Official Title: An Open-Label, Multicenter, Phase IB Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Anti-Tumor Activity of RO7296682 in Combination with Atezolizumab in Participants with Advanced and/or Metastatic Solid Tumors

NCT Number: NCT04642365

Document Date: Protocol Version 4: 21-Dec-2022

PROTOCOL

TITLE:	**AN OPEN-LABEL, MULTICENTER, PHASE IB STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY ANTI-TUMOR ACTIVITY OF RO7296682 IN COMBINATION WITH ATEZOLIZUMAB IN PARTICIPANTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS**
PROTOCOL NUMBER:	BP42595
VERSION:	4
EUDRACT NUMBER:	2020-003164-82
IND NUMBER:	151864
TEST PRODUCT:	RO7296682 and atezolizumab
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 20 August 2020
DATE AMENDED:	Version 2: 3 March 2021 Version 3: 16 December 2021 Version 4: see electronic signature and date stamp on the final page of this document

PROTOCOL ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, MULTICENTER, PHASE IB STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY ANTI-TUMOR ACTIVITY OF RO7296682 IN COMBINATION WITH ATEZOLIZUMAB IN PARTICIPANTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please keep the signed original form in your study files, and return a copy to your local Site Monitor.

PROTOCOL AMENDMENT, VERSION 4
RATIONALE

Immune-mediated pericardial disorders, immune-mediated myelitis, and facial paresis have been defined as new identified risks for atezolizumab. Protocol BP42595 has been amended to incorporate these changes (Section 8.3.6 and Appendix 12).

Furthermore, the management guidelines for infusion-related reactions/cytokine-release syndrome (Section 8.3.9.2) and for pulmonary events, hepatic events, gastrointestinal events, endocrine events, immune-mediated myocarditis, pancreatic events, dermatologic events, neurologic disorders, immune-mediated meningoencephalitis, renal events, and immune-mediated myositis (Appendix 12) have been updated.

The general recommendations for management of any other AEs that may occur but are not specifically listed in the organ specific immune-mediated adverse event management guidelines in Appendix 12 have been aligned with the Investigator's Brochure (Section 8.3.9.3).

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BML	Below measurable limit
C1D1	Cycle 1 Day 1
CL	Clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central nervous system
CPI	Checkpoint inhibitor
COVID-19	Coronavirus disease 2019
CR	Complete response
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ctDNA	Circulating tumor DNA
CTL	Cytotoxic T lymphocyte
DCR	Disease control rate
DLAE	Dose-limiting adverse event
DLT	Dose-limiting toxicities
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ECOG	Eastern Cooperative Oncology Group
EiH	Entry into human
EOI	End of infusion

Abbreviation	Definition
EsC	Esophageal cancer
EU	European Union
EWOC	Escalation with overdose control
FDA	Food and Drug Administration
FFPE	Formaldehyde fixed-paraffin-embedded
FSH	Follicle-stimulating hormone
GGT	Gamma-glutamyl transferase
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis
HNSCC	Head and neck squamous cell carcinoma
HR	Heart rate
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICU	Intensive care unit
IDO	Indoleamine-pyrrole 2,3-dioxygenase
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG	Immunoglobulin G
imAE	Immune-mediated adverse event
IMC	Internal Monitoring Committee
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
iRECIST	Immune response evaluation criteria in solid tumors
IUD	Intrauterine device
IV	Intravenous
IxRS	Interactive (voice/web) response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoproteins
LFT	Liver function test
LPLV	Last participant, last visit
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MAS	Macrophage activation syndrome
mCRM	Modified continual reassessment method

Abbreviation	Definition
MEL	Melanoma
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple-gated acquisition scan
NCI	National Cancer Institute
NGS	Next generation sequencing
NSAESI	Non-serious adverse event of special interest
NSCLC	Non-small cell lung cancer
OBD	Optimal biological dose
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
OvCa	Ovarian cancer
PD	Pharmacodynamic
PD	Progressive disease (Appendix 14 only)
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Prothrombin time
Q3W	Every 3 weeks
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia's correction factor
RBR	Research biosample repository
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RO	Receptor occupancy
ROPRO	Real wOrld PROgnostic (score)
RP2D	Recommended Phase 2 dose
RR	RR interval
SAE	Serious adverse event
SC	Subcutaneous
SD	Stable disease

Abbreviation	Definition
SDEC	Safety and Dose Escalation Committee
SoA	Schedule of activities
SoC	Standard of care
$t_{1/2}$	Half-life
TDO	Tryptophan 2,3-dioxygenase
Teff	T-effector cells
t_{max}	Time of maximum concentration observed
TME	Tumor microenvironment
TNBC	Triple-negative breast cancer
Treg	T-regulatory cell
TSH	Thyroid-stimulating hormone
TTE	Transthoracic echocardiogram
UC	Urothelial carcinoma
ULN	Upper limit of normal
V	Volume
Vss	Volume of distribution at steady-state
WES	Whole exome sequencing
WGS	Whole genome sequencing
WOCBP	Women of childbearing potential

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**AN OPEN-LABEL, MULTICENTER, PHASE IB STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY ANTI-TUMOR ACTIVITY OF RO7296682 IN COMBINATION WITH ATEZOLIZUMAB IN PARTICIPANTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS**
SHORT TITLE	**A PHASE IB STUDY TO EVALUATE RO7296682 IN COMBINATION WITH ATEZOLIZUMAB IN PARTICIPANTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS**
PROTOCOL NUMBER:	BP42595
VERSION:	*4*
TEST PRODUCT:	RO7296682
PHASE:	I

RATIONALE

Patients with advanced solid tumors have benefitted from recent treatment modalities beyond chemotherapy, and in particular, from checkpoint inhibitor (CPI) therapy. However, despite recent advances with CPI treatment, many patients are refractory to or acquire resistance to current therapies, with response rates varying between 20% and 30% when used as monotherapy. There is therefore an urgent unmet medical need to define rational combination therapies to overcome resistance mechanisms. Multiple studies exploring transcriptome data and/or cell phenotypes have explored the contribution of T-regulatory cell (Treg) tumor infiltration to cancer outcome. Tregs suppress antigen-specific anti-tumor immune responses, thus allowing for tumor growth. High levels of Tregs are associated with poor prognosis in several human cancers. CD25 (the IL-2 receptor alpha chain) is a highly expressed cell surface lineage marker of Tregs and is critical for their survival. RO7296682 is a monoclonal antibody (mAb) designed to bind selectively to CD25 in order to deplete Tregs, while not interfering with the IL-2 signaling. There is accumulating evidence that programmed death-1 (PD-1) is expressed on activated Treg cells; thus, the activity of Treg cells could be influenced by PD-1/L1 pathway blockade. Combining RO7296682 with atezolizumab (TECENTRIQ®), a mAb that targets the programmed death-ligand 1 (PD-L1), may complement the mechanism of action of atezolizumab and result in improved anti-tumor activity. This Phase Ib study aims to establish the safety, pharmacokinetics (PK) and pharmacodynamics (PD) as well as preliminary anti-tumor activity of RO7296682 in combination with atezolizumab in selected solid tumors.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
All Parts (Dose Escalation [Part I] and Dose Expansion [Part II and Part III])	
To evaluate the safety, tolerability, maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) (Part I only) of RO7296682 when administered in combination with atezolizumab.	• Nature and frequency of adverse events (AEs) with severity determined according to NCI CTCAE v5.0 • Nature and frequency of dose-limiting toxicities (DLTs) in Part I
Primary (Dose Expansion Part II and Part III)	
To evaluate the preliminary anti-tumor activity of RO7296682 when administered in combination with atezolizumab.	• Objective response rate (ORR) according to RECIST v1.1
Secondary (Dose Escalation, Part I)	
To evaluate the preliminary anti-tumor activity of RO7296682 when administered in combination with atezolizumab.	• ORR according to RECIST v1.1
Secondary (Dose-Escalation [Part I] and Dose Expansion, Part II and Part III)	
To further characterize the anti-tumor activity of RO7296682 when administered in combination with atezolizumab.	• Disease control rate (DCR) defined as response rate (RR) and stable disease (SD) • Duration of response (DoR) • Progression-free survival (PFS) All according to RECIST v1.1 • Overall survival (OS), if data are mature at the time of analysis
To investigate the pharmacokinetic (PK) profile of RO7296682 and atezolizumab after administration of RO7296682 in combination with atezolizumab.	• PK profiles and parameters derived for RO7296682 and atezolizumab, as appropriate, including but not limited to: o Area under the curve (AUC) o Minimum (C_{min}) and maximum (C_{max}) concentration o Time of maximum concentration (T_{max}) o Volume of distribution at steady-state (Vss) o Half-life ($t_{1/2}$)
To characterize the pharmacodynamic (PD) effects of RO7296682 in combination with atezolizumab on peripheral blood cells and/or the tumor microenvironment.	Correlate RO7296682 exposure and clinical endpoints with baseline levels and on-treatment changes of blood and tumor biomarkers, including but not limited to: • Treatment-induced changes in Treg levels in blood and/or tumor • Treatment-induced changes in Teff/Treg ratio of blood and tumor

OVERALL DESIGN

STUDY DESIGN

Study BP42595 is an open-label, multicenter, basket trial to evaluate the anti-tumor activity of RO7296682 in combination with atezolizumab over a range of advanced and/or metastatic solid tumors. The study includes three parts as described below.

- Part I: RO7296682 dose escalation in combination with atezolizumab.
- Part II: RO7296682 dose expansion in combination with atezolizumab in participants with an [redacted].
- Part III: RO7296682 in combination with atezolizumab in tumor-specific expansion cohorts.

TREATMENT GROUPS AND DURATION

Part I

To determine the RP2D/MTD, safety, tolerability, PK, and PD profile of escalating doses of RO7296682 when administered with a fixed dose of atezolizumab in participants with advanced and/or metastatic non-small cell lung cancer (NSCLC), melanoma (MEL), head and neck squamous cell carcinoma (HNSCC), esophageal cancer (EsC), triple-negative breast cancer (TNBC), and ovarian cancer (OvCa) who have progressed on all standard therapies, are intolerant to standard of care (SoC), and/or are non-amenable to SoC, or for whom SoC does not exist. The starting dose of RO7296682 will be [redacted] mg and the maximum dose is planned to be [redacted] mg.

Part II

Part II will commence once the RP2D/MTD of RO7296682 in combination with atezolizumab in Part I has been determined. Participants must fulfill the following criteria:

- Histologically confirmed advanced and/or metastatic NSCLC, MEL, HNSCC.
- [redacted] tumor phenotype confirmed centrally based on the most recent archival tumor specimen.
- Acquired resistance to most recent PD-1/PD-L1 treatment.

Part III

Part III is exploratory, adaptive in nature, and designed to add or stop expansion cohorts, based on emerging data from this study or other RO7296682 studies and based on emerging treatment landscapes (e.g., chemotherapy in addition to PD-1/PD-L1 treatment in certain indications). Should the emerging treatment landscape warrant adding new combination partner(s) as SoC in addition to RO7296682 and atezolizumab, a new cohort exploring the new combination in a particular indication will be opened after a protocol amendment. Enrollment in one of the three Part III tumor cohorts (namely NSCLC, HNSCC, and MEL) will commence according to specific gating criteria.

The IMPs are:

- RO7296682 administered via IV infusion as ascending flat doses (every three weeks [Q3W]).
- Atezolizumab administered via IV infusion at 1200 mg (Q3W).

LENGTH OF STUDY

The maximum duration of the study for each participant will be up to 31 months, divided as follows:

- Screening: Days -28 to -1.
- Treatment Period: Cycle 1 Day 1 (C1D1) to Month 24 (may be modified if supported by emerging data).
- End of Treatment Visit: 28 (± 7) days after last dose.

- Safety follow-up: 135 (± 30) days after last treatment with RO7296682 in combination with atezolizumab.
- Survival follow-up: 90 (± 7) days after the safety follow-up visit; then every 3 months (± 14 days) until death, lost to follow-up, or until study closure by the Sponsor, whichever occurs first.

END OF STUDY

The end of the study is defined as the date of the last participant's last visit per protocol (includes the safety follow-up visit 135 [± 35] days after last dose of study drug) or the date on which the last data point from the last participant required for statistical analysis is received (last participant, last observation), whichever is the latest date. Because of the exploratory nature of this clinical study, its conduct can be discontinued at any time at the discretion of the Sponsor.

INTERNAL MONITORING COMMITTEE

For Part III (Dose Expansion) of this study, an Internal Monitoring Committee will be used to review accumulating clinical data in order to assess subject risk and benefit on an ongoing basis.

PARTICIPANT POPULATION

The participants in this study will be adult male and female participants with advanced and/or metastatic solid tumors, who fulfill all eligibility criteria.

KEY INCLUSION CRITERIA

- Diagnosis of advanced and/or metastatic solid tumors. Participants whose tumors have known sensitizing mutations must have experienced disease progression (during or after treatment) or intolerance to treatment with a respective targeted therapy. More detailed inclusion criteria for Parts I, II, and III are defined in Section 5.1 of the protocol.
- Measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1. (RECIST v1.1). Previously irradiated lesions must not be counted as target lesions, unless there has been demonstrated progression in the lesion and no other target lesions are available.
- Life expectancy of ≥ 12 weeks, as assessed by the Investigator and supported by the Real wOrld PROgnostic (ROPRO) score. In case the patient's score is above the cut-off of 0.7, the patient may still be enrolled provided that per the Investigator's judgment the clinical benefits of enrollment will outweigh the risks.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
- Participants must have progressed on all standard therapies, are intolerant to and/or are non-amenable to SoC.
- Able to provide the most recent archival tumor tissue samples. If no archival samples are available, refer to inclusion criteria for Part I and Part II and appendices for Part III.
- Able to provide skin punch biopsy at screening and at C2D8.
- For Part II and Part III able to provide a fresh tumor biopsy at screening and C2D8.
- Adequate organ functions.
- Additional adequate laboratory parameters obtained prior to the first study treatment (C1D1): serum albumin; prothrombin time (PT); activated partial thromboplastin time (aPTT).
- Participants on therapeutic anticoagulation must be on a stable anticoagulant regimen.
- Adequate contraception.

Specific Inclusion Criteria for Parts I, II, and III

See Section 5.1 of the protocol.

KEY EXCLUSION CRITERIA

- Known hypersensitivity to any of the components of RO7296682 and atezolizumab.
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion protein.
- Participants who experienced infusion-related reactions (IRRs), skin toxicity, and/or immune-mediated AEs of Grade ≥ 3 in conjunction with previous CPI treatment are excluded (with the exception of endocrinopathy managed with replacement therapy or controlled type 1 diabetes mellitus on a stable insulin regimen).
- AEs from any prior anti-cancer therapy that have not resolved to Grade ≤ 1 except for alopecia, vitiligo, or endocrinopathy managed with replacement therapy, and Grade ≤ 2 peripheral neuropathy.
- History or clinical evidence of central nervous system (CNS) primary tumors or metastases including leptomeningeal metastases.
- Participants with another invasive malignancy in the last two years.
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.
- Severe dyspnea or requiring supplemental oxygen therapy at rest.
- Significant cardiovascular disease within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina.
- Known active bacterial, viral, fungal, mycobacterial, or other pathogens, or any major episode of infection.
- Positive HIV test at screening.
- Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
- Vaccination with live vaccines within 28 days prior to C1D1 or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab.
- Known clinically significant liver disease.
- Major surgical procedure or significant traumatic injury within 28 days prior to first RO7296682 and atezolizumab infusion, or anticipation of the need for major surgery before end of treatment period.
- Participants with current or history of wound healing complications and/or participants with open wounds until complete resolution.
- Prior allogeneic stem cell or solid organ transplantation.
- Dementia or altered mental status that would prohibit informed consent.
- History of Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug rash with eosinophilia and systemic symptoms.
- Active or history of autoimmune disease or immune deficiency.
- Prior treatment with CPIs, immunomodulatory agents and/or mAbs, and/or mAb derived therapies, or immunostimulatory agents is not allowed. For Part II only: Prior treatment with anti-CTLA4 is prohibited.
- Prior treatment with a CC chemokine receptor 4 (CCR4)-targeting (e.g., mogamulizumab) or a CD25-targeting agent (e.g., basiliximab) is prohibited. Note: patients previously treated with single agent RO7296682 in the WP41188 study may be included in this study.
- Treatment with standard radiotherapy, any chemotherapeutic agent, targeted therapy, or treatment with any other investigational drug within 28 days or 5 half-lives of the drug (whichever is shorter), prior to C1D1 is prohibited.
- Treatment with systemic immunosuppressive medications.
- Radiotherapy within the last 4 weeks before start of study drug treatment.

NUMBER OF PARTICIPANTS

The maximum total number of participants in the dose escalation portions of Part I will be approximately 60 DLT evaluable participants on a Q3W schedule.

Approximately 60 CPI-experienced participants with NSCLC, HNSCC, and MEL will be enrolled in the expansion cohort in Part II.

In Part III, each tumor-specific cohort for NSCLC, HNSCC, and MEL may be opened for approximately 20 response-evaluable participants.

CONCOMITANT MEDICATIONS

Use of the following therapies is prohibited during the study and for at least 28 days or 5 half-lives of the study drug (whichever is shorter), prior to initiation of study treatment, unless otherwise specified below:

- Investigational or unlicensed/unapproved agents.
- Immunotherapy/radio-immunotherapy.
- Chemotherapy/targeted therapy.
- Radiotherapy (with the exception of limited field palliative radiotherapy).
- Biologic agents (e.g., bevacizumab, cetuximab)
  Note: Insulin is allowed.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) 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 RO7296682/atezolizumab.
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide.
- Live, attenuated vaccines (e.g., Flu – Mist® influenza vaccine) are prohibited at any time during the study, and for 5 months following the last dose of study treatment.

1.2 SCHEMATIC OF STUDY DESIGN

An overview of the study design is provided in Figure 1 and an overview of mandatory and optional tissue samples is provided in Figure 2.

Figure 1 Overview of Study Design

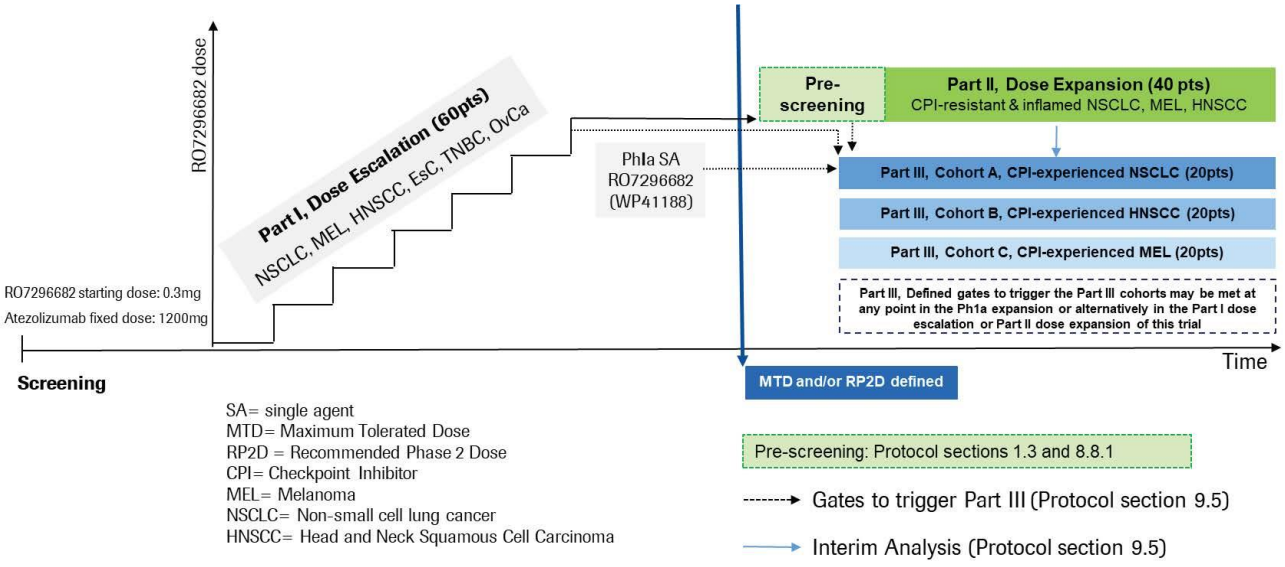
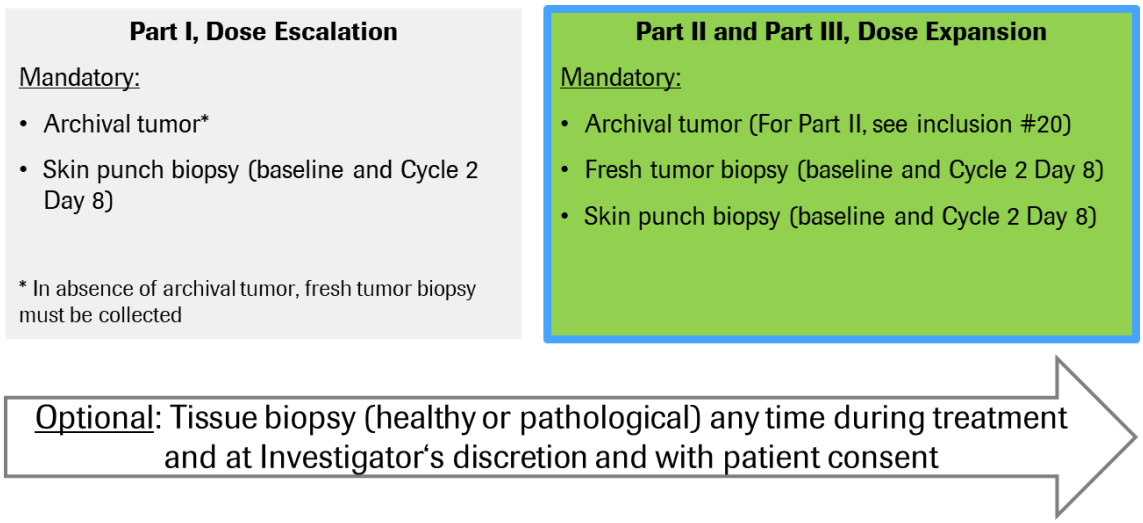


Figure 2 Overview of Mandatory and Optional Tissue Samples



1.3 SCHEDULE OF ACTIVITIES

The schedule of the activities (SoA) for Parts I, II, and III is provided in Table 1. The SoA for PK/PD sampling is provided in Table 2 for Part I and in Table 3 for Parts II and III.

Table 1 Schedule of Activities for all Parts (21-Day Cycle, Q3W)

Protocol section	Cycle	Pre-screening	Screening / Baseline	Cycle 1					Cycle 2			Cycle 3				Cycle 4					Cycle 5	Subsequent Cycles to 24 Months	End of Treatment (EoT)/ Early Discontinuation	End of Study / Safety Follow-up	Survival Follow up	Unscheduled Safety (for IRR/CRS refer to Table 2 and Table 3)
	Study visit window					± 1 d	± 2d		± 2d		± 2d	± 2d		± 2d		± 2d		± 1 d	± 2d		± 2d	± 2d	28 (± 7) days after last dose	135 (± 30) days after last dose	90 (± 7) days after Safety FU visit and then every 3 months (± 14 days)	
	Day		D-28 to D-1	Day 1	Day 2	Day 4	Day 8	Day 15	Day 1	Day 2	Day 8	Day 1	Day 2	Day 8	Day 15	Day 1	Day 2	Day 4	Day 8	Day 15	Day 1	Day 1				
	Study Week			1			2	3	4		5	7		8	9	10			11	12	13	≥ 16				
	ASSESSMENTS																									
8.8.1	Pre-Screening ICF for archival tumor	x (Part II only)																								
8.2.11	Electronic symptom questionnaire (optional)		x (Part II only)	x (continously monitored; Part II only)																						
5.1	Informed Consent		x																							
	Eligibility criteria		x																							
8.2.8	Demography		x																							
	Medical/Cancer History		x																							
8.2.1	Complete physical exam		x																							
8.1.1	Brain CT/MRI		x																							(x)
8.2.6	Chest X-ray		x																							(x)
8.2.5	Echocardiography (TTE/MUGA)		x																							
8.2.3	Oxygen saturation		x																							
8.2.8	Smoking status		x																							
8.2.10	ROPRO		x																							
8.2.2	Height		x																							
	Weight		x	x					x			x				x					x	x	x	x		(x)
8.2.9	ECOG		x	x					x			x				x					x	x	x	x		(x)
8.2.3 and 6.1.1	Vital Signs		x	Section 6.1.1	x	x	x	x	Section 6.1.1	x	x	Section 6.1.1	x	x	x	Section 6.1.1	x	x	x	x	Section 6.1.1	Section 6.1.1	x	x		(x)
8.2.1	Targeted physical exam			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		(x)
8.2.4	Triplicate 12-lead ECG		x	pre-dose					pre-dose			pre-dose											x			(x)
8.3	Adverse Events		x (continously monitored)																							(x)
6.5	Previous and Concomitant Treatments		x (continously monitored)																							(x)
	STUDY DRUG ADMINISTRATION																									
6.1.1	Administration of atezolizumab			x					x			x				x					x	x				
	Administration of RO7296682			x					x			x				x					x	x				
6.1.2	Premedication			(x)					(x)			(x)				(x)					(x)	(x)				
	TUMOR ASSESSMENT																									
8.1.1 and 8.1.2	CT/MRI scan		x												x							x	x	x		(x)

Table 1 Schedule of Activities for all Parts (21-Day Cycle, Q3W) (cont.)

Protocol section	Cycle	Pre-screening	Screening / Baseline	Cycle 1					Cycle 2			Cycle 3				Cycle 4					Cycle 5	Subsequent Cycles to 24 Months	End of Treatment (EoT)/ Early Discontinuation	End of Study / Safety Follow-up	Survival Follow up	Unscheduled Safety (for IRR/CRS refer to Table 2 and Table 3)
	Study visit window					± 1 d	± 2d		± 2d		± 2d	± 2d		± 2d		± 2d		± 1 d	± 2d		± 2d	± 2d	28 (± 7) days after last dose	135 (± 30) days after last dose	90 (± 7) days after Safety FU visit and then every 3 months (± 14 days)	
	Day		D-28 to D-1	Day 1	Day 2	Day 4	Day 8	Day 15	Day 1	Day 2	Day 8	Day 1	Day 2	Day 8	Day 15	Day 1	Day 2	Day 4	Day 8	Day 15	Day 1	Day 1				
	Study Week			1			2	3	4		5	7		8	9	10			11	12	13	≥ 16				
	LOCAL LABORATORY ASSESSMENTS																									
8.2.7 and Appendix 4	Lipids		x																							(x)
	Viral serology (HBV, HCV, HIV)		x																							(x)
	Auto-antibody Panel		x						x			x										every 6 cycles after Cycle 3		x		(x)
	TSH, free T3 (or total T3), free T4		x	x					x			x				x					x	x	x	x		(x)
	Hematology		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		(x)
	Clinical Chemistry		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		(x)
	Coagulation		x	x			x	x	x			x				x					x	x	x	x		(x)
	Urinalysis		x	x			x	x	x		x	x		x		x			x		x	x	x	x		(x)
	Pregnancy Test		x	Urine or serum pregnancy test performed prior to each treatment, with result available prior to dosing																			x	x		(x)
	IgE/Tryptase			Collected centrally and locally. Please refer to Table 2, Table 3 and Appendix 4																						(x)
	CENTRAL LABORATORY ASSESSMENTS																									
	Refer to Table 2 and Table 3 for sample collection timepoint details																									
	BIOPSIES																									
8.8	Archival biopsy	x (Part II only)	Refer to Table 2 and Table 3 for sample collection timepoint details																							
	Fresh tumor biopsy																									
	Healthy skin punch biopsy																									
	Optional biopsy																									
	MICROBIOME (optional)																									
8.9.1.2	**Nutritional assessment**		x																							
	Stool samples		x																	x (and every 12 weeks or at colitis)						(x)
	POST-STUDY																									
8.11.4	Survival follow-up (including patients who screen-failed due to ROPRO)																								x	

Table 2 Pharmacokinetics/Pharmacodynamics for Part I Dose Escalation

Cycle	Day	Scheduled Time (h)	Time-window	PK RO7296682[a, b, c]	ADA RO7296682[a, b, c]	PK Atezolizumab[a, b, c]	ADA Atezolizumab[a, b, c]	Receptor Occupancy	PD blood FACS	PD Cytokines	Archival sample	Mandatory healthy skin punch biopsy[e]	Optional Biopsy[f]	Blood GEP	TCR Vß	Soluble tumor and inflammation markers	Clinical Genotyping (DNA)	RBR (DNA)	RBR (RNA)	IgE/Tryptase[d]
Screening/ Baseline	D-28 to D-1							x			x	x	Any visit							
Cycle 1	Day 1	Predose - Atezolizumab and RO7296682	-4h	x	x	x	x	x	x	x				x	x	x	x	x	x	
		EOI - Atezolizumab	+ 30min			x														
		EOI - RO7296682	+ 30min	x				x	x	x										
		EOI+3 - RO7296682	± 30min	x																
	Day 2	24 - RO7296682	± 2h	x																
	Day 4	72 - RO7296682	± 24h	x				x	x	x										
	Day 8	168 - RO7296682	± 48h	x				x	x	x										
	Day 15	336 - RO7296682	± 48h	x				x	x	x										
Cycle 2	Day 1	Predose - Atezolizumab and RO7296682	-4h	x	x	x	x	x	x	x										
		EOI - RO7296682	+ 30min	x				x		x										
	Day 8	168 - RO7296682	± 48h						x	x		x								
Cycle 3	Day 1	Predose - Atezolizumab and RO7296682	-4h	x	x	x	x	x	x	x				x	x	x				
		EOI - RO7296682	+ 30min	x				x												
Cycle 4	Day 1	Predose - Atezolizumab and RO7296682	-4h	x	x	x	x	x	x	x										
		EOI - Atezolizumab	+ 30min			x														
		EOI - RO7296682	+ 30min	x				x	x	x										
		EOI+3 - RO7296682	± 30min	x																
	Day 2	24 - RO7296682	± 2h	x																
	Day 4	72 - RO7296682	± 24h	x				x	x	x										
	Day 8	168 - RO7296682	± 48h	x				x	x	x										
	Day 15	336 - RO7296682	± 48h	x				x	x	x										
Cycle 5	Day 1	Predose - Atezolizumab and RO7296682	-4h	x	x	x	x	x		x				x	x	x				
		EOI - RO7296682	+ 30min	x				x												
Subsequent Cycles[b]	Day 1	Predose - Atezoluzimab and RO7296682	-4h	x	x	x	x	x only at cycle of tumor assessment	x only at cycle of tumor assessment	x only at cycle of tumor assessment										
		EOI - RO7296682	+ 30min	x				x only at cycle of tumor assessment												
End of Treatment (EoT) Visit	28 days (± 7) after last dose	At visit		x	x	x	x	x	x	x				x	x	x				
Safety FU (135d after last dose)		At visit		x	x	x	x													
In addition, samples to be taken at the following instances:																				
In the event of an IRR/CRS ≥ G2 or with clinical signs of hypersensitivity reaction		At visit		x	x	x	x			x			Any visit							x
DLT		At visit		x	x	x	x			x										x
Unscheduled Visit		At visit		x	x	x	x	x	x	x										x

Table 3 Pharmacokinetics/Pharmacodynamics for Part II and Part III Dose Expansions

Cycle	Day	Scheduled Time (h)	Time-window	PK RO7296682[a, b, c]	ADA RO7296682[a, b, c]	PK Atezolizumab[a, b, c]	ADA Atezolizumab[a, b, c]	PD blood FACS	PD Cytokines	Archival sample	Mandatory fresh tumor biopsy[e]	Mandatory healthy skin biopsy[e]	Optional Biopsy[f]	Blood GEP	TCR Vß	Clinical Genotyping (DNA)	RBR (DNA)	RBR (RNA)	IgE/Tryptase[d]	ctDNA	WES ctDNA
Pre-screening										x (Part II)[g]											
Screening/	D-28 to D-1									x (Part III)	x	x									
Cycle 1	Day 1	Predose - Atezoluzimab and RO7296682	-4h	x	x	x	x	x	x					x	x	x	x	x		x	x
		EOI - Atezolizumab	+30min			x															
		EOI - RO7296682	+30min	x																	
	Day 2	EOI - RO7296682	± 2h	x		x		x													
	Day 8	EOI - RO7296682	± 48h	x		x		x	x												
Cycle 2	Day 1	Predose - Atezoluzimab and RO7296682	-4h	x	x	x	x	x	x												
		EOI - RO7296682	+30min	x																	
	Day 8	168 - RO7296682	± 48h								x	x									
Cycle 3	Day 1	Predose - Atezoluzimab and RO7296682	-4h	x	x	x	x							x	x					x	
		EOI - RO7296682	+30min	x																	
Cycle 4	Day 1	Predose - Atezoluzimab and RO7296682	-4h	x	x	x	x	x	x												
		EOI - Atezolizumab	+30min			x															
		EOI - RO7296682	+30min	x																	
Cycle 5	Day 1	Predose - Atezoluzimab and RO7296682	-4h	x	x	x	x							x	x					x	
		EOI - RO7296682	+30min	x																	
Subsequent Cycles[b]	Day 1	Predose - Atezoluzimab and RO7296682	-4h	x	x	x	x	x only at cycle of tumor assessment	x only at cycle of tumor assessment												
		EOI - RO7296682	+30min	x																	
End of Treatment (EoT) Visit	28 days (± 7) after last dose	At visit		x	x	x	x	x	x					x	x					x	
Safety FU (135d after last dose)		At visit		x	x	x	x														
In addition, samples to be taken at the following instances:																					
In the event of an IRR/CRS ≥ G2 or with clinical signs of hypersensitivity reaction		At visit		x	x	x	x		x				Any visit						x		
DLT		At visit		x	x	x	x		x										x		
Unscheduled Visit		At visit		x	x	x	x	x	x										x		

Footnotes for Table 2 and Table 3

a	All blood samples for PK assessments will be collected from an IV line in the opposite arm to the one for drug infusion. All times after EOI timepoint are to be taken from the end of infusion. Post dose samples except EOI are to be taken from the time of RO7296682 administration.
b	Up to Cycle 5: PK and ADA samples should be taken at **indicated timepoints**. Subsequent cycles until 6 months after 1st dose: PK and ADA samples will be taken on **Day 1** of **each cycle**. Subsequent cycles after first 6 months of treatment: PK and ADA samples will be taken only **Day 1** at **cycle of tumor assessments**.
c	PK samples will be taken (where feasible) at the time of development of any of the following events, or at the earliest possible convenience thereafter: * **DLT** * **Dose reduction** or **treatment reduction** or **interruption** due to IRR event ≥ Grade 2 or hypersensitivity - At time of interruption, collect the unscheduled PK sample and clearly record the reason this collection (i.e., due to interruption) - At infusion restart and completion, collect scheduled pre, (mid – where applicable) and post infusion time-points as noted per SoA . Note: the re-start time after the dose interruption is taken as the reference timepoint.
d	**Tryptase** and **IgE** samples will be collected for **local** analysis at onset of the reaction. If tryptase and/or IgE are elevated, a second sample for **central** IgE/tryptase analysis will be collected approximately 48 hours after onset of the reaction.
e	**Mandatory fresh tumor biopsies** collected at baseline and C2D8 for: - Part II and Part III participants only **Mandatory healthy skin punch biopsies** collected at baseline and C2D8 for: - All Parts (I, II and III)
f	**Optional biopsies** from pathological and healthy tissue may be taken at the investigator's discretion and with participant's consent at different time points. For example, but not limited to Adverse Events, disease progression or long-lasting stable disease in order to characterize the immune resistance mechanisms.
g	For Part II: please refer to protocol Section 5.1 and 8.8.1 for details on the **archival samples** and for obtaining a **pre-screening Informed consent form**.

2. INTRODUCTION

RO7296682 is a monoclonal antibody (mAb) designed to bind selectively to CD25 (the IL-2 receptor alpha chain) in order to deplete T-regulatory cells (Tregs), while not interfering with the IL-2 signaling. Combining RO7296682 with atezolizumab (TECENTRIQ®), a mAb that targets the programmed death-ligand 1 (PD-L1), may complement the mechanism of action of atezolizumab and result in improved anti-tumor activity.

This Phase Ib study aims to establish the safety, pharmacokinetics (PK), and pharmacodynamics (PD) as well as preliminary anti-tumor activity of RO7296682 in combination with atezolizumab in selected solid tumors. For details, refer to the Investigator's Brochure.

2.1 STUDY RATIONALE

Patients with advanced solid tumors have benefitted from recent treatment modalities beyond chemotherapy, and in particular, from checkpoint inhibitor (CPI) therapy. However, despite recent advances with CPI treatment, many patients are refractory to or acquire resistance to current therapies, with response rates varying between 20% and 30% when used as monotherapy (Topalian et al. 2015). There is therefore an urgent unmet medical need to define rational combination therapies to overcome resistance mechanisms. The mechanisms underlying primary and secondary resistance to various anti-tumor agents are numerous and in many cases remain poorly understood. Multiple studies exploring transcriptome data and/or cell phenotypes have explored the contribution of Treg tumor infiltration to cancer outcome (Cai et al. 2019).

Anti-CD25/RO7296682, a Treg-depleter agent

Tregs suppress antigen-specific anti-tumor immune responses, thus allowing for tumor growth. CD25 is a highly expressed cell surface lineage marker of Tregs and is critical for their survival. In this study, RO7296682, which selectively binds to CD25, will be assessed as a Treg-depleting strategy. RO7296682 is designed to mediate FcγRIIIa-dependent, CD25-targeted cell cytotoxicity (also known as antibody-dependent cell cytotoxicity) and antibody-dependent cellular phagocytosis (Buettner et al. 2018 and Kellner et al. 2017). The Fc region of RO7296682 is afucosylated and therefore outcompetes human IgG1 isotypes for binding to FcγRIIIa. RO7296682 has low affinity to CD25 and relies on avidity for effective binding. This results in preferential binding to Tregs, which are CD25 high, while it spares CD25 low expressing cells such as cytotoxic T lymphocytes (CTLs). An additional key feature of RO7296682 is that it binds CD25 while not blocking IL-2 signaling, particularly in activated T-effector cells (Teffs).

Treatment targeting the PD-1/L1 pathway

The PD-1/L1 pathway serves as an immune checkpoint to temporarily dampen the immune response in states of chronic antigen stimulation such as cancer. PD-L1 is an extracellular protein that downregulates immune response through binding to its two receptors, programmed death-1 (PD-1) and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005, Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T cell proliferation and activation, cytokine production and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007, Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank et al. 2007), and elevated PD-L1 expression is associated with a worse prognosis. Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T cells immunity. Atezolizumab, which targets the PD-1/L1 pathway, has demonstrated overall survival (OS) benefit across various malignancies, including non-small cell lung cancer (NSCLC).

Treg depletion with PD-L1 pathway blockade

There is accumulating evidence that PD-1 is expressed on activated Treg cells; thus, the activity of Treg cells could be influenced by PD-1/L1 pathway blockade (Wang et al. 2020, Kamada et al. 2019). Administration of an anti-PD-1/L1 agent may increase proliferation and activity of Treg cells, thereby enhancing their suppression activity towards CD4+ and CD8+ T cells. Treg cells present in the tumor microenvironment (TME) would act as a sink towards IL-2, a key proliferative cytokine needed for the expansion of cytotoxic T cells, resulting in a suppressed cytotoxic activity of immune effector cells. Combining RO7296682 (a Treg deplete) and atezolizumab should therefore help restore cancer cell killing via Teffs, by removing one of the resistance mechanisms following the administration of a PD-1/L1 agent.

In preclinical models, RO7296682 has demonstrated the potential to deplete Tregs and therefore enhance T-cell responses against engrafted tumors. In murine tumor models, the survival benefit of the combination of RO7296682 with anti-PD-1/L1 was established and superior to both antibodies when dosed individually.

This study investigates the combination of RO7296682 with atezolizumab (anti-PD-L1) to couple beneficial modifications of the immune microenvironment via RO7296682 with its Treg-depletion activity and via atezolizumab with its immune activation properties.

The rationale for the study design, including the study population, is provided in Section 4.2.

2.2 BACKGROUND

High levels of Tregs are associated with poor prognosis in several human cancers (Jenkins et al. 2018). CD25 is a highly expressed cell surface marker of Tregs and critical for their survival. RO7296682 preferentially binds to Tregs, while it spares CD25 low expressing cells such as CTLs. RO7296682, particularly in combination with other immune-modifying agents (such as atezolizumab) has the potential to improve anti-cancer outcomes.

RO7296682 is currently assessed as a single agent in an entry into human (EiH) Phase I study (WP41188) in participants with solid tumors. A summary of the clinical data is provided below.

Clinical Safety Data of RO7296682 in Study WP41188

As of the clinical cut-off date 10 June 2020, 21 patients had been treated with RO7296682 up to a dose of [redacted] mg. All 21 patients experienced at least one adverse event (AE), the majority of which were Grade 1 or Grade 2 in severity. There were 14 Grade 3 events reported from 8 patients, of which one was considered related. No Grade 4 or Grade 5 event was reported. Preliminary safety data suggest that RO7296682 is generally well tolerated with no dose-limiting toxicities (DLTs) observed so far in the dose-escalation part of the study. Please refer to the Investigator's Brochure for further details of the safety profile.

Clinical Pharmacokinetic and Immunogenicity Data of RO7296682 in WP41188

Preliminary data are available from the dose range [redacted] mg to [redacted] mg and were analyzed via non-compartmental analysis. RO7296682 PK was time-independent. No apparent target mediated drug disposition could be observed, even at the lowest dose tested. The clearance of 0.4 L/d falls within the range of a typical mAb (0.2 L/d to 0.5 L/d), approximately 2-fold higher than that of a typical IgG1 antibody in humans (Ryman et al. 2017).

Preliminary immunogenicity data showed negative treatment-emergent ADA titers in all treated patients.

Clinical Pharmacodynamics Data of RO7296682 in WP41188

Preliminary data are available from 16 patients in the dose escalation part of the WP41188 study. Relevant peripheral blood Treg depletion (defined as a reduction to or below 25% of baseline) was observed in 4 out of 9 patients that received RO7296682 in doses ranging from 1 mg to 2 mg.

A detailed description of the chemistry, pharmacology, and safety of RO7296682 is provided in the Investigator's Brochure.

2.3 BENEFIT/RISK ASSESSMENT

This study evaluates the safety, tolerability, and anti-tumor activity of RO7296682 in combination with atezolizumab in participants who have exhausted their standard of care (SoC) treatment.

RO7296682 is hypothesized to provide a significantly improved chance of addressing the large unmet medical need that remains for many patients with cancer, including CPI-naïve and CPI-experienced/resistant patients. Depleting CD25-expressing Tregs without affecting the number and function of Teffs, and without interfering with IL-2 signaling, has the potential to translate into clinical benefit in patients with cancer. The effects of RO7296682 are expected to create an environment that enhances the probability of an effective anti-tumor immune response. Available non-clinical data demonstrate that RO7296682 or its mouse surrogate are active and induce tumor reduction in different tumor mouse models as well as deplete Tregs in peripheral blood and tissues.

Clinical efficacy of anti-PD-1/L1 mAbs are well established. However, treatment options in CPI-experienced patients are still limited and represent an unmet need warranting research to understand the mechanisms of resistance and novel combination therapies targeting the TME. RO7296682 is hypothesized to address this large unmet medical need of CPI-experienced/resistant patients with cancer by depleting CD25-expressing Tregs and restoring the immune response to tumor cells. Available nonclinical data in mouse demonstrated an enhanced anti-cancer response of the combination therapy compared to PD-L1 or RO7296682 treatment alone (see Investigator's Brochure). Tumor types with the highest likelihood of benefit from Treg depletion were selected for this study. This was based on in-house analysis (refer to Section 4.2.1 and Section 4.2.2).

Immune-mediated AEs are a potential risk for Treg depleters, whereas they are identified risks associated with atezolizumab treatment (see atezolizumab and RO7296682 Investigator's Brochures). The expected PD effect of RO7296682 is to deplete Tregs and convert the immunosuppressive TME into a pro-inflammatory phenotype. Since a possible consequence of this mode of action is an increased adaptive T-cell immune response, a potential for the exacerbation of immune-mediated toxicities when combining RO7296682 with atezolizumab exists.

The protocol will include the following measures to prevent, minimize, and/or manage such toxicities:

- Patients with a history of autoimmune disease will be excluded from this study.
- Dose-modification guidelines.
- Pre-medication guidelines.
- Management guidelines for potential RO7296682 and atezolizumab-associated risks.

More detailed information about the known and expected benefits in the context of potential risks and expected AEs of RO7296682, is provided in the Investigator's Brochure.

In the setting of the COVID-19 pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from COVID-19. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of COVID-19.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13; Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from COVID-19 is altered by cancer immunotherapy.

Severe 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 (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 atezolizumab in combination with RO7296682. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from COVID-19.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab in combination with RO7296682 and clinical and radiologic features for COVID-19–related interstitial pneumonia. Thus, Investigators should use their clinical judgment when evaluating and managing participants with pulmonary symptoms.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 4.

Note: Due to the adaptive nature of Part III, additional cohorts, which are not described in this protocol, may be added in the study (see Appendix 6, Appendix 7, Appendix 8, and Appendix 9). For a rationale, see Appendix 9.

Table 4 Objectives and Endpoints

Objectives	Endpoints
Primary	
All Parts (Dose Escalation [Part I] and Dose Expansion [Part II and Part III])	
To evaluate the safety, tolerability, maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) (Part I only) of RO7296682 when administered in combination with atezolizumab.	• Nature and frequency of adverse events (AEs) with severity determined according to NCI CTCAE v5.0 • Nature and frequency of dose-limiting toxicities (DLTs) in Part I
Primary (Dose Expansion Part II and Part III)	
To evaluate the preliminary anti-tumor activity of RO7296682 when administered in combination with atezolizumab.	• Objective response rate (ORR) according to RECIST v1.1
Secondary (Dose Escalation, Part I)	
To evaluate the preliminary anti-tumor activity of RO7296682 when administered in combination with atezolizumab.	• ORR according to RECIST v1.1
Secondary (Dose-Escalation [Part I] and Dose Expansion [Part II and Part III])	
To further characterize the anti-tumor activity of RO7296682 when administered in combination with atezolizumab.	• Disease control rate (DCR) defined as response rate (RR) and stable disease (SD) • Duration of response (DoR) • Progression-free survival (PFS) All according to RECIST v1.1 • Overall survival (OS), if data are mature at the time of analysis
To investigate the pharmacokinetic (PK) profile of RO7296682 and atezolizumab after administration of RO7296682 in combination with atezolizumab.	• PK profiles and parameters derived for RO7296682 and atezolizumab, as appropriate, including but not limited to: o Area under the curve (AUC) o Minimum (C_{min}) and maximum (C_{max}) concentration o Time of maximum concentration (T_{max}) o Volume of distribution at steady-state (Vss) o Half-life ($t_{1/2}$)
To characterize the pharmacodynamic (PD) effects of RO7296682 in combination with atezolizumab on peripheral blood cells and/or the tumor microenvironment.	Correlate RO7296682 exposure and clinical endpoints with baseline levels and on-treatment changes of blood and tumor biomarkers, including but not limited to: • Treatment-induced changes in Treg levels in blood and/or tumor • Treatment-induced changes in Teff/Treg ratio of blood and tumor

Objectives	Endpoints
Exploratory (All Parts)	
To evaluate the anti-drug immune response after treatment with RO7296682 in combination with atezolizumab.	• Incidence and titer of anti-drug antibodies (ADA) to RO7296682 during the study relative to the prevalence of ADA at baseline • Incidence and titer of ADA to atezolizumab during the study relative to the prevalence of ADA at baseline
To evaluate the preliminary anti-tumor activity of RO7296682 when administered in combination with atezolizumab.	• ORR • DCR • DoR • PFS All according to iRECIST
To characterize PD effects and duration of PD response following the administration of RO7296682 in combination with atezolizumab.	• Changes in number, frequency, activation status, and distribution of blood and tumor infiltrating lymphocytes (TILs) • Immune contexture (i.e., expression levels of inhibitory or activation molecules on immune cells) • Changes in circulating tumor DNA (ctDNA) levels (Parts II and III)
To explore biologic markers that might act as predictors of safety and/or anti-tumor activity of the combination of RO7296682 and atezolizumab.	Including, but not limited to de novo occurrence and/or change from baseline in: • Soluble molecules (e.g., levels and kinetics of inflammatory or inhibitory cytokines). • Immune-phenotypic characteristics (i.e. levels of expression on immune cells of inhibitory or activation molecules). • Tissue genetic factors (i.e., Teff, Treg, etc. gene signatures).
To explore the effect of Treg depletion in the skin immune contexture.	• Treatment-induced changes in Treg levels in the skin as compared to baseline.
To explore degree of target binding of RO7296682 (in association with PK) via a receptor occupancy (RO) assay.	• Evaluate RO via ex-vivo assay (Part I only)
To explore the effect of Treg depletion on the gut microbiome.	• Treatment-induced changes of the gut microbiome as compared to baseline.

4. STUDY DESIGN

4.1 OVERALL DESIGN

Study BP42595 is an open-label, multicenter, basket trial to evaluate the anti-tumor activity of RO7296682 in combination with atezolizumab over a range of advanced and/or metastatic solid tumors. The study includes three parts as described below.

Part I: RO7296682 dose -escalation in combination with atezolizumab

To determine the recommended Phase 2 dose (RP2D)/maximum tolerated dose (MTD), safety, tolerability, PK, and PD profile of escalating doses of RO7296682 when administered with a fixed dose of atezolizumab in participants with advanced and/or metastatic NSCLC, melanoma (MEL), head and neck squamous cell carcinoma (HNSCC), esophageal cancer (EsC), triple-negative breast cancer (TNBC), and ovarian cancer (OvCa) who have progressed on all standard therapies, are intolerant to SoC, and/or are non-amenable to SoC, or for whom SoC does not exist. The starting dose of RO7296682 will be [redacted] mg and the maximum dose is planned to be [redacted] mg.

Part II: RO7296682 dose expansion in combination with atezolizumab in participants with an [redacted]

Part II will commence once the RP2D/MTD of RO7296682 in combination with atezolizumab in Part I has been determined. Participants must fulfill the following criteria (see Sections 5.1 and 5.2 for details):

- Histologically confirmed advanced and/or metastatic NSCLC, MEL, HNSCC.
- [redacted] confirmed centrally based on the most recent archival tumor specimen.
- Acquired resistance to most recent PD-1/PD-L1 treatment.

Part III: RO7296682 in combination with atezolizumab in tumor-specific expansion cohorts

Part III is exploratory, adaptive in nature, and designed to add or stop expansion cohorts, based on emerging data from this study or other RO7296682 studies (for gating criteria, see Section 9.5) and based on emerging treatment landscapes (e.g., chemotherapy in addition to PD-1/PD-L1 treatment in certain indications). Should the emerging treatment landscape warrant adding new combination partner(s) as SoC in addition to RO7296682 and atezolizumab, a new cohort exploring the new combination in a particular indication will be opened after a protocol amendment (see Appendix 9).

Enrollment in one of the pre-defined Part III tumor cohorts (namely NSCLC, HNSCC and MEL) may commence (without a protocol amendment) provided the gates described in Section 9.5 have been met.

4.1.1 Length of the Study

The maximum duration of the study for each participant will be up to 31 months, divided as follows:

- Screening: Days -28 to -1.

- Treatment Period: C1D1 to Month 24 (may be modified if supported by emerging data).
- End of Treatment Visit: 28 (± 7) days after last dose
- Safety follow-up: 135 (± 30) days after last treatment with RO7296682 in combination with atezolizumab.
- Survival follow-up: 90 (± 7) days after the safety follow-up visit; then every 3 months (± 14 days) until death, lost to follow-up, or until study closure by the Sponsor, whichever occurs first.

4.1.2 Dose Escalation Decision Criteria

The decision to escalate will be made by the Safety and Dose Escalation Committee (SDEC), as described in Appendix 11. The SDEC is composed of key Sponsor-based functional representatives and study investigators (see Section 4.1.4) and will meet regularly during Part I. Details on the SDEC are available in the SDEC charter.

In Part I, a modified continual reassessment method (mCRM) with escalation with overdose control (EWOC) will guide the dose escalation to determine the MTD (Neuenschwander et al. 2008). The decision to escalate (or not) to the next dose level will be made when at least three participants in a cohort will have completed the DLT period, following the review of all relevant safety information collected.

The dose-DLT relationship will be described by a Bayesian two-parameter logistic model where the probability of DLT is a function of dose (for further information, see Appendix 11). The model will be used:

- To estimate the MTD (defined as the dose with the highest probability that the DLT rate is within the target interval of 20% to 33%, and a probability less than 25% to be associated with a DLT rate superior to 33%).
- To recommend a dose for the next cohort complying to pre-specified safety rules (e.g., dose increments from one cohort to the next bounded to 200%). These safety rules are detailed in Appendix 11.

A minimally informative bivariate normal prior for the parameters of the DLT dose-response curve is constructed for this model in order to have a weak impact on the final MTD determination. For the dose-toxicity relationship, it is conservatively assumed that it would be very unlikely that 15% or higher DLT rates are associated with the first dose of RO7296682 in combination with atezolizumab and that a 35% or lower DLT rate is associated with maximum planned dose of RO7296682.

The model will be continuously updated as new participant information becomes available, including data collected during the DLT period for the current cohort and data collected during the treatment period from the previous cohorts.

Dose-Escalation Process

The DLT period starts from the first administration of RO7296682 and atezolizumab and ends 7 days after the second administration of RO7296682 and atezolizumab. To remain DLT evaluable, a delay in receiving the second dose of maximum 2 days can be allowed if agreed by the SDEC.

The first participant at each dose level must have completed at least 7 days from the first dose before the second participant can be treated at this dose level. If the first participant experiences a DLT within the first 7 days of treatment, a period of at least 7 days must also be maintained between the second and third participant. This pattern must be maintained for subsequent participants until a period of at least 7 days without a DLT has been completed between participants. Once achieved, all subsequent participants in a cohort can be enrolled with no fixed observation period between participants.

The design will continue as described, assigning participants to the current maximal dose allowed as estimated from all of the DLT data cumulatively, until one of the predefined stopping criteria are satisfied (Appendix 11) or the predetermined sample is reached, whichever comes first.

Built-in safety constraints are in place to prevent exposing participants to undue risk of toxicity. The dose escalation process will utilize a Bayesian model-based approach alongside with clinical judgment to guide dose selection during the study (Section 4.2).

- In the absence of a DLT event:
  - A dose increment of 200% is allowed (i.e., next dose could be as high as 3-fold the previous dose). Indeed, a 3-fold dose increment has been assumed in a recent Food and Drug Administration (FDA) oncology review of first-in-human studies for immune-activating agents as this is approximately equivalent to half-log dose increment, which is a common approach for biologics and was also the approach observed for the majority of investigational new drugs in the dataset for the first few escalation steps (Saber et al. 2017).
  - Based on the knowledge from the single agent RO7296682 study (WP41188), doses of RO7296682 suggested by the model in this study can be overruled (either downward or upward) after consultation with the study investigators, i.e. clinical judgment, can override model estimates when selecting the next dose. In this instance, the dose increment may be larger than 3-fold but must not exceed 6-fold. However, 6-fold increases can only be applied for the dose levels up to a dose of [redacted] mg.
- After the first DLT event has been observed:
  - The maximum allowed dose increment is reduced to 100% (i.e., up to 2-fold) for later cohorts. If there is only 1 accumulated DLT, no DLT in the most recent 2 cohorts, and provided the current dose is less than [redacted] mg, it is allowed to

switch back to a dose increment of 200% (i.e., up to 3-fold). Otherwise, the maximum dose increment of 100% (i.e., up to 2-fold) remains.

  - In addition, if single agent MTD has been determined in the dose-escalation study (WP41188), the upper limit to allow switching back to a dose increment of 200% (i.e. 3-fold) will be reset to 6-fold lower than single agent MTD and will overrule the above- mentioned [redacted] mg.

- After 2 DLTs have been observed, a dose increment of 100% (i.e., 2-fold) must be maintained for all subsequent cohorts.

A formal notification of the decision for the next dose will be communicated to all study sites by the Sponsor after the SDEC meeting.

If deemed necessary to further characterize the safety, PK, clinical activity, and/or PD profile of RO7296682 in combination with atezolizumab, additional participants (up to 5 per cohort) may be enrolled at a specific dose level.

Upon determination of the MTD/RP2D, Part I (Dose Escalation) participants may be allowed to escalate to the MTD/RP2D after discussion and agreement between the Sponsor and the Investigator, provided the lower dose level was tolerated and the individual benefit/risk assessment is positive.

Part I dose escalation may be halted prior to identification of MTD and upon sufficient characterization of RO7296682 in regards to safety, PK, clinical activity, and PD.

4.1.2.1 Dose-Limiting Toxicities

For the purpose of this study, a DLT will be defined as any of the following events occurring during the DLT window and not attributable to underlying disease or intercurrent illness:

- Hematological toxicities defined as:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Any non-hematological toxicities Grade ≥ 3 except for:
  - [redacted]
  - [redacted]

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

- Additional DLTs not fulfilling the above criteria
  - [redacted]

During the dose escalation phase, participants who withdraw before the end of the DLT period, and participants who did not receive two doses of RO7296682 in combination with atezolizumab for reasons other than DLTs, will be replaced to ensure that at least 3 DLT evaluable participants have been assessed prior to moving to the next dose level (see Section 7 for replacement rules). The DLT will be counted for each dose separately and each participant will contribute one single representative data point to the EWOC design.

4.1.2.2 Individual Dose Increase for Participants in a Dose-Escalation Cohort (Part I)

At the discretion of the Investigator and in agreement with the Sponsor, intra-participant dose escalation for individual participants treated at lower RO7296682 doses may be considered for treatment at higher doses of RO7296682 than those allocated at the time of enrollment, if the doses are considered safe. Thus, after completing at least 9 weeks on treatment or after the first tumor assessment, whichever comes first, at one dose level with no major safety concerns, a participant may receive a higher RO7296682 dose level at the next scheduled cycle within the participant's dosing schedule, which is at least one dose level below the highest currently evaluated dose or up to the MTD and/or the RP2D of RO7296682, if reached. If intra-participant dose escalation for an individual participant is considered, treatment must be administered as indicated in Section 6.1.1

as if it was the first administration to the study participant (i.e., 4-hour infusion for the first higher dose of RO7296682).

4.1.3 Stopping Rules Criteria for Dose-Escalation

Built-in safety constraints are in place in the dose-escalation process to prevent exposing participants to undue risk of toxicity. The mCRM with EWOC will propose to stop the dose-escalation under the following circumstances:

- [redacted]

OR

- [redacted]

OR

- [redacted]

Due to the exploratory nature of this study, any part of its conduct can be discontinued at any time at the discretion of the Sponsor. The Sponsor will notify the Investigators and Health Authorities if the study is discontinued or the development program is terminated.

4.1.4 Communication Strategy

Screening starts with the signature of the study Informed Consent Form (ICF). Patients should be formally screened in the study interactive (voice/web) response system (IxRS) as soon as consented, to allow for the assignment of a participant's screening ID. A participant is considered enrolled into the study when eligibility is confirmed by the investigational site and entered in the study IxRS system.

During the **dose escalation (Part I),** information will be communicated, as follows:

- For all participants, during dose escalation Part I, it is anticipated that the Investigator(s) will inform the Sponsor that a participant has been dosed and provide a brief summary of the status of the participant in terms of safety and tolerability to RO7296682 in combination with atezolizumab.
- In the event of a DLT, the Investigator will contact the Sponsor immediately to discuss participant status and action taken/to be taken.
- The Sponsor will organize SDEC meetings with the Investigators to discuss the safety and tolerability of RO7296682 in combination with atezolizumab and the dose selected for the next cohort.

The SDEC meeting will be conducted prior to each dose-escalation, by teleconference, in presence of the Investigators, the Medical Monitor, the Sponsor Clinical Team, and any other person the Investigators consider necessary to assist with the decision. During each teleconference:

- National Cancer Institute common terminology criteria for adverse events (NCI-CTCAE [v5.0]) toxicities (see Appendix 2) will be discussed along with available PK, ADA, and PD data, in addition to safety laboratory results and any other available data that may assist the dose-escalation decision process.
- Dose escalation will only proceed to the next dose level if the Investigators and the Sponsor are satisfied with the safety profile of the previous cohort and agree to move to the next dose level.
- The dose level of RO7296682 will be approved during the SDEC meeting and documented in writing.

For Part II ongoing medical data review will be performed by the Sponsor together with the investigators.

- **For Part III** (Dose Expansion) accumulating clinical data review will be performed by an Internal Monitoring Committee (IMC). For details, see Appendix 1, Section 3.3.

In addition to these communications, the Sponsor and Investigators will be in regular contact throughout the study by email/telephone/fax.

The Sponsor will be available 24 hours a day to discuss any medical or study-related issues that may arise during the conduct of this study.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

Part I: In Part I, dose-escalation participants with advanced and/or metastatic NSCLC, MEL, HNSCC, OvCa, TNBC, and EsC tumors will be enrolled. The indication selection was based on internal prevalence analyses on FOXP3 expression in order to select tumor types that are expected to be most responsive to Treg depletion. For details of the analyses, refer to the Investigator's Brochure.

Part II: For signal seeking purposes, Part II was designed to include tumor types and patient characteristics that are most likely to derive clinical benefit from Treg depletion (through RO7296682) and from checkpoint inhibition (through atezolizumab). In-house analysis of tumor samples (archival and fresh biopsy) have shown a strong correlation of [redacted] (as defined by [redacted]) and [redacted]. To this end, Part II will include participants with NSCLC, MEL, and HNSCC who present with an [redacted] (see Section 5.1, [redacted]) In addition, Part II participants must have experienced initial benefit from PD-1/PD-L1 treatment before they ultimately progressed (acquired resistance; see Section 5.1). It has been suggested that upon PD-1/PD-L1 treatment Tregs express PD-1 at equivalent levels as CD8+ or CD4+ effector/memory T cells,

thereby enhancing the Treg proliferation and suppressive function (Wang et al 2020, Kamada et al 2019). The requirement of initial benefit was incorporated in order to rule out primary resistance towards checkpoint inhibition.

Part III: Part III is designed to further explore signals (i.e., clinical benefit) that were generated from this or the single agent WP41188 study and/or based on emerging treatment landscapes affecting the SoC in a particular indication (e.g., chemotherapy in addition to checkpoint blockade as part of the SoC treatment). Enrollment of participants in tumor-specific cohorts may be triggered provided the gating criteria in Section 9.5 have been met. The tumor-specific cohorts will enable further investigation of clinical benefit in a less restrictive population by removing the [redacted] or acquired CPI-resistance criteria required in Part II. In the current protocol, the specifics for the NSCLC, HNSCC, and MEL cohorts have been outlined in Appendix 6, Appendix 7 and Appendix 8. Should the emerging data suggest that other indications, patient characteristics, or drug combinations warrant further investigation, a new cohort will be opened through a protocol amendment, addressing also the needs of a potential safety run-in/dose escalation phase with additional treatments like SoC chemotherapy (Appendix 9).

4.2.2 Rationale for the mCRM-EWOC Design

Part I dose escalation will be carried out according to a mCRM-EWOC design and based on the occurrence of DLTs. The mCRM-EWOC design has many favorable characteristics:

- It adaptively fits a dose DLT response curve by incorporating toxicity data from eligible participants among different cohorts, and preclinical or clinical information from compounds with similar modes of action via the prior.
- The design also locates the MTD more efficiently, without pre-specifying exact dose levels for each cohort. Dose selections are made based on the DLT dose response curve measured by a 2 parameter logistic model over the dose range, subject to clinical judgment and mandated safety constraints that limit the size of dose increments. Moreover, the EWOC algorithm highly reduces risks of exposing participants to overly toxic doses. Of note, the model provides only the upper limit for recommended dose. A dose lower or higher than the model recommended dose may be selected based on clinical judgment.

4.2.3 Rationale for Biomarker Assessments

According to the mode of action of RO7296682, depletion of Tregs will lead to reinvigoration of the anti-tumor immune response in the TME. As such, the goal of the biomarker assessments is to confirm the RO7296682 mode of action at the tumor site, when administered in combination with atezolizumab, and establish a dose−response relationship.

In-house tumor sample analyses and real world data have shown a strong correlation of [redacted] and [redacted]. Therefore, archival tumor samples will be collected at screening from all participants enrolled in the study and analyzed for immune-phenotype and immune contexture in all parts of the study. In order to test the effect of the treatment in a patient population that could benefit the most from the therapy, Part II of the study will enroll only participants with [redacted] as assessed by prospectively characterizing the tumor immune-phenotype on the archival tissue.

Treatment-induced intra-tumoral PD changes will be assessed by examining alterations in the number, activation/differentiation status, and location of intra-tumoral residing immune cells. In particular, a reduction of Tregs and/or an increase in Teff/Treg is expected. This will be monitored closely in all samples. Moreover, the expression of tumor markers (including but not limited to PD-L1) associated with response to RO7296682 will be examined. These changes will be assessed in mandatory, fresh, paired tumor biopsy samples collected from participants enrolled in Parts II and III.

RO7296682 treatment may result in changes in peripheral blood immune cells and soluble circulating markers such as cytokines or tumor markers. Hence, in all parts of the study, plasma samples will be analyzed with respect to the presence or changes in levels of cytokines, inflammation, and soluble tumor markers that may be associated with treatment benefits. Moreover, blood samples will be assessed with respect to alterations of immune cells in their absolute counts and activation/differentiation status as well as their functional capacity following treatment with RO7296682. Receptor occupancy (RO) assessments following treatment with RO7296682 in combination with atezolizumab will also be undertaken to evaluate the degree of target binding of RO7296682 (in association with PK) in Part I only.

Finally, in order to evaluate the value of circulating tumor DNA (ctDNA) as a response predictor to RO7296682 in combination with Atezolizumab, the dynamics of plasma ctDNA will be analyzed in relation to tumor size variations and response to treatment. Changes in ctDNA level will be assessed in samples collected in Parts II and III of the study.

In order to determine if and by how much RO7296682 in combination with atezolizumab affects Treg homeostasis in the immune contexture of healthy tissue, mandatory healthy skin punch biopsies will be collected at baseline and on treatment, at the same time points as the mandatory tumor biopsies. It is expected that analyses from such healthy tissues could provide critical information regarding a differential between numbers of activated Treg in the tumor and the non-activated Treg in the healthy tissue.

If preliminary data suggest that modification of the on-treatment tumor biopsy or healthy skin punch biopsy time point would be appropriate, alternative on-treatment biopsy time-points may be considered.

Optional tumor and/or healthy tissue biopsies may be taken at any time point and in all parts of the study (Parts I-III), for example, due to either skin-related AEs, disease progression, or long-lasting stable disease (SD) as per Investigator discretion and if the participant consents to these samples being taken to aid the understanding of immune resistance or homeostasis mechanisms.

Finally, all specimens will be used also for research purposes to identify additional biomarkers that may be useful to predict and monitor response to RO7296682 in combination with atezolizumab and safety, assess PD effects of RO7296682 in combination with atezolizumab, and investigate any mechanisms of resistance to therapy. Additional biomarkers may be measured if initial data lead to strong scientific rationale for these measurements.

4.2.4 Rationale for Real wOrld PROgnostic Score

The Real wOrld PROgnostic (ROPRO) score serves as an objective tool to assess the patient's life expectancy and has been shown to enable prognosis of OS homogeneously across solid cancer indications (Becker et al. 2020). The ROPRO score consists of routinely collected clinical parameters (listed in Section 8.2.10) reflecting both the tumor biology and patient characteristics. It has been shown to strongly outperform other risk scores, such as the Royal Marsden Hospital Score. Patients with elevated ROPRO scores (upper 10%) had a 7.91-fold (95% confidence interval [CI] 7.45–8.39) increased death hazard compared with that of patients with low scores (lower 10%). Refer to Appendix 10 for data demonstrating that a poor ROPRO score correlates with reduced probability of 12-week survival.

In this study, the ROPRO score serves to objectively support the Investigator with the assessment of the commonly used inclusion criteria "Life expectancy, in the opinion of the Investigator, of ≥ 12 weeks" (see Section 5.1). Patients who demonstrate a poor ROPRO score, should be excluded unless clinical judgment may determine potential clinical benefit and thereby the inclusion of the patient in the study. Such decisions will be clearly documented.

4.2.5 Rationale for Optional Stool Sample Collection

The gut microbiome has been shown to be a key determinant of immune regulation in cancer, in part by influencing T-cell driven anti-tumor responses (Routy et al. 2018). For example, antibiotic treatment is associated with poor survival outcomes to anti-PD-1 therapy in NSCLC, renal cell carcinoma, and urothelial carcinoma (UC) (Elkrief et al. 2019). Conversely, the risk of colitis with CITs may be predicted on the basis of a patient's pretreatment microbiome (Dubin et al. 2016; Chaput et al. 2017). In addition, the role of Tregs in influencing the progression of inflammatory bowel disease and the development of colorectal cancer has been established in the literature (van Herk et al. 2016; Neurath 2020). Thus, heterogeneity in microbiome composition across patients may be a relevant driver of safety events, in addition to efficacy.

This study will examine a participant's microbiome at baseline and on-treatment in order to investigate potential changes by RO7296682 in combination with atezolizumab.

4.3 JUSTIFICATION FOR DOSE

4.3.1 Rationale for Dosage Selection of Atezolizumab

Atezolizumab is approved for the treatment of patients with locally advanced or metastatic UC and those with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy at a dose of 1200 mg as an intravenous infusion over 60 minutes every 3 weeks (Q3W) until disease progression or unacceptable toxicity. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

4.3.2 Rationale for Dosage Selection of RO7296682

The starting dose and regimen of RO7296682 in combination with atezolizumab is defined as [redacted] mg administered Q3W by IV administration. The RO7296682 starting dose and schedule were selected based on several factors, including non-clinical toxicology, exposure and efficacy studies of RO7296682 and clinical experience from RO7296682 administered as a single agent in study WP41188:

Non-clinical toxicology data

RO7296682 was tested in combination with atezolizumab in a whole blood assay to investigate the potential of the combination to trigger systemic cytokine release. When compared with single agent RO7296682 in the same assay, [redacted] Therefore, at the starting dose of [redacted] mg for RO7296682 combined with atezolizumab at the dose of [redacted] mg, [redacted] after the IV administration. In addition, the combination of atezolizumab and RO7296682 was tested in mouse models for efficacy assessment. [redacted] were reported in these pharmacological models.

Clinical data from single agent study WP41188

RO7296682 is being investigated as a single agent in the ongoing WP41188 Phase I study. At the time of clinical cutoff date 10 June 2020 (in order to produce validated safety outputs), 21 participants had received multiple ascending doses of RO7296682 up to [redacted] mg on a Q3W schedule and had not shown any dose limiting toxicity event. The safety profile, PK, and immune-related PD effects in the peripheral blood were analyzed to define the starting dose in this study.

At the time of finalizing the first version of this protocol, the highest cleared dose of RO7296682 in the ongoing WP41188 study was [redacted] mg [redacted]. Further dose increments will be explored in the WP41188 study until MTD or optimal biological dose is reached.

Based on the clinical experience from study WP41188, the selected RO7296682 starting dose of [redacted] mg is expected to be safe and result in exposure levels that will initiate no or minimal PD response, either from a [redacted] or from a [redacted]. Indeed, starting at [redacted], a consistent PD response is observed with a [redacted]

Analyzing the RO7296682 PK data at doses from [redacted] to [redacted] mg [redacted], preliminary exposure estimates [redacted] Given the preliminary data, RO7296682 PK is considered [redacted] and shows [redacted]

Given the risk for overlapping toxicities between an anti-CD25 agent and a CPI targeting the PD-1/L1 pathway (see Investigator's Brochure), the proposal of a known safe starting dose of RO7296682 [redacted] mg is considered adequate for the initiation of the study.

4.3.2.1 Definition of Optimal Biological Dose

Pharmacