1.94 million cancer deaths (Global Cancer Observatory 2020). For most advanced malignancies, the impact of current therapy on improving the quality of life, slowing progression of disease, prolonging survival, or curing patients, is inadequate.

Current available treatment options for patients with locally advanced, recurrent, or metastatic solid tumor disease include surgery, chemotherapy, hormone therapy, targeted therapy, immunotherapy, and radiation therapy (National Cancer Institute 2021). Increasingly, therapies are being administered as combination treatments to cancer patients. Administration of these therapies frequently involves multiple infusions, followed by separate observation times, resulting in long clinic days

for the patient. [redacted]

2.2.2 Background on Tiragolumab

Tiragolumab is a fully human IgG1/κ monoclonal antibody (mAb) derived in open monoclonal technology rats that binds to T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains (TIGIT) and prevents its interaction with poliovirus receptor. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (456 amino acid residues each) and two light chains (220 amino acid residues each). [redacted]

Tiragolumab is designed to promote tumor-specific immune responses and to complement the activity of PD-1/PD-L1 pathway inhibitors, such as atezolizumab. The combined inhibition of the TIGIT and PD-1/PD-L1 pathways by tiragolumab and atezolizumab, respectively, has demonstrated promising clinical activity in the Phase I Study GO30103 and the Phase II Study CITYSCAPE (GO40290). Study GO30103 is a first-in-human, combined Phase Ia/Ib, open-label, dose-escalation, multicenter study. In this study, the administration of tiragolumab and atezolizumab is being studied in sequential IV infusion and IV co-infusion cohorts. The combination of tiragolumab and atezolizumab is being evaluated across a wide range of metastatic and locally advanced diseases, with encouraging data observed.

In the Phase Ib portion of Study GO30103, responses occurred in *participant*s with metastatic cancers with varying degrees of PD-L1 expression following treatment with an anti-TIGIT antibody, tiragolumab, in combination with an anti–PD-L1 antibody, atezolizumab. Data from the randomized Phase II Study CITYSCAPE indicate that combination therapy with tiragolumab plus atezolizumab may confer increased efficacy benefit in patients with untreated, PD-L1–positive, metastatic non–small cell lung cancer (NSCLC) relative to atezolizumab therapy alone.

Tiragolumab in combination with atezolizumab was well-tolerated in both the Phase I GO30103 and Phase II CITYSCAPE studies. Adverse events with potentially immune-mediated causes have been observed with a higher frequency for tiragolumab in combination with atezolizumab in the CITYSCAPE study. However, the imbalance was mostly attributed to rash and infusion-related reactions (IRRs; both Grade 1 to 2). The frequency of reported Grade 3 to 4 immune-mediated adverse events was similar between the tiragolumab and atezolizumab combined treatment arm compared with atezolizumab treatment alone.

To date, immune-mediated adverse events have been manageable with standard medical practice supplemented with corticosteroids, immunosuppressive agents, and/or hormone replacement therapy.

Detailed information on tiragolumab is provided in the Tiragolumab and Atezolizumab IV FDC Investigator's Brochure.

2.2.3 Background on Atezolizumab

Atezolizumab is a humanized IgG1 mAb 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.

[redacted]

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

Detailed information on atezolizumab is provided in the Tiragolumab and Atezolizumab IV FDC Investigator's Brochure.

2.3 BENEFIT–RISK ASSESSMENT

The purpose of this study is to assess the safety, pharmacokinetics, and immunogenicity of tiragolumab and atezolizumab IV FDC, to address the need for more convenient administration options for patients with locally advanced, recurrent, or metastatic solid tumors. Tiragolumab in combination with atezolizumab was tolerated in the Phase I Study GO30103 and the Phase II Study CITYSCAPE (Section 2.2.2).

[redacted]

The study will be monitored by an Internal Monitoring Committee (IMC), [redacted]

[redacted].

See Appendix 5 and Appendix 6 for information on anticipated risks for tiragolumab and atezolizumab IV FDC and risk mitigation measures, including guidelines for managing adverse events associated with tiragolumab and atezolizumab IV FDC.

More detailed information about the known benefits and risks of tiragolumab and atezolizumab may be found in the Tiragolumab and Atezolizumab IV FDC Investigator's Brochure.

2.3.1 COVID-19 Benefit–Risk Assessment

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, participants 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 the immune checkpoint blockade may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses (Schorer et al. 2020; 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 cancer immunotherapy.

Severe SARS-CoV-2 infection appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL 2, and 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 participant develops acute SARS-CoV-2 infection while receiving tiragolumab and atezolizumab IV FDC. At this time, there is insufficient evidence for causal association between tiragolumab and atezolizumab IV FDC 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 tiragolumab and atezolizumab IV FDC and clinical and radiologic features for SARS-CoV-2–related interstitial pneumonia (see Appendix 5 for further risks associated with combination use of tiragolumab and atezolizumab IV FDC). Thus, investigators should use their clinical judgment when

evaluating and managing participants with pulmonary symptoms (see Appendix 6 for management guidelines).

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

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

In alignment with clinical practice procedures, factors to consider when making the individualized decision for participants receiving tiragolumab and atezolizumab IV FDC treatment to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the participant 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-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 6.8).

3. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, pharmacokinetics, and immunogenicity of tiragolumab and atezolizumab IV FDC (administered Q3W) in participants with locally advanced, recurrent, or metastatic solid tumors. Specific objectives and corresponding endpoints for the study are outlined in Table 3.

Table 3 Objectives and Endpoints

Primary Objective	Corresponding Endpoint
• To evaluate the safety and tolerability of tiragolumab and atezolizumab IV FDC	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0. – The severity of CRS will also be determined according to the ASTCT CRS Consensus Grading Scale.
Secondary Objectives	**Corresponding Endpoints**
• To characterize the pharmacokinetics of tiragolumab and atezolizumab following administration of IV FDC	• Serum concentrations of tiragolumab and atezolizumab at specified timepoints for the following parameters: – Area under the concentration–time curve at Cycle 1 – C_{max} at Cycle 1 – Additional PK parameters such as C_{min} at Cycle 1 and CL will be reported as appropriate.
• To evaluate the immune response to tiragolumab and atezolizumab following IV FDC administration by measuring anti-tiragolumab and anti-atezolizumab antibodies	• Prevalence of ADAs to tiragolumab at baseline and the incidence of treatment emergent ADAs to tiragolumab during the study • Prevalence of ADAs to atezolizumab at baseline and the incidence of treatment emergent ADAs to atezolizumab during the study
Exploratory Objectives	**Corresponding Endpoints**
• [redacted]	• [redacted]

Table 3 Objectives and Endpoints (cont.)

Exploratory Objectives (cont.)	Corresponding Endpoints (cont.)
• [redacted]	• [redacted] – [redacted] – [redacted] – [redacted] – [redacted]
• [redacted]	• [redacted] • [redacted]
• [redacted]	• [redacted] • [redacted] • [redacted]

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CL = clearance; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CR = complete response; CRS = cytokine release syndrome; DOR = duration of response; FDC = fixed dose combination; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PD = pharmacodynamic; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; [redacted]; V_{ss} = volume of distribution at steady state.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase II, single-arm, open-label, multicenter study designed to evaluate the safety, pharmacokinetics, and immunogenicity of tiragolumab and atezolizumab IV FDC administered in participants with locally advanced, recurrent, or metastatic solid tumors. Participants must have histologically-confirmed PD-L1–selected solid tumors (see Table 4) whose disease is locally advanced, recurrent, or metastatic and for whom an investigational agent in combination with an anti–PD-L1 antibody is considered an acceptable treatment option. Participants must not have received prior checkpoint inhibitor treatment for their cancer (CPI-Naive).

The study will enroll 40–60 participants [redacted] at approximately 50 sites globally. Participants must provide written informed consent prior to entering screening for the study. Participants must meet all eligibility criteria (see Section 5.1 and Section 5.2) for participation in the study and may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion (see Section 5.4). Participants are not required to re-sign the consent form if they are re-screened within 60 days after previously signing the consent form. For participants who are rescreened, all eligibility criteria must be re-evaluated and screening assessments should be repeated as applicable to meet the eligibility criteria outlined in Section 5. The investigator will record reasons for screen failure in the screening log (see Section 8).

[redacted]

Participants will receive tiragolumab 600 mg and atezolizumab 1200 mg IV FDC, administered intravenously on Day 1 of each 21-day cycle. Treatment may be continued until radiographic disease progression per investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or loss of clinical benefit, as assessed by the investigator (see Section 4.1.1), for participants that continue treatment after radiographic disease progression, or unacceptable toxicity.

Participants will undergo tumor assessments at screening and during the treatment period as indicated in Section 8.1.1 and Section 1.3.

During the study, serum samples will be collected to monitor tiragolumab and atezolizumab pharmacokinetics and to detect the presence of antibodies to tiragolumab and atezolizumab. Participant samples, which include tumor tissue, plasma, and serum, will also be collected for exploratory biomarker assessments (see Section 8.7).

The IMC will review all cumulative safety data at regular intervals during the study, starting with the safety run-in review (see Section 4.1.2 for further details). Safety assessments will include the incidence, nature, and severity of adverse events, and other protocol-specified tests such as laboratory abnormalities, that are deemed critical to the safety evaluation of the study. All participants will be monitored for adverse events during the adverse event reporting period (see Section 8.3.1 and Appendix 3).

After study treatment discontinuation, survival follow-up information and new anti-cancer therapy will be collected by means of telephone calls, participant medical records, and/or clinic visits approximately every 3 months or more frequently until death (unless the participant withdraws consent or the Sponsor terminates the study) (see Section 1.3).

A study schema is provided in Section 1.2 (see Figure 1). A schedule of activities and a sample collection schedule are provided in Section 1.3 (see Table 1 and Table 2).

4.1.1 Treatment after Disease Progression

During the study, participants who meet criteria for disease progression per RECIST v1.1 (see Appendix 9) and show evidence of clinical benefit may continue study treatment, at the investigator's discretion, provided that the participant meets all of the following criteria:

- Evidence of clinical benefit, as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values (e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease
- No 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
- Participants must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial radiographic progression per RECIST v.1.1.

For participants who receive study treatment beyond radiographic disease progression (as defined by growth of existing lesions, new lesions, or recurrence of previously resolved lesions), tumor assessments and new lesions will continue to be assessed by the investigator according to RECIST v1.1.

4.1.2 Internal Monitoring Committee

An IMC will evaluate cumulative safety data at regular intervals during the study, beginning with the initial safety run-in review without temporary suspension of enrollment. The safety run-in review will consist of data from a minimum of the first 6 participants who have received at least one dose of study treatment and who have completed safety follow-up assessments for at least 21 days in the study. After the safety run-in review, the IMC meetings will be conducted at the timepoints when the recruitment has reached approximately 20 participants *and then approximately* 40 participants. Study team members will be excluded from the IMC membership. The IMC will follow a charter that outlines the IMC's roles and responsibilities.

The IMC may make recommendations regarding study conduct, including but not limited to the following: continuing the study as per the protocol, performing additional safety analyses, amending the study protocol, holding participant enrollment pending further safety evaluations, enrolling additional participants at a specific dose level and/or schedule to obtain additional safety data, holding/discontinuing study treatment, or terminating the study.

The IMC Chair may request additional safety reports and may call for additional meetings of the IMC to review ongoing safety data for a benefit–risk balance assessment.

The IMC may share preliminary results from these safety analyses with appropriate Roche employees and with the investigators, as the IMC Chair deems necessary. Further details on IMC membership, scope, frequency, and process will be outlined in a separate IMC charter.

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

The study will enroll 40-60 participants [redacted] with histologically-confirmed PD-L1–selected solid tumors (see Table 4) whose disease is locally advanced, recurrent, or metastatic and for whom a clinical trial of an investigational agent in combination with an anti–PD-L1 antibody is considered an acceptable treatment option.

[redacted]

Enrollment will focus on participants who have esophageal adenocarcinoma (EAC), esophageal squamous cell carcinoma (ESCC), *gastric cancer (GC),* gastroesophageal junction cancer (GEJ), HCC, melanoma, NSCLC, renal cell cancer (RCC), squamous cell carcinoma of the head and neck (SCCHN), and urothelial bladder cancer (UBC) at prespecified and analytically validated PD-L1 cutoffs as described in Table 4. The [redacted] at Roche Tissue Diagnostics central testing laboratory. Additional tumor types may be added as the PD-L1 cutoffs become available.

[redacted]

4.2.3 Rationale for Primary Endpoint Selection

Tiragolumab and atezolizumab IV FDC is a new formulation. The primary objective of this study is to characterize the safety and tolerability of the tiragolumab and atezolizumab IV FDC formulation. The following will be studied:

- Incidence and severity of adverse events, with severity determined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0)
  - The severity of cytokine release syndrome (CRS) will also be determined according to the American Society for Transplantation and Cellular Therapy (ASTCT) Cytokine Release Syndrome (CRS) Consensus Grading Scale.

The NCI CTCAE v5.0 severity grading scale provides a standardized methodology for the description and exchange of safety information in oncology research.

Risks associated with CIT can be broadly classified into autoimmune toxicity and cytokine-associated toxicity. Cytokine-associated toxicity, also known as CRS, is a non–antigen-specific toxicity that occurs as a result of high-level immune activation, especially when immune-based therapies have become more potent (Lee et al. 2014). The ASTCT CRS Consensus Grading Scale is being employed in this study as an additional standard to evaluate any events of CRS. This grading system is based largely on the degree or type of intervention administered to a participant (Lee et al. 2019) and will further assist the investigator in early clinical intervention for CRS. After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. All serious adverse events will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. In addition, adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment, regardless of initiation of subsequent anti-cancer therapy.

4.2.4 Rationale for the Secondary Pharmacokinetic and Immunogenicity Endpoints

The proposed use of Cycle 1 area under the concentration–time curve (AUC) and maximum serum concentration (C_{max}) as the secondary pharmacokinetic (PK) endpoints is on the basis that AUC and C_{max} are typical PK comparability parameters for drugs administered by IV route. Additionally, due to time varying pharmacokinetics observed with some monoclonal antibodies, Cycle 1 pharmacokinetics will be assessed for comparison with prior data following sequential administration of the individual drugs. Additional parameters such as minimum serum concentration (C_{min}) and clearance (CL) will help in overall PK characterization. The PK data will be compared descriptively with historical data to verify consistency between the IV FDC formulation and sequential IV infusions with the individual drugs. Additional graphical and numerical analysis may be conducted as data allow for it.

An intensive sampling schedule is proposed to characterize the pharmacokinetics of tiragolumab and atezolizumab. The sample collection schedule is designed to adequately capture the distribution and elimination phases of both tiragolumab and atezolizumab. The sampling scheme herein will allow the determination of AUC and C_{max} at Cycle 1.

Anti-drug antibody (ADA) samples will be collected before and after tiragolumab and atezolizumab IV FDC treatment to check for an immune response to tiragolumab and atezolizumab.

subtypes, and tumor mutational burden. The evaluation of biomarkers may help to identify which patients may benefit the most from treatment with tiragolumab in combination with atezolizumab and may help to guide future development of novel therapeutic and diagnostic options.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

[redacted]

[redacted]

[redacted]

4.4 END OF STUDY DEFINITION

The end of this study is defined as the date of the last visit of the last participant in the study or the date at which the last data point required for safety follow-up is received from the last participant. The end of the study is expected to occur 24 months after the last participant is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

4.5 DURATION OF PARTICIPATION

*Before participants are discontinued from the study, t*reatment will continue until disease progression per investigator-assessed RECIST v1.1, loss of clinical benefit, or intolerable toxicity related to study treatment, after which participants will be followed for survival and anti-cancer treatment.

The total duration of study participation for each individual is expected to range from 1 day to more than 4 months.

5. STUDY POPULATION

The study will enroll approximately 40–60 participants [redacted] with histologically-confirmed PD-L1–selected solid tumors (see Table 4) whose disease is locally advanced, recurrent, or metastatic and for whom an investigational agent in combination with an anti–PD-L1 antibody is considered an acceptable treatment option. Participants must not have received prior checkpoint inhibitor treatment for their cancer (CPI-Naive).

The description above defines a population in which it is ethically acceptable and feasible to evaluate the safety, tolerability, and pharmacokinetics of novel therapies intended for the treatment of patients with advanced malignancies. Participants will have PD-L1–selected (see Table 4) histologically-confirmed tumors. Enrollment will focus on participants who have EAC, ESCC, *GC,* GEJ, HCC, melanoma, NSCLC, RCC,

SCCHN, and UBC. Additional tumor types may be added as the PD-L1 cutoffs become available.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Potential participants are eligible to be included in the study only if all of the following criteria apply:

- Signed Informed Consent Form
- Age ≥18 years at the time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- ECOG Performance Status of 0 or 1 (see Appendix 10)
- Life expectancy ≥12 weeks
- Adequate hematologic and end organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment (Day 1 of Cycle 1):
  - ANC ≥1,500 cells/μL without granulocyte colony–stimulating factor
  - WBC count ≥2,500/μL
  - Lymphocyte count ≥500/μL
  - Platelet count ≥100,000/μL (without transfusion within 14 days prior to Day 1 of Cycle 1)
  - Hemoglobin ≥9 g/dL
  - Total bilirubin ≤1.5×upper limit of normal (ULN) with the following exception:
  - AST and ALT ≤3×ULN
  - $ALP \leq 2.5 \times ULN$
  - Serum albumin ≥2.5 g/dL
  - INR and aPTT ≤1.5×ULN

    This applies only to participants who are not receiving therapeutic anticoagulation.

    Participants receiving therapeutic anticoagulation should be on a stable regimen.

- Measured or calculated creatinine clearance ≥50 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:

$$\frac{(140-\text{age}) \times (\text{weight in kilograms}) \times (0.85 \text{ if female})}{72 \times \text{creatinine in mg/dL}}$$

- Recovery (i.e., improvement to Grade 1 or better) from all acute toxicities from previous therapy, excluding alopecia
- Negative HIV test at screening
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
- For female participants of childbearing potential (including female participants who had a tubal ligation), negative serum pregnancy test within 14 days prior to initiation of study treatment (Day 1 of Cycle 1)
- For female participants of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agree to refrain from donating eggs, as defined below:
  - Female participants must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 5 months after the final dose of tiragolumab and atezolizumab IV FDC.
  - Participants must refrain from donating eggs during this same period.
  - A female participant is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a female participant with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

- Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For male participants: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:
  - With a female partner of childbearing potential or pregnant female partner, male participants must remain abstinent or use a condom during the treatment period and for 90 days after the final dose of tiragolumab and atezolizumab IV FDC to avoid exposing the embryo. Male participants 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 individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

5.1.1 Cancer-Specific Inclusion Criteria

Potential participants are eligible to be included in the study only if all of the following cancer-specific criteria apply:

- Histologic documentation of locally advanced, recurrent, or metastatic malignancy, *ineligible for definitive local therapy,* for which a clinical trial of an investigational agent in combination with an anti–PD-L1 antibody is considered an acceptable treatment option
  - [redacted]
- No prior treatment with checkpoint inhibitor therapies (CPI-Naive), including but not limited to anti–PD-1/PD-L1, anti–CTLA-4, and anti-TIGIT
  - Prior treatment with other anti-cancer therapy is acceptable. Adequate washout periods of at least 3 weeks from the last dose of the prior anti-cancer treatment until the first dose of study treatment are required to avoid any unintended

overlap in exposure between a prior systemic cancer therapy and the current study treatment *(exceptions noted in Section 5.2.1)*.

  - Participants must be advised of all other appropriate available therapies.

- Measurable disease per RECIST v1.1 (see Appendix 9)
  - Previously irradiated lesions should not be counted as target lesions.
  - Lesions that are intended to be biopsied should not be counted as target lesions.
- Submittal of archival tumor and/or fresh tumor tissue to the RTD central laboratory for PD-L1 evaluation prior to enrollment
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

5.1.2 Additional Inclusion Criteria for Indication-Specific Cancer

Potential participants are eligible to be included in the study only if all of the following additional indication-specific criteria apply:

- NSCLC:
  - Participants whose tumors have a known sensitizing epidermal growth factor receptor (*EGFR*) mutation must also have experienced disease progression (during or after treatment) or have an intolerance to treatment with an *EGFR* tyrosine kinase inhibitor(s)*, if available and approved by local regulatory authorities*. For participants with EGFR T790M mutation–positive NSCLC, one of those EGFR tyrosine kinase inhibitors must have been osimertinib if *available and* approved for the treatment of EGFR T790M mutation–positive NSCLC after progression on other EGFR tyrosine kinase inhibitors.
  - Participants whose tumors have a known anaplastic lymphoma kinase (*ALK*) rearrangement must also have experienced disease progression (during or after treatment) or have an intolerance to treatment with an *ALK* tyrosine kinase inhibitor(s) *if available and approved*.

  - Participants whose tumors have a known *ROS1* rearrangement must also have experienced disease progression (during or after treatment) or have an intolerance to treatment with *a ROS1* tyrosine kinase inhibitor(s) *if available and approved*.
  - Participants whose tumors have a *BRAF*^{V600E} mutation must also have experienced disease progression (during or after treatment) or have an intolerance to treatment with dabrafenib in combination with trametinib *if available and approved*.
- *GC or* GEJ or EAC or ESCC:
  - Participants with *Types I–III* GEJ tumor, defined by Rüdiger Siewert et al. (2000) as adenocarcinoma with the tumor center located within 5 cm *of* the anatomic esophagogastric junction, are eligible for the study.
  - Participants whose tumors are *HER2*-positive must also have experienced disease progression (during or after treatment) or intolerance to treatment with *HER2*-targeting antibody/*HER2* inhibitor(s) *if available and approved*.

- SCCHN: consisting of oral cavity, oropharynx, hypopharynx, or larynx not amenable to curative therapy
  - 
  - Human papillomavirus status for *oropharyngeal* SCCHN must be known .
- UBC: includes renal pelvis, ureters, urinary bladder, and urethra
  - 
- Melanoma: advanced metastatic cutaneous melanoma only (ocular and mucosal melanoma are excluded).
  - Participants whose tumors have a known *BRAF*^{V600E} mutation must also have experienced disease progression (during or after treatment) or have an intolerance to *BRAF* inhibitor(s) and/or mitogen-activated protein kinase inhibitor(s).
- RCC: RCC with component of clear cell histology and/or component of sarcomatoid histology.

5.2 EXCLUSION CRITERIA

Potential participants are excluded from the study if any of the following criteria apply:

- Pregnancy or breastfeeding, or intention of becoming pregnant during the study or within 5 months after the final dose of tiragolumab and atezolizumab IV FDC
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater, see Appendix 11), myocardial infarction within the previous 3 months, unstable arrhythmias, and/or unstable angina
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease or current alcohol abuse
- Poorly controlled Type 2 diabetes mellitus, defined as a screening hemoglobin $A1_C \geq 8\%$ or a fasting plasma glucose ≥ 160 mg/dL (or 8.8 mmol/L)
- Major surgical procedure within 28 days prior to Day 1 of Cycle 1 or anticipation of need for a major surgical procedure during the study
- Any other diseases, metabolic dysfunction, physical examination finding, and/or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or may render the participant at high risk from treatment complications
- History of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, *granulomatosis with polyangiitis*, Sjögren syndrome, Bell's palsy (of autoimmune etiology only), Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 7 for a more comprehensive list of autoimmune diseases), with the following caveats:
  - [redacted]
  - [redacted]
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone > 10 mg/day, cyclophosphamide, azathioprine, methotrexate,

thalidomide, and tumor necrosis factor−α [TNF-α] antagonists) within 2 weeks prior to Day 1 of Cycle 1

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

- History of idiopathic pulmonary fibrosis, pneumonitis (including drug-induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan
  - [redacted].
- Active tuberculosis
- Severe infections within 4 weeks prior to Day 1 of Cycle 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Recent infections not meeting the above criteria for severe infections, including the following:
  - Signs or symptoms of infection within 2 weeks prior to Day 1 of Cycle 1
  - Received oral or IV antibiotics within 2 weeks prior to Day 1 of Cycle 1
  - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
- Prior allogeneic bone marrow transplantation or prior solid organ transplantation
- Administration of a live, attenuated vaccine within 4 weeks before Day 1 of Cycle 1 or anticipation that such a live attenuated vaccine will be required during the study
  - [redacted].
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to CHO-cell products
- Allergy or hypersensitivity to components of the tiragolumab and atezolizumab IV FDC formulation

5.2.1 Cancer-Specific Exclusion Criteria

- Any anti-cancer therapy, whether investigational or approved, including chemotherapy, hormonal therapy, and/or radiotherapy, within 3 weeks prior to initiation of study treatment, with the following exceptions:
  - Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer
  - Hormone-replacement therapy or oral contraceptives
  - Tyrosine kinase inhibitor(s) (TKIs) approved by local regulatory authorities for treatment of cancer that have been discontinued >7 days prior to Day 1 of Cycle 1; baseline scans must be obtained after discontinuation of prior TKIs, and criteria pertaining to adverse events attributed to prior cancer therapies must be met.
  - Herbal therapy >1 week before Day 1 of Cycle 1
  - Palliative radiotherapy for painful metastases or metastases in potentially sensitive locations (e.g., epidural space) >2 weeks prior to Day 1 of Cycle 1
  - *Stereotactic radiotherapy, whole-brain radiotherapy, or neurosurgical resection for CNS metastases per exclusion criteria for CNS metastases.*
- Prior treatment with CPIs including but not limited to anti-TIGIT, anti–PD-L1, anti–PD-1, anti–CTLA-4
- Less than 5 drug-elimination half-lives (approximately 100 days for typical MAb) from the last dose of MAbs, and MAb-Derived Therapies (excluding CPIs) and the proposed Day 1 of Cycle 1. Therapies include but are not limited to agonists of co-stimulatory receptors and T-cell recruiting bispecifics.
- Less than 6 weeks between the last dose of prior immunomodulators and the proposed Day 1 of Cycle 1. [redacted]
- Less than 6 weeks or 5 drug-elimination half-lives, whichever is shorter, of prior treatment with cancer vaccines and/or cytokines have elapsed between the last dose and the proposed Cycle 1, Day 1.
- Any history of an immune-mediated Grade 4 adverse event attributed to prior cancer immunotherapy (other than endocrinopathy managed with replacement therapy or asymptomatic elevation of serum amylase or lipase)
- Any history of an immune-mediated Grade 3 adverse event attributed to prior cancer immunotherapy (other than endocrinopathy managed with replacement therapy or asymptomatic elevation of serum amylase or lipase) that resulted in permanent discontinuation of the prior immunotherapeutic agent and/or occurred ≤ 6 months prior to Day 1 of Cycle 1

- Any immune-mediated adverse events related to prior cancer immunotherapy (other than endocrinopathy managed with replacement therapy or stable vitiligo) must have resolved completely to baseline.
  - [redacted]
- Adverse events from prior anti-cancer therapy that have not resolved to Grade ≤ 1 except for alopecia, vitiligo, or endocrinopathy managed with replacement therapy
- Patients with the pulmonary lymphoepithelioma-like carcinoma subtype of NSCLC
- Primary central nervous system (CNS) malignancy, untreated CNS metastases, or active CNS metastases (progressing or requiring corticosteroids for symptomatic control)
  - [redacted]
- Leptomeningeal disease
- Uncontrolled tumor-related pain
  - [redacted]
  - [redacted]

[redacted]

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
  - Patients with indwelling catheters (e.g., PleurX® catheters) are allowed.
- Malignancies other than disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer, or ductal carcinoma in situ)
- Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium greater than or equal to ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab
  - [redacted]
- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 2 weeks prior to screening

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per individual) at the investigator's discretion. Individuals are not required to re-sign the consent form if they are re-screened within 60 days after previously signing the consent form.
The investigator will maintain a record of reasons for screen failure (see Section 8).

6. STUDY TREATMENT(S) AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

The investigational medicinal product (IMP) for this study is tiragolumab and atezolizumab IV FDC. Appendix 12 identifies all investigational and non-investigational medicinal products for this study.

6.1 STUDY TREATMENTS ADMINISTERED

Table 5 provides a description of assigned study treatments for this study.

Table 5 Study Treatment Description

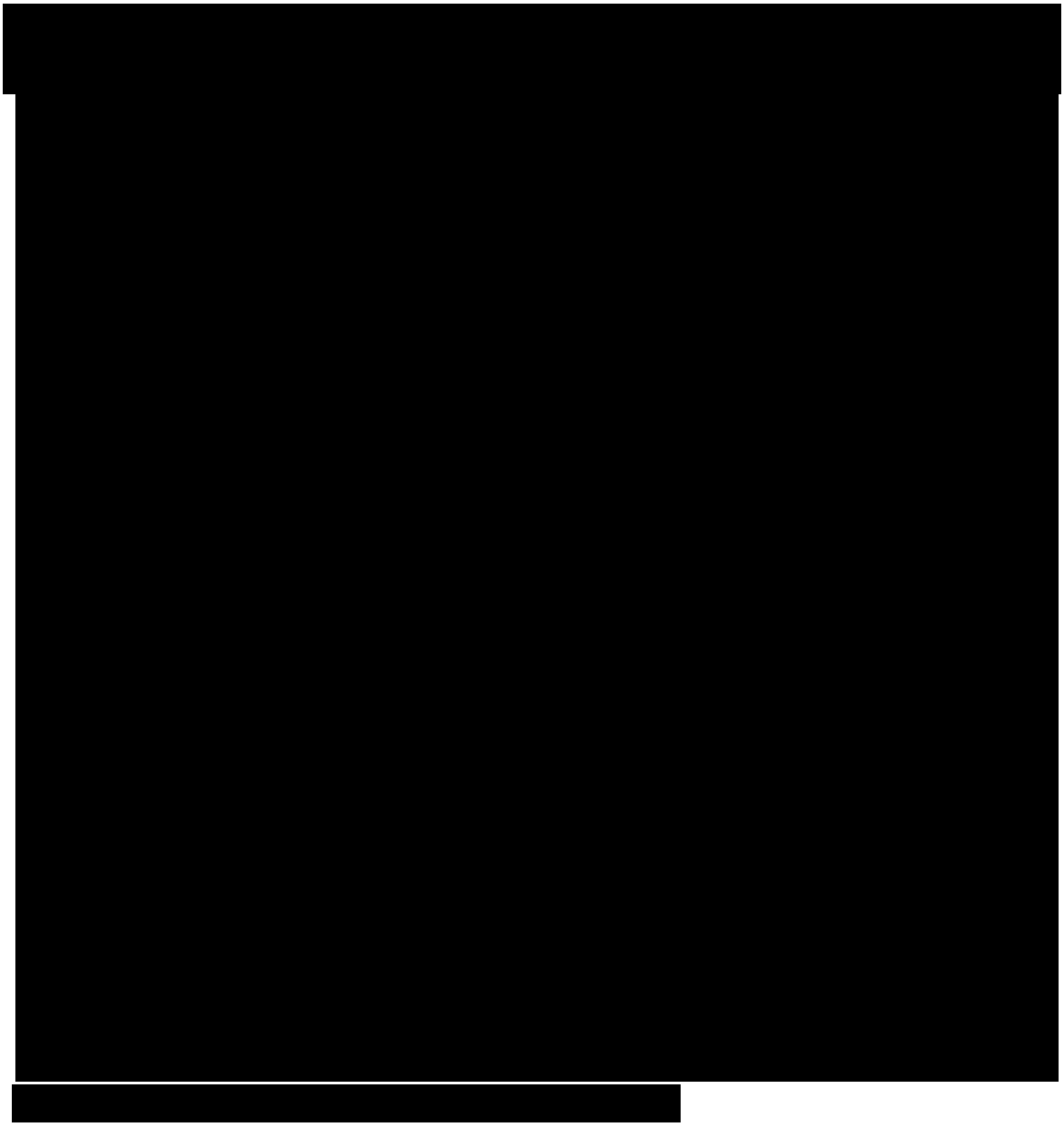
	Tiragolumab and Atezolizumab IV FDC
Use	Experimental
Drug form	Liquid concentrate
Unit dose strengths	[redacted] mg/mL tiragolumab [redacted] mg/mL atezolizumab
Dosage levels	Tiragolumab 600 mg combined with atezolizumab 1200 mg
Formulations	Refer to the Tiragolumab and Atezolizumab IV FDC Investigator's Brochure
Packaging	[redacted] mL glass vials
Labeling	Per local requirements
Route of administration	IV infusion
Source	Sponsor

FDC = fixed-dose combination.

Guidelines for treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 5 and Appendix 6.

Administration of tiragolumab and atezolizumab IV FDC 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 8.

Tiragolumab and atezolizumab IV FDC infusions will be administered per the instructions outlined in Table 6.



Guidelines for medical management of IRRs are provided in Appendix 6.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

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

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using an interactive voice or web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

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

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and the Tiragolumab and Atezolizumab IV FDC Investigator's Brochure for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT

This is a single-arm, non-randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number from an IxRS.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the electronic Case Report Form (eCRF). The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration eCRF. Cases of accidental overdose

or medication error, along with any associated adverse events, should be reported as described in Appendix 3.

6.5 DOSE MODIFICATION

Modification of the tiragolumab and atezolizumab IV FDC dose is not permitted.

If study treatment has to be temporarily interrupted or permanently discontinued to manage toxicity, tiragolumab and atezolizumab IV FDC can be interrupted or discontinued (see Appendix 5 and Appendix 6).

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

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

A participant will be eligible to receive Roche IMP (tiragolumab and atezolizumab) after completing the study if all of the following conditions are met:

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

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

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

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

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

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities until participant status returns to the pre-overdose status.

6.8 CONCOMITANT THERAPY

Any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by a participant in addition to protocol–mandated treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit must be recorded on the Concomitant Medications eCRF(s) along with the following information:

- Reason for use (indication)
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

6.8.1 Permitted Therapy

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

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 5.1)
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)
  - Live, attenuated vaccines are not permitted (see Section 5.2).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled or low-dose corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) is permitted:
  - [redacted]
  - [redacted]

[redacted]

In general, investigators should manage a participant's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 6.8.2 and 6.8.3) as clinically indicated, per local standard practice. Participants who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 8).

6.8.2 Cautionary Therapy

6.8.2.1 Cautionary Therapy for Tiragolumab and Atezolizumab IV FDC-Treated Participants

Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with tiragolumab and atezolizumab IV FDC. 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 tiragolumab and atezolizumab IV FDC therapy (see Appendix 6 for details).

6.8.2.2 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 6.8.1) may be used during the study at the discretion of the investigator.

6.8.3 Prohibited Therapy

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

- Investigational therapy within 28 days prior to initiation of study treatment and during study treatment
- Concomitant therapy intended for the treatment of cancer (including but not limited to chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, for various time periods prior to starting study treatment, depending on the agent (see Section 5.2), and during study treatment, until disease progression is documented, and the participant has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section 6.8.1 for details)
- Live, attenuated vaccines (e.g., FluMist) within 4 weeks prior to initiation of study treatment, during study treatment, and for 5 months after the final dose of study treatment
- Systemic immunostimulatory agents (including but not limited to IFNs and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with study treatment

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study for additional assessments. See the schedule of activities (see Section 1.3) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

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

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

- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Use of any anti-cancer therapy not allowed per protocol
- Radiographic disease progression per RECIST v1.1 (unless study treatment is continued beyond radiographic progression)
- For participants treated beyond radiographic disease progression per RECIST v1.1, 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 4.1.1 for details).

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

Participants will return to the clinic for a treatment discontinuation visit ≤30 days after the final dose of study drug or within 30 days from the date the decision was made to permanently discontinue study treatment.

After treatment discontinuation, information on survival status and new anti-cancer therapy will be collected via telephone calls, participant medical records, and/or clinic visits approximately every 3 months, or more frequently, until death (unless the participant withdraws consent or the Sponsor terminates the study).

See schedule of activities in Section 1.3 (see Table 1) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment. If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study treatment is required by the investigator when a study participant meets the criteria for abnormal liver tests as outlined in Appendix A3-7.6 or if the investigator believes that it is in best interest of the participant to discontinue.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3, Table 1). See the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) 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.

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

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

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

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the schedule of activities (see Section 1.3, Table 1), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a detailed record of all participants screened, to document eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., complete blood count) and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the timeframe defined in the schedule of activities.

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol will be recorded at baseline. Any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant within 7 days prior to initiation of study treatment will be recorded at baseline. Demographic data, including age, sex, and self-reported race or ethnicity, will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

8.1 EFFICACY ASSESSMENTS

8.1.1 Tumor and Response Evaluations

Participants will undergo tumor assessments at screening, every 6 weeks (±7 days) for the first 48 weeks following treatment initiation (Day 1 of Cycle 1), and every 9 weeks (±7 days) thereafter, regardless of dose delays. Participants will continue to undergo tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for participants who continue treatment after radiographic treatment progression), as determined by the investigator, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Participants who are treated beyond

disease progression per investigator-assessed RECIST v1.1 will undergo tumor assessments at the schedule described above after initial documentation of progression, or more frequently, if clinically indicated, regardless of time in study until treatment is discontinued (see Section 4.1.1 for details). At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected. Participants who discontinue study treatment (for any reason, including but not limited to clinical decline or toxicity) in the absence of radiographic disease progression per investigator-assessed RECIST v1.1 will continue to undergo tumor response assessments at the same frequency until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments should continue regardless of whether a participant starts a new anti-cancer therapy.

All measurable and/or evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening, so long as they meet criteria per RECIST v1.1.

8.1.1.1 Radiographic Assessments

Screening assessments must include CT scans with contrast (per institutional standard operating procedures) of the chest, abdomen, and pelvis. If a CT scan with contrast is contraindicated (e.g., in participants with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and magnetic resonance imaging (MRI) scans (with contrast, if feasible) of the abdomen and pelvis should be performed. CT or MRI scans of other disease sites should be performed as clinically indicated.

All known or suspected sites of disease should be assessed at screening and at subsequent assessments with the use of the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST v1.1 should be used when recording data and should again be used for all subsequent assessments.

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

For participants with bone lesions, bone scans, PET 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. Participants should undergo bone scans if bone disease cannot be assessed by another modality (e.g., CT scan).

All participants must undergo an MRI or CT scan (with contrast) of the brain at screening to evaluate CNS metastasis. A brain MRI scan is the preferred imaging method for evaluating CNS metastases as it is more sensitive than CT for identifying brain metastases; however, CT of the brain is acceptable if MRI is contraindicated. If a CT scan with contrast is performed and the presence of brain metastases is considered equivocal, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases. Participants with active or untreated CNS metastases are not eligible for the study (see Section 5.2). At subsequent (post-screening) tumor assessments, participants with a history of irradiated brain metastases at screening are not required to undergo brain scans unless clinically indicated (e.g., in participants with neurologic symptoms); irradiated brain metastases do not need to be categorized and followed as target or non-target lesions at baseline or at subsequent tumor assessments.

Further investigations such as bone scans and CT scans of the neck should also be performed as indicated by the underlying disease (e.g., a head and neck CT scan is indicated for participants with HNSCC) and if there is any clinical suspicion of disease at any site that may not be demonstrated by the minimum schedule of assessments listed above. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

All measurable and/or evaluable lesions identified at screening should be re-assessed at subsequent tumor evaluations according to the schedule described above. 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).

Tumor assessments must be continued at the same frequency after disease progression per RECIST v1.1 for participants who receive treatment beyond progression.

Radiographic images must be evaluated by a qualified, certified expert.

8.1.1.2 Response Evaluation

Objective response will be determined by the investigator at specified timepoints according to RECIST v1.1 (see Appendix 9). Assessments should be performed by the same individual, if possible, to ensure internal consistency across visits.

[redacted]

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the participant's weight and height, the head, eyes, ears, nose, and throat, and the

cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

A brief physical examination will include a limited, symptom-directed physical examination. Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities (i.e., beyond expected variation or normal age-related changes) should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed while the participant is in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of one pulse and three blood pressure measurements (three consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the three blood pressure readings will be recorded on the eCRF.

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.

8.2.3 Performance Status

Performance status will be measured using the ECOG Performance Status Scale (see Appendix 10) and may be assessed throughout the study as specified in the schedule of activities (see Section 1.3).

8.2.4 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the schedule of activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR interval, and QRS interval.

ECGs for each participant should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that

same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site.

8.2.5 Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event CRF (see Appendix 3).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days of the final dose of study treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.2.6 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3 and will be conducted as outlined in Appendix 2.

8.2.7 Auto-Antibody Testing

Serum samples will be obtained for auto-antibody testing, including but not necessarily limited to anti-nuclear antibody, anti–double-stranded DNA, anti–neutrophil cytoplasmic antibodies, and thyroid peroxidase antibody, will be performed according to the schedule of assessments (see Section 1.3). If inflammatory arthritis develops, cyclic citrullinated peptide and rheumatoid factor antibody titers will also be evaluated. Additional serum collection for auto-antibody testing should be performed as clinically indicated.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

[redacted]

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available. [redacted]

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

The investigator will be informed of any device deficiencies detected at the testing site that might have an impact on clinical study participants (e.g., a test result leading to inappropriate participant management decision). This will enable the investigator to assess for and report any adverse events associated with the device deficiency (see Appendix 3).

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

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

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

Drug	Document
Tiragolumab and Atezolizumab IV FDC	Tiragolumab and Atezolizumab IV FDC Investigator's Brochure

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

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

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of tiragolumab and atezolizumab IV FDC.

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 90 days after the final dose of tiragolumab and atezolizumab IV FDC.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 4. The Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 3.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

An IMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

8.3.8 Adverse Events of Special Interest

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 the investigator becomes aware of the event; see Section A3-5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3-7.6)
- Suspected transmission of an infectious agent by a 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 participant exposed to a medicinal product. This term applies only when a contamination of the 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, infusion-related reactions, cytokine release syndrome, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis

- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 5 and Appendix 6.

8.3.9 Medical Monitors and Emergency Medical Contacts

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

8.4 PHARMACOKINETICS

Serum samples will be collected for measurement of serum concentrations of tiragolumab and atezolizumab as specified in the schedule of activities (see Section 1.3). Concentration data may be pooled with data from other studies using established population PK models to derive PK parameters such as CL, volume of distribution at steady state (V_{ss}), and AUC, as warranted by the data. Population PK analysis may be reported separately.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each dose administration and PK sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of tiragolumab and atezolizumab. [redacted]

[redacted] Participant confidentiality will be maintained. [redacted]

8.5 PHARMACODYNAMICS

See Section 8.7 for information on pharmacodynamic biomarkers.

8.6 GENETICS

Genetic biomarker assessments will not be performed in this study.

8.7 BIOMARKER ASSESSMENTS

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Serum and plasma samples for exploratory research on biomarkers
- Archival or newly collected tumor tissue sample obtained at baseline for determination of PD-L1 and for exploratory research on biomarkers.
  - [redacted]
  - [redacted]
  - [redacted]
- Tumor tissue sample obtained at the time of progression, if deemed clinically feasible, for exploratory research on biomarkers
  - [redacted]
  - [redacted]

Biomarker samples collected at participating sites and biomarker samples requiring separate consent are described in Section 8.10.

[redacted]

Screening tumor tissue, plasma and serum samples, including those collected from individuals who do not enroll in the study, may be used for research and/or development of disease-related tests or tools.

Biomarker samples will be collected according to the schedule outlined in Section 1.3 (see Table 1 and Table 2). Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

[redacted]

- [redacted]

[redacted]

8.8 IMMUNOGENICITY ASSESSMENTS

Immunogenicity will be assessed by measurement of anti-drug antibodies (ADAs) to tiragolumab and atezolizumab in serum samples collected from participants according to the schedule of sample collections (Table 2). Samples will be screened for ADAs, and the titer will be reported for confirmed positive samples. Other analyses may be performed to further characterize immunogenicity of atezolizumab or tiragolumab or the associated methods, if needed. Concurrent PK samples will be evaluated to enable interpretation of the ADA data.

[redacted]

[redacted]

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

[redacted]

8.10 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY (PARTICIPANTS PROVIDING SEPARATE CONSENT AT PARTICIPATING SITES)

8.10.1 Overview of the Research Biosample Repository

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

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

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

8.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.10) will not be applicable at that site.

8.10.3 Sample Collection

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

- Leftover blood, serum, plasma, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

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

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

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

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

8.10.4 Data Protection, Use, and Sharing

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

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

Data generated from RBR samples will be analyzed in aggregate rather than on an individual participant basis. Thus, there will be no identification and reporting of

incidental findings to investigators or participants. In addition, given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants, unless required by law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a participant may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant 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 participant'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.

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

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

8.10.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples and may withdraw their consent at any time and for any reason during the storage period.
A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

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

8.10.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global.rcr-withdrawal@roche.com

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

8.10.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to an individual's 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.

9. STATISTICAL CONSIDERATIONS

This single-arm study is aimed at assessing the safety, tolerability, pharmacokinetics, immunogenicity, preliminary efficacy, and biomarker expression of Q3W tiragolumab and atezolizumab IV FDC (prepared from one vial).

9.1 STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested for this study.

9.2 SAMPLE SIZE DETERMINATION

The study is intended to obtain descriptive assessment of safety, pharmacokinetics, immunogenicity, efficacy, and biomarker expression in the treated population, so the sample size does not reflect explicit power and Type I error considerations.

A total sample of 40–60 participants [redacted] is considered sufficient and appropriate for the exploratory purposes of the study.

The primary objective of the study involves safety and tolerability of the study drug, as assessed by the incidence and severity of adverse events. The probability of observing at least one adverse event, depending on the underlying incidence, with the minimum sample size of 40 evaluable participants is presented in Table 7.

Table 7 Probability of Detecting One or More Adverse Events According to the Adverse Event Incidence Rate

True Incidence of Adverse Events	Expected Probability of Detecting One or More Adverse Events (n = 40)
[redacted]	

9.3 ANALYSIS SETS

The following *analysis sets* will be defined for purposes of analysis:

- Full analysis set (FAS): All the enrolled study participants
- Safety analysis set: All participants who receive any amount of study treatment
- PK-*evaluable* set: All participants included in the safety analysis set who have at least one *evaluable post-baseline* PK assessment available
- *ADA-evaluable set: All participants included in the safety analysis set who have at least one ADA assay result*

All primary safety analyses, other safety analyses, and the analysis of exploratory efficacy endpoints and biomarkers, will be carried out on the safety analysis set.

The *PK-evaluable set* will be used for all the statistical analyses of PK endpoints.

The ADA-evaluable set will be used for all the statistical analyses of immunogenicity endpoints.

All the remaining analyses *including* summaries of study conduct will be carried out on the FAS population.

9.4 STATISTICAL ANALYSES

The Statistical Analysis Plan will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary endpoints.

9.4.1 General Considerations

In general, descriptive analyses will be carried out for all endpoints. Continuous variables will be summarized using means, standard deviations, medians, and ranges; categorical variables will be summarized using counts and percentages.

The PK analysis set will consist of all *participants* with at least one *evaluable post-baseline* PK assessment. Consequently, no or a few data are expected to be missing for primary and secondary study endpoints, and no missing value imputation strategy is planned. *Similarly, the ADA-evaluable set will also consist of all participants with at least one ADA assessment, and no missing value imputation is planned.*

9.4.2 Primary Endpoints

The primary endpoints are safety endpoints, as defined in Section 3 (see Table 3), which include the incidence and severity of adverse events, as assessed by the investigator, according to NCI CTCAE v5.0 and also according to the ASTCT CRS Consensus Grading Scale for CRS.

Safety analyses will be performed on the safety analysis set (see Section 9.3).

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms.
All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events with worsening severity or those leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade by means of the appropriate descriptive statistics. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

9.4.3 Secondary Endpoints

The secondary endpoints are PK and immunogenicity endpoints, as defined in Section 3 (see Table 3).

The pharmacokinetics of tiragolumab and atezolizumab IV FDC will be characterized following treatment administration. The individual exposure metrics for tiragolumab and atezolizumab IV FDC (AUC at Cycle 1, C_{max} at Cycle 1, C_{min} at Cycle 1, and CL) will be derived and summarized (geometric mean, mean, standard deviation, coefficient of variation, etc.). AUC at Cycle 1 and C_{max} at Cycle 1 will be compared descriptively with

historical PK data of tiragolumab and atezolizumab following IV sequential administration. Population PK analysis and comparison will be performed and reported separately. Additional graphical and numerical analysis may be conducted as appropriate.

The baseline prevalence of ADAs and postbaseline incidence of treatment-emergent ADAs to tiragolumab and atezolizumab will be summarized and analyzed by the appropriate descriptive statistics.

9.4.4 Exploratory Endpoints

9.4.4.1 Exploratory Efficacy Endpoints

[redacted]

9.4.4.2 Exploratory Pharmacokinetic Endpoints

[redacted]

9.4.4.3 Exploratory Immunogenicity Endpoints

[redacted]

9.4.4.4 Exploratory Biomarker Endpoints

[redacted]

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will not be provided to study investigators or participants unless required by law.

9.4.5 Other Safety Analyses

Safety will also be assessed through summaries of exposure to study treatment, changes in laboratory test results and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles) will be summarized with descriptive statistics.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, 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.

9.4.6 Other Analyses

9.4.6.1 Summaries of Conduct of Study

Summaries of study conduct will include all enrolled participants in the study.

The number of participants who enroll, discontinue, or complete the study will be summarized. Reasons for treatment discontinuations and premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

9.4.6.2 Summaries of Demographics and Baseline Characteristics

Demographic and baseline characteristics, such as age, sex, race, weight, type of malignancy, duration of malignancy, site of metastatic disease, and so forth will be summarized using descriptive statistics and tables. Baseline data are the last data obtained prior to initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

9.4.6.3 Immunogenicity Analyses

The immunogenicity objective for this study is to evaluate the immune response to tiragolumab and atezolizumab IV FDC by assessing the following:

- The immunogenicity analyses will include participants with at least one ADA assessment.
- The numbers and proportions of participants who are treatment-emergent ADA-positive and participants who are ADA-negative during both the treatment and follow-up periods for tiragolumab and atezolizumab IV FDC will be summarized.
- Safety, efficacy, and PK endpoints may be evaluated by ADA status and reported using descriptive statistics.

[redacted]

[redacted]

An IMC will monitor the initial safety based on safety data from a minimum of the first 6 participants who have received at least one dose of study treatment and who have completed safety follow-up assessments for at least 21 days in the study.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

A1. TABLE OF CONTENTS

A1-1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- 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
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation 536/2014 (European Economic Area sites only), and all other applicable local regulations

A1-2 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 study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1-3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or the participant's legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant or the participant’s legally authorized representative.

A1-4 DATA PROTECTION

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

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1-5 *ADMINISTRATIVE STRUCTURE*

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

Approximately 50 sites globally will participate to enroll 40-60 participants. Enrollment will occur through an interactive voice or web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, auto-antibodies, immunogenicity, biomarker, and pharmacokinetic analyses), as specified in Section 8. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected (see Appendix 2).

A1-6 DISSEMINATION OF CLINICAL STUDY DATA

Study data, which may include imaging data, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

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

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

A1-7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic Case Report Forms (CRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered on the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including but not limited to Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

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

A1-8 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered on the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1-9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1-10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site 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.

A1-11 PROTOCOL DEVIATIONS

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

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) • Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and lactate dehydrogenase • Coagulation: INR and aPTT • Thyroid function testing: TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 • Serum ferritin and C-reactive protein • [redacted] • [redacted] • [redacted] • [redacted] • Pregnancy test: All female participants of childbearing potential will have a serum pregnancy test at screening (within 14 days prior to study treatment). Urine pregnancy tests will be performed at specified subsequent visits (see Section 1.3, Table 1). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. • Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood) [redacted]

Investigators must document their review of each laboratory safety report.

Appendix 3
Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

A3. TABLE OF CONTENTS

A3-1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication
  - Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- " Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition

- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)
  - The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3-2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3-1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life threatening
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.
  - Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.
- Results in persistent disability or incapacity
  - The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  - This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly or birth defect
- Other situations:
  - Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]; see Section A3-3.2); 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 electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3-5 for reporting instructions).

A3-3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND/OR SERIOUS ADVERSE EVENTS

A3-3.1 Adverse Event and Serious Adverse Event Recording

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3-3.2 Assessment of Severity

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE v5.0 grading scale. The investigator will use the grading scale in Table A3-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table A3-1 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]

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
Note: Based on the most recent version of NCI CTCAE v5.0, which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A3-5 for reporting instructions), per the definition of serious adverse event in Section A3-2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3-5 for reporting instructions), per the definition of serious adverse event in Section A3-2.

The ASTCT CRS Consensus Grading Scale (see Table A3-2) (Lee et al. 2019) should be used in addition to NCI CTCAE when reporting severity of CRS (see Section A3-7.1 for details on CRS reporting).

Table A3-2 ASTCT CRS Consensus Grading Scale

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

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

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

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

A3-3.3 Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3-3.4 Follow-up of Adverse Events and Serious Adverse Events

A3-3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes 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

[redacted] resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3-3.4.2 Sponsor Follow-Up

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

A3-4 REPORTING OF SERIOUS ADVERSE EVENTS

A3-4.1 Serious Adverse Event Reporting to the Sponsor via an Electronic Collection Tool

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3-5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3-5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as they become available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken offline, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3-5.

A3-4.2 Serious Adverse Event Reporting to the Sponsor via Paper CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3-5.

A3-5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS, *MEDICAL DEVICE ADVERSE EVENTS,* AND ADVERSE EVENTS OF SPECIAL INTEREST

A3-5.1 Events That Occur prior to Study Treatment Initiation

[redacted]

[redacted].

A3-5.2 Events That Occur after Study Treatment Initiation

[redacted]. *Reports will be submitted via the EDC system and will be sent to Roche Safety Risk Management by the EDC system.*

In the event that the EDC system is unavailable, 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 (all serious adverse events) or Investigational Medical Device Adverse Event and Device Deficiency Form (non-serious investigational medical device related), using the fax number or email address provided to investigators. Once the EDC system is available, information will need to be entered and submitted via the EDC system.

Instructions for reporting events that occur more than *90 days* after the final dose of study treatment are provided in Section A3-6.

A3-6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period ([redacted]), 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 [redacted], 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 *(study drug related events), or Investigational Medical Device Adverse Event and Device Deficiency form (medical device related)* using the fax number or email address provided to investigators.

A3-7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and 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 of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3-7.1 Infusion-Related Reactions and Cytokine Release Syndrome

There may be significant overlap in signs and symptoms of infusion-related reactions (IRRs) and cytokine release syndrome (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 infusion and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "cytokine release syndrome") on the Adverse Event eCRF. If possible, 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 of an IRR should be recorded on the dedicated Infusion-Related Reaction eCRF or Cytokine Release Syndrome eCRF, as appropriate.

If a participant experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

A3-7.2 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 gastrointestinal 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.

A3-7.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3-5 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

A3-7.4 Abnormal Laboratory Values

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected.
A laboratory value abnormality that is not associated with the underlying disease 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., dose 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

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 × upper limit of normal (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 A3-7.3 for details on recording persistent adverse events).

A3-7.5 Abnormal Vital Sign Values

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease 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., dose 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 (e.g., 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 A3-7.3 for details on recording persistent adverse events).

A3-7.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) 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 $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN 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 A3-7.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3-5).

A3-7.7 Deaths

For this protocol, mortality is an exploratory efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period [redacted] hat are attributed by the investigator solely to progression of the underlying cancer 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 A3-5). An Independent Monitoring Committee will monitor the frequency of deaths from all causes.

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

Deaths that occur after the adverse event reporting period should be reported as described in Section A3-6.

A3-7.8 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").

A3-7.9 Lack of Efficacy or Worsening of Underlying Cancer

Medical occurrences or symptoms of deterioration that are anticipated as part of underlying cancer at baseline should not be recorded as adverse events. However, deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. When recording an unanticipated worsening of underlying cancer on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of underlying cancer").

A3-7.10 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 A3-2), 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 participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition.
  - The participant has not experienced an adverse event.
- Hospitalization due solely to progression of the underlying cancer

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

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

A3-7.11 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (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
- Medication error: accidental deviation in the administration of a drug
  - In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events but may result in adverse events.

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3-5). For tiragolumab and atezolizumab IV fixed-dose combination (FDC), adverse events associated with special situations should be recorded as described below for each situation:

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

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

All special situations associated with tiragolumab and atezolizumab IV FDC, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

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

A3-7.12 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

A3-8 *MEDICAL DEVICE ADVERSE EVENTS*

This study will comply with International Standard (ISO) 20916 on in vitro diagnostic medical devices—clinical performance studies using specimens from human subjects—good study practice and Regulation (E.U.) 2017/746 on in vitro diagnostic medical devices requirements for medical device adverse event collection and reporting for events associated with the use of [redacted]

Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

REPORTING MEDICAL DEVICE ADVERSE EVENTS

See Section A3-5 for details on reporting medical device adverse events in participants. User injury adverse events must be reported using the paper Investigational Medical Device Adverse Event and Device Deficiency Form.

Appendix 4
Collection of Pregnancy Information

A4. TABLE OF CONTENTS

A4-1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of tiragolumab and atezolizumab IV FDC. 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 the investigator becomes aware of the pregnancy), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event electronic Case Report Form (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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A4-2 PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 90 days after the final dose of tiragolumab and atezolizumab IV FDC. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy

Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A4-3 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 the investigator becomes aware of the event; see Section A3-5).

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 the investigator becomes aware of the event; see Section A3-5). 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.

A4-4 Abnormal Pregnancy Outcomes

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3-5).

Appendix 5
Safety Plan: Management of Identified and Potential Risks

A5. TABLE OF CONTENTS

The anticipated important safety risks for tiragolumab and atezolizumab IV FDC are outlined below. Please refer to the Tiragolumab and Atezolizumab IV FDC Investigator's Brochure for a complete summary of safety information. Several measures will be taken to ensure the safety of study participants. Eligibility criteria have been designed to exclude individuals at high risk for toxicities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below. Management guidelines for all risks associated with tiragolumab and atezolizumab IV FDC are described in Appendix 6.

A5-1 RISKS ASSOCIATED WITH STUDY DRUGS

The safety plan for participants in this study is based on clinical experience with tiragolumab and atezolizumab in completed and ongoing studies, published data on similar molecules, clinical experience with tiragolumab alone and in combination with atezolizumab in Phase I and II studies, and the clinical safety profile of atezolizumab as a single agent. The anticipated important safety risks for tiragolumab, atezolizumab, and tiragolumab in combination with atezolizumab are outlined below. Please refer to the Tiragolumab and Atezolizumab IV FDC Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of study participants. Eligibility criteria have been designed to exclude individuals at higher risk for toxicities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dose modification and treatment interruption or discontinuation, are provided below. See Appendix 3 and Appendix 4 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

Participants 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).

Severe coronavirus 2019 (COVID-19) appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-γ (IFN-γ) (Merad and Martin 2020). If a participant develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of

COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

A5-1.1 Risks Associated with Tiragolumab

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

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

A5-1.1.1 Infusion-Related Reactions

Because tiragolumab is a therapeutic monoclonal antibody (mAb) and targets immune cells, IRRs associated with hypersensitivity reactions and/or target-mediated cytokine release may occur. Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

IRRs have been reported in patients treated with tiragolumab, with or without atezolizumab. The majority of events were mild to moderate and manageable.

To minimize the risk and sequelae of IRRs, [redacted]. All infusions will be administered in an appropriate medical setting.

See Appendix 8 for guidance on anaphylaxis precautions and Appendix 6 for guidance on management of IRRs.

A5-1.1.2 [redacted]

The use of tiragolumab to block the immune inhibitory receptor TIGIT serves to increase a baseline T-cell and NK-cell immune response, especially in combination with other checkpoint inhibitors (i.e., atezolizumab). A disruption in the functioning of immune checkpoint molecules may lead to imbalances in immunologic tolerance that result in an unchecked immune response, [redacted].

[redacted]

A5-1.1.3 Immune-Mediated Adverse Events

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

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

Patients with a history of autoimmune disease will be excluded from this study (see Section 5.2 and Appendix 7).

Management guidelines for individual suspected immune-mediated adverse events are provided in Appendix 6.

A5-1.1.4 Lymphopenia

[redacted] Lymphopenia is a potential risk with tiragolumab.

Transient decreases in lymphocyte count without clinical sequelae have been observed in patients treated with tiragolumab, with or without atezolizumab.

Patients with a lymphocyte count < 500 cells/μL will be excluded from this study (see Section 5), and CBCs will be monitored regularly during the study (see Section 1.3, Table 1).

A5-1.1.5 Embryofetal Toxicity

Embryofetal toxicity is a potential risk with tiragolumab. Administration of tiragolumab is expected to have adverse effects on pregnancy based on the expression of TIGIT on decidual NK and CD^{+} T cells (Powell et al. 2017; van der Zwan et al. 2018; Vento-Tormo et al. 2018) and the expected role of these cells in the recognition and response to foreign fetal, placental, and viral antigens at the maternal-fetal interface as well as maintenance of maternal-fetal tolerance. No reproductive or teratogenicity

studies in animals have been conducted with tiragolumab. There are no clinical studies of tiragolumab in pregnant women. Tiragolumab should not be administered to pregnant women.

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

A5-1.2 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs, immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, nephritis, myositis, pericardial disorders, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH).

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.

Guidelines for managing patients who experience anticipated adverse events are provided in Appendix 6.

A5-1.3 Risks Associated with Combination Use of Tiragolumab and Atezolizumab

Based on results from clinical data with tiragolumab and atezolizumab, there are known and potential overlapping toxicities in patients treated with tiragolumab and atezolizumab. Because the expected pharmacologic activity of these two molecules is to increase adaptive T-cell immune responses, there is the possibility of heightened immune responses.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a list of identified risks associated with tiragolumab in combination with atezolizumab. Based on the mechanism of action of tiragolumab and atezolizumab, additional immune-mediated adverse events are potential overlapping toxicities associated with combination use of tiragolumab plus atezolizumab.

A5-1.4 Risks Associated with the Use of Tiragolumab and Atezolizumab IV FDC

It is anticipated that the safety profile of tiragolumab and atezolizumab IV FDC is similar to that observed in tiragolumab and atezolizumab as single agents or in combination (see Section A5-1.1 to Section A5-1.3).

Immune-mediated adverse events following treatment with tiragolumab and atezolizumab IV FDC are anticipated to be amenable to monitoring and manageable in the setting of this study. The extensive experience with immune checkpoint inhibitors to date has been incorporated into the design and safety management plan (see Section A5-2 and Appendix 6) in order to reduce the potential risks to participating patients. Patients with a history of autoimmune disease will be excluded from this study (see Section 5.2 and Appendix 7). Patients previously treated with approved or experimental checkpoint inhibitor therapy will also be excluded from participation in this study. [redacted]

A5-2 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A5-2.1 Dose Modifications

There will be no dose modifications, including dose reductions, for tiragolumab and atezolizumab IV FDC in this study.

A5-2.2 Treatment Interruption

Tiragolumab and atezolizumab IV FDC treatment may be temporarily suspended in participants experiencing toxicity considered to be related to study treatment.

[redacted]

The decision to re-challenge participants with tiragolumab and atezolizumab IV FDC should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed. Tiragolumab and atezolizumab IV FDC 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.

REFERENCES

Joller N, Hafler JP, Brynedal B, et al. Cutting edge: TIGIT has T cell-intrinsic inhibitory functions. J Immunol. 2011;186:1338–42.

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Powell RM, Lissauer D, Tamblyn J, et al. Decidual T cells exhibit a highly differentiated phenotype and demonstrate potential fetal specificity and a strong transcriptional response to IFN. J Immunol 2017;199:3406–17.

van der Zwan A, Bi K, Norwitz ER, et al. Mixed signature of activation and dysfunction allows human decidual $CD8^{+}$ T cells to provide both tolerance and immunity. Proc Natl Acad Sci USA 2018;115:385–90.

Vento-Tormo R, Efremova M, Botting RA, et al. Single-cell reconstruction of the early maternal-fetal interface in humans. Nature 2018;563:347–53.

Appendix 6
Risks Associated with Tiragolumab and/or Atezolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab and Atezolizumab IV FDC

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

Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.

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

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

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

DOSE MODIFICATIONS

There will be no dose modifications for tiragolumab and atezolizumab IV FDC in this study.

TREATMENT INTERRUPTION

Tiragolumab and atezolizumab IV FDC treatment may be temporarily suspended in *participants* experiencing toxicity considered to be related to study treatment. [redacted]

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

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, dyspnea, fever, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Participants will be assessed for pulmonary signs and symptoms throughout the study.

Appendix 6: Risks Associated with Tiragolumab and Atezolizumab IV FDC and Guidelines for Management of Adverse Events Associated with Tiragolumab and Atezolizumab IV FDC

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table A6-1.

Table A6-1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]

BAL = bronchoscopic alveolar lavage; FDC = fixed-dose combination.

[a] [redacted]

[b] [redacted]

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

[d] [redacted]

Table A6-1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]

BAL = bronchoscopic alveolar lavage; FDC = fixed-dose combination.

[redacted]

[a] [redacted]

[b] [redacted]

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

[d] In case of pneumonitis, tiragolumab and atezolizumab IV FDC should not be resumed after permanent discontinuation.

HEPATIC EVENTS

Participants eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table A6-2.

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

Table A6-2 Management Guidelines for Hepatic Events

Event	Management
Guidelines for participants <u>without</u> hepatocellular carcinoma	
[redacted]	[redacted]
[redacted]	[redacted] • [redacted] [a] • [redacted] • [redacted] • [redacted] [c]

FDC = fixed-dose combination; LFT = liver function test.

[a] [redacted]

[b] [redacted]

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

Table A6-2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Guidelines for participants without hepatocellular carcinoma (cont.)	
[redacted]	[redacted]
Guidelines for participants with hepatocellular carcinoma	
[redacted]	[redacted]

FDC=fixed-dose combination; LFT=liver function test.

[redacted]

[redacted]

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

Table A6-2 Management Guidelines for Hepatic Events (cont.)

Guidelines for participants with hepatocellular carcinoma (cont.)	
Event	Management
[redacted]	• [redacted] [c] • [redacted] • [redacted] • [redacted] • [redacted]

FDC = fixed-dose combination; LFT = liver function test.

[a] [redacted]

[b] [redacted]

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

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table A6-3.

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 A6-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]

FDC=fixed-dose combination; GI=gastrointestinal

[redacted]

[redacted]

c Resumption of tiragolumab and atezolizumab IV FDC may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab and atezolizumab IV FDC should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A6-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
[redacted]	• [redacted][a] • [redacted]. • [redacted] • [redacted].[b] • [redacted][c]
[redacted]	• [redacted][c] • [redacted] • [redacted] • [redacted]. • [redacted]

FDC=fixed-dose combination; GI=gastrointestinal.

a [redacted]

b [redacted]

c Resumption of tiragolumab and atezolizumab IV FDC may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab and atezolizumab IV FDC should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table A6-4.

Participants 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. Participants should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone 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 A6-4 Management Guidelines for Endocrine Events

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

FDC = fixed-dose combination; MRI = magnetic resonance imaging.

[a] [redacted]

[b] [redacted]

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

Table A6-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

FDC = fixed-dose combination; MRI = magnetic resonance imaging.

[redacted]

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

Table A6-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
[redacted]	• [redacted] [a] [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

FDC = fixed-dose combination; MRI = magnetic resonance imaging.

[a] [redacted]

[b] [redacted]

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

Table A6-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
[redacted]	• [redacted][a] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]
[redacted]	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted]

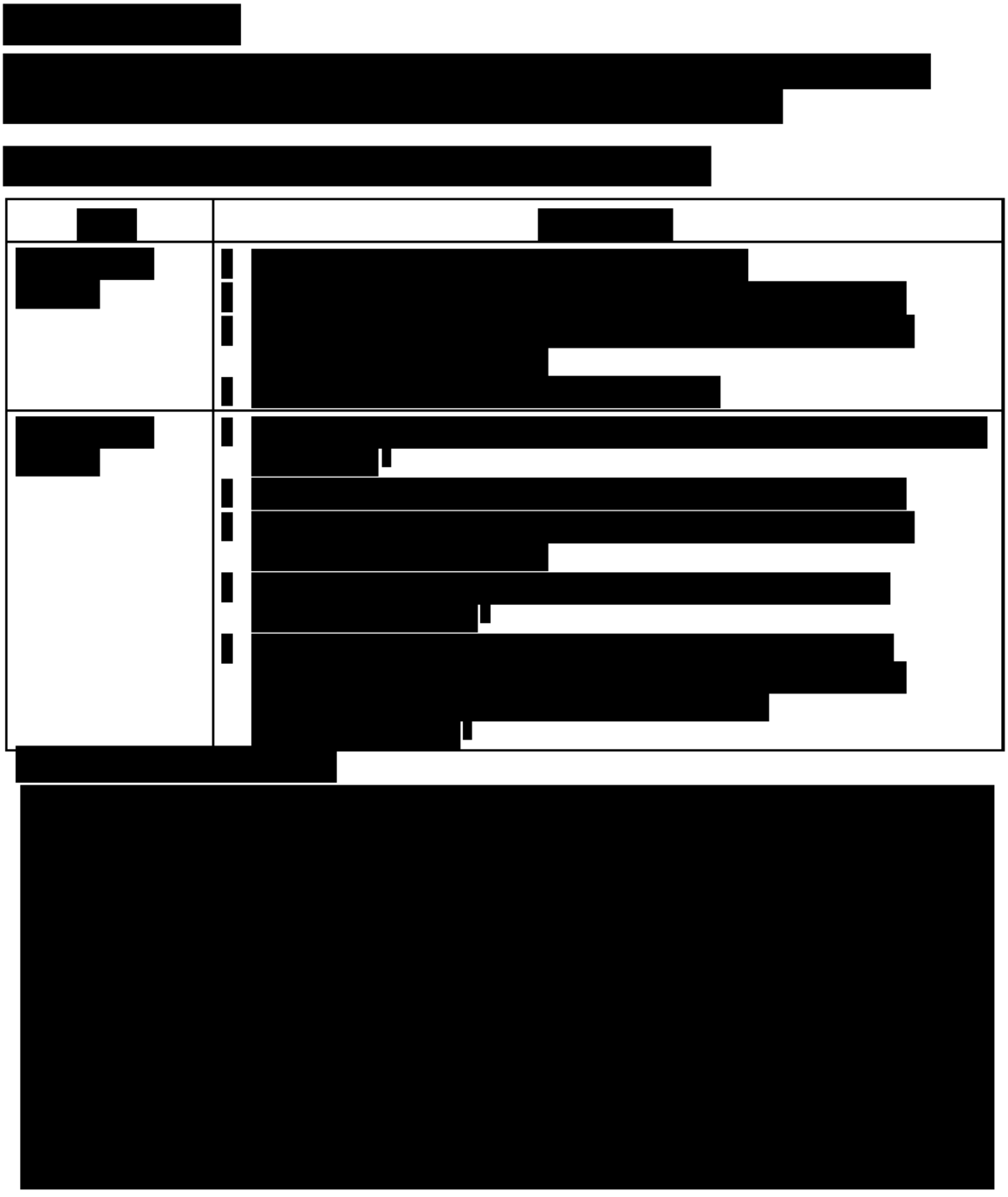
FDC = fixed-dose combination; MRI = magnetic resonance imaging.

[a] [redacted]

[b] [redacted]

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

Appendix 6: Risks Associated with Tiragolumab and Atezolizumab IV FDC and Guidelines for Management of Adverse Events Associated with Tiragolumab and Atezolizumab IV FDC



[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

IMMUNE-MEDIATED CARDIAC EVENTS

[redacted]. Management guidelines for cardiac events are provided in Table A6-6.

IMMUNE-MEDIATED MYOCARDITIS

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

[redacted]

Participants with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-6.

IMMUNE-MEDIATED PERICARDIAL DISORDERS

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

[redacted]

Appendix 6: Risks Associated with Tiragolumab and Atezolizumab IV FDC and Guidelines for Management of Adverse Events Associated with Tiragolumab and Atezolizumab IV FDC

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]

[redacted]

a [redacted]

INFUSION-RELATED REACTIONS

[redacted]

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

of tiragolumab or atezolizumab administration and are generally mild to moderate in severity. Guidelines for medical management of IRRs during Cycle 1 are provided in Table A6-7. [redacted].

Table A6-7 Management Guidelines for Infusion-Related Reactions

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted][a]

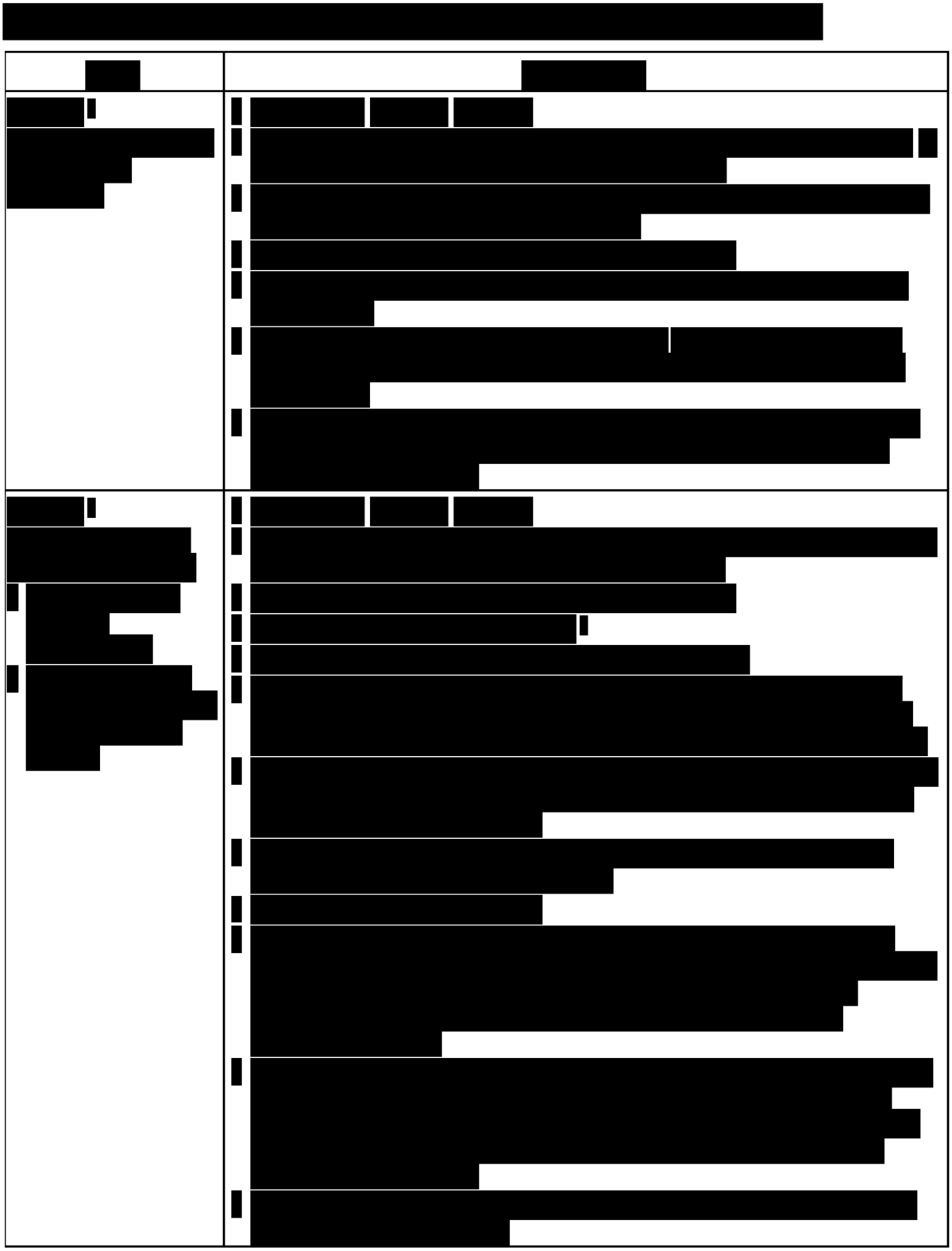
FDC = fixed-dose combination; IRR = infusion-related reaction.

[a] Resumption of tiragolumab and atezolizumab IV FDC may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge participants with tiragolumab and atezolizumab IV FDC should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

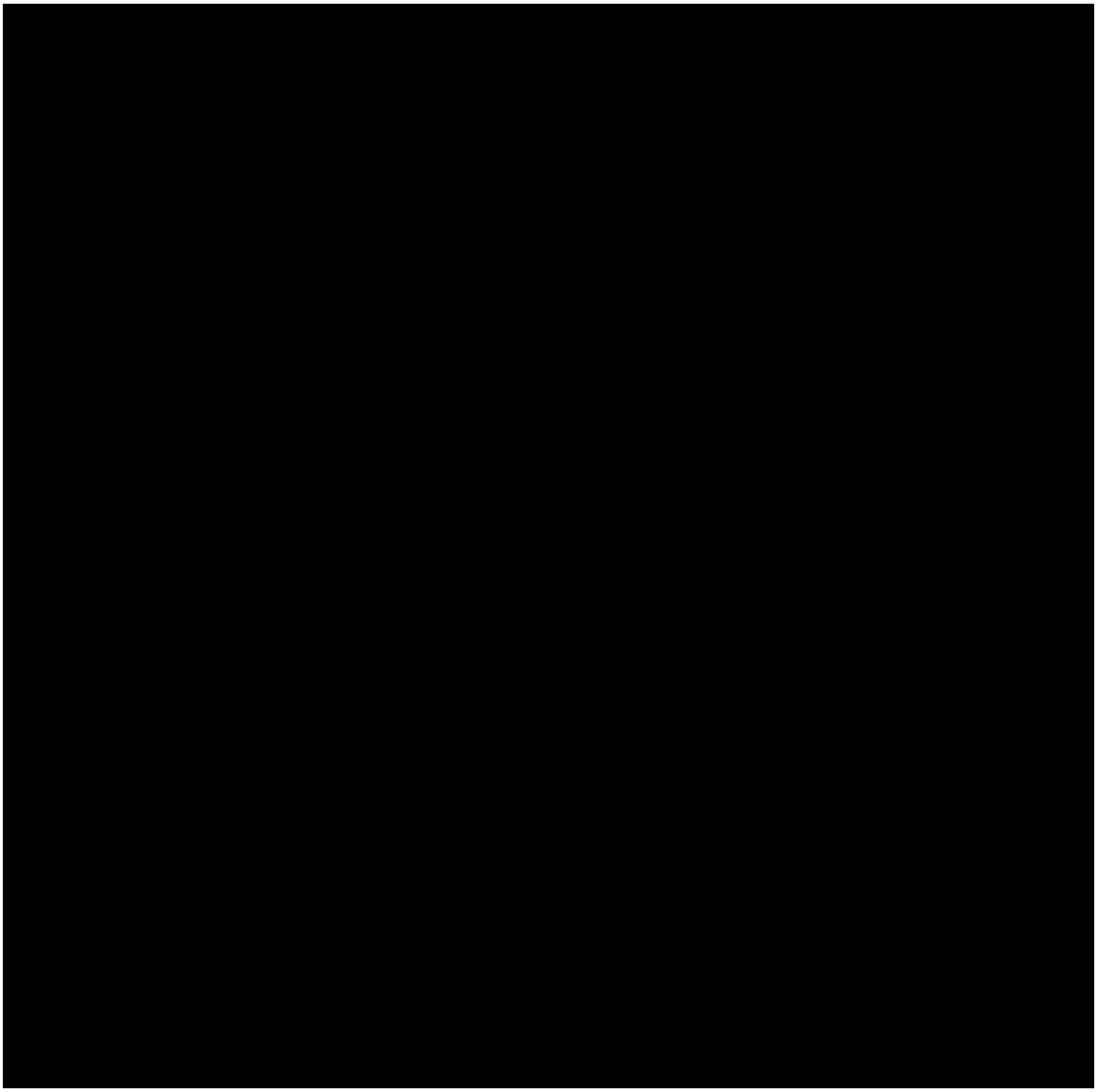
Appendix 6: Risks Associated with Tiragolumab and Atezolizumab IV FDC and Guidelines for Management of Adverse Events Associated with Tiragolumab and Atezolizumab IV FDC

[redacted]

Appendix 6: Risks Associated with Tiragolumab and Atezolizumab IV FDC and Guidelines for Management of Adverse Events Associated with Tiragolumab and Atezolizumab IV FDC



Appendix 6: Risks Associated with Tiragolumab and Atezolizumab IV FDC and Guidelines for Management of Adverse Events Associated with Tiragolumab and Atezolizumab IV FDC



PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table A6-9.

Appendix 6: Risks Associated with Tiragolumab and Atezolizumab IV FDC and Guidelines for Management of Adverse Events Associated with Tiragolumab and Atezolizumab IV FDC

Table A6-9 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
[redacted]	[redacted]
[redacted]	• [redacted] [a] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]

FDC=fixed-dose combination; GI=gastrointestinal.

[a] [redacted]

[b] [redacted]

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

Table A6-9 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
[redacted]	• [redacted] [a] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] [c]
[redacted]	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted]

FDC = fixed-dose combination; GI = gastrointestinal.

[a] [redacted]

[b] [redacted]

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

DERMATOLOGIC EVENTS

The majority of cases of rash reported with the use of tiragolumab and/or atezolizumab were mild in severity and self-limiting, with or without pruritus. [redacted] Management guidelines for dermatologic events are provided in Table A6-10.

Table A6-10 Management Guidelines for Dermatologic Events

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]

FDC = fixed-dose combination.

[redacted]

[redacted]

c Resumption of tiragolumab and atezolizumab IV FDC may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab and atezolizumab IV FDC should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A6-10 Management Guidelines for Dermatologic Events (cont.)

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

FDC = fixed-dose combination.

[a] [redacted]

[b] [redacted]

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

NEUROLOGIC DISORDERS

Participants may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. *Myasthenia may be associated with myositis (see section on immune-mediated myositis) and participants should be managed accordingly.*

Management guidelines for neurologic disorders are provided in Table A6-11, with specific guidelines for myelitis provided in Table A6-12.

Table A6-11 Management Guidelines for Neurologic Disorders

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

a [redacted]

b [redacted]

c [redacted]

Table A6-11 Management Guidelines for Neurologic Disorders (cont.)

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

[redacted]

a [redacted]

b [redacted]

c [redacted]

Appendix 6: Risks Associated with Tiragolumab and Atezolizumab IV FDC and Guidelines for Management of Adverse Events Associated with Tiragolumab and Atezolizumab IV FDC

[redacted]

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	

[redacted]

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any participant 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.

[redacted]

Participants with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-13.

Table A6-13 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
[redacted]	• [redacted]

FDC = fixed-dose combination.

RENAL EVENTS

Eligible participants must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Participants 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 participant to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Participants with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-14.

Table A6-14 Management Guidelines for Renal Events

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

[redacted]

a [redacted]

b [redacted]

c [redacted]

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. [redacted]

Participants with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-15.

Table A6-15 Management Guidelines for Immune-Mediated Myositis

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]

[redacted]

a [redacted]

b

c [redacted]

Table A6-15 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
[redacted]	• [redacted]

[redacted]

a [redacted]

b [redacted]

c [redacted]

Table A6-15 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
[redacted]	• [redacted]

[redacted]

a [redacted]

b [redacted]

c [redacted]

[redacted]

[redacted]

[redacted]

Appendix 6: Risks Associated with Tiragolumab and Atezolizumab IV FDC and Guidelines for Management of Adverse Events Associated with Tiragolumab and Atezolizumab IV FDC

[redacted]

Event	Management
[redacted]	[redacted]

[redacted]

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Appendix 7
Preexisting Autoimmune Diseases and Immune Deficiencies

Participants should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Participants 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 participants with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Participants 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 tiragolumab and atezolizumab for participants who have previously experienced a severe or life-threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Appendix 8
Anaphylaxis Precautions

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

REQUIRED EQUIPMENT AND MEDICATION

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

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), SC, IV, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

PROCEDURES

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

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

Ask the participant to return for a second immunogenicity sample collection at the time of washout, if appropriate.

Appendix 9
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 the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions and 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 lungs, 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, positron emission tomography (PET) 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 participant, these are preferred for selection as target lesions.

Lesions with prior local treatment:

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

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the

treatment start and not usually more than 4 weeks prior to 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 assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

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

CT AND MRI SCANS

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

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without MRI 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 participants who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (with or without MRI IV contrast) 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 participant should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality because the same lesion may appear to have a different size using a new modality.

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

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

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and 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 20×30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

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

CALCULATION OF SUM OF DIAMETERS

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

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to <10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, given that 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 is 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 is 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 during 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 the 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 the 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 "unequivocal 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 following criteria used to determine objective tumor response for target lesions are provided:

- 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 a CR or a PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

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

- CR: Disappearance of all non-target lesions
  - 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
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

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

NEW LESIONS

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

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

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A9-1 provides a summary of the overall response status calculation at each response assessment timepoint for participants.

Table A9-1 Criteria for Overall Response at a Single Timepoint

Target Lesions	Non-Target Lesions	New Lesions	Timepoint Response
CR	CR	No	CR
CR	Non-CR/non-PD or NE	No	PR
PR	CR, non-CR/Non-PD, or NE	No	PR
SD	CR, non-CR/Non-PD, or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
CR	NED [a]	No	CR
PR	NED [a]	No	PR
SD	NED [a]	No	SD

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

[a] No non-target lesions identified at baseline.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

SPECIAL NOTES ON RESPONSE ASSESSMENT

Participants with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "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 treatment. The objective response status of such participants is to be determined by evaluation of target and non-target lesions as shown in Table A9-1.

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.

Fluorodeoxyglucose (FDG)-PET is **not yet validated** for use in clinical trials to determine response but may complement CT/MRI in the assessment of progression.

FDG-PET imaging to identify new lesions is described in the following table.

Baseline FDG-PET	Post-Baseline FDG-PET	Determination
Negative FDG-PET	Positive FDG-PET	New lesion (PD)
None	Positive FDG-PET corresponds to a new site of disease confirmed by CT/MRI	New lesion (PD)
None	Positive FDG-PET not confirmed as a new site of disease on CT/MRI	Additional follow-up CT/MRI scans are needed to determine if there is truly progression occurring at that site. If so, new lesion (PD) with the date of PD being the date of the initial abnormal FDG-PET scan date If not, it is not a new lesion.
None	Positive FDG-PET that corresponds to a preexisting site of disease on CT/MRI that is not progressing on the basis of the anatomic images	Not a new lesion

CT = computed tomography; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography.

Note: A positive FDG-PET scan lesion indicates one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

REFERENCES

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

Schwartz LH., Litiére S, de Vries SE, et al. RECIST 1.1–update and clarification: from RECIST Committee. Eur J Cancer 2016; 62:132–7.

Appendix 10
Eastern Cooperative Oncology Group (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

Appendix 11
New York Heart Association Classification of Functional Cardiac Capacity

Class	Description
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

From: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964:114.

Appendix 12
Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Product Name	IMP Designation	Marketing Authorization Status in EEA and UK	Used within Marketing Authorization
tiragolumab + atezolizumab IV FDC (RO7538483)	IMP (test product)	Not approved	Not applicable

EEA = European Economic Area; FDC = fixed-dose combination; IMP = investigational medicinal product; UK = United Kingdom

Appendix 13 Protocol Amendment History

A rationale for the current amendment precedes the Table of Contents.

PROTOCOL AMENDMENT, VERSION 3: (3 MARCH 2023)

Protocol GO44096 has been amended [redacted] Changes to the protocol, along with a rationale for each change, are summarized below:

- To align with Table 2 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples, plasma samples have been added to the collection for biomarker assessments throughout(Sections 1.3, 4.1, 4.2.5, and 8.7).
- [redacted]
- The language regarding administration of subsequent infusions of tiragolumab and atezolizumab, and the observations after administration of subsequent infusions have been simplified for clarity (Section 6.1).
- [redacted]
- [redacted]
- [redacted]

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.

PROTOCOL AMENDMENT, VERSION 2: (14 DECEMBER 2022)

[redacted] Additionally, the protocol has been amended to align with the Tiragolumab Investigator's Brochure (IB), Version 7 and the Atezolizumab IB, Version 19 and addenda.

Appendix 13: Protocol Amendment History

Changes to the protocol, along with a rationale for each change, are summarized below:

- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front matter and Section 8.3.9). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.
- The synopsis has been simplified to align with CTR and other guidelines.
- [redacted]
- The Schedule of Activities has been updated to include the optional prescreening Informed Concent Form (ICF) for PD-L1 testing alongside the Master ICF (Section 1.3, Table 1).
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Clarified that tissue analysis will be performed by Roche Tissue Diagnostics central laboratory (Section 1.3, Table 1, and Sections 4.1 and 5.1.1)
- [redacted]
- [redacted]
- [redacted]
- In alignment with the In Vitro Diagnostic Medical Devices Regulation, the Clinical Investigation Identification Number (CIV ID) has been added to the title page of the

protocol. Text has also been added to indicate that the [redacted] is investigational and reference to the associated clinical performance study plan has been included (Section 8.7).

- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 8.10.6).
- [redacted]
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section A1–4).
- [redacted]
- The Sponsor record retention policy has been clarified (Section A1–7).
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- The association between anti-drug antibodies (ADAs) and infusion-related reactions (IRRs) to tiragolumab has been removed as a low incidence of ADAs against tiragolumab and no association between ADAs and IRRs have been observed to date (Section A5–1.1.1).
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

[redacted]

  - [redacted]

- Risk descriptions in the atezolizumab and/or tiragolumab adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 19 (Appendix 6).

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.

Appendix 14
Abbreviations

Abbreviation or Term	Definition
ADA	anti-drug antibody
ALK	anaplastic lymphoma kinase
ASCO-CAP	American Society of Clinical Oncology–College of American Pathologists
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration–time curve
CC	cervical cancer
CCP	cyclic citrullinated peptide
CHO	Chinese hamster ovary
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CIT	cancer immunotherapy
CL	*clearance*
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CRO	contract research organization
CSR	cytokine release syndrome
CR	complete response
CT	computed tomography
DAIDS	Division of AIDS
DOR	duration of response
EBUS-TBNA	endobronchial ultrasound-transbronchial needle aspiration
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	*Electrocardiogram*
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ER	estrogen receptor
ESCC	esophageal squamous cell carcinoma
Fc	fragment crystallizable
FDC	fixed-dose combination
FFPE	formalin-fixed paraffin-embedded

Appendix 14: Abbreviations

Abbreviation or Term	Definition
FNA	fine-needle aspiration
GC	*gastric cancer*
GEJ	gastroesophageal junction cancer
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HNSCC	head and neck squamous cell carcinoma
ICH	International Council for Harmonisation
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IMC	*Internal Monitoring Committee*
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISH	in situ hybridization
IVD	*in vitro diagnostic*
IxRS	interactive voice or web-based response system
LPLV	last participant, last visit
mAb	monoclonal antibody
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PET	positron emission tomography
PK	pharmacokinetic
PR	partial response

Appendix 14: Abbreviations

Abbreviation or Term	Definition
Q3W	every 3 weeks
Q4W	every 4 weeks
QTcF	QT interval corrected through use of Fridericia's formula
RCC	renal cell cancer
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RF	rheumatoid factor
RBC	red blood cell
RBR	Research Biosample Repository
RTD	Roche Tissue Diagnostics
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SITC	Society for Immunotherapy of Cancer
TC	tumor cell
TIGIT	T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains
TKI	*tyrosine kinase inhibitor*
TNBC	triple-negative breast cancer
TNF–α	tumor necrosis factor–α
TPS	tumor proportion score
UBC	urothelial bladder cancer
ULN	upper limit of normal
V_{ss}	volume of distribution at steady state
WBC	white blood cell
WES	whole exome sequencing
WGS	whole genome sequencing

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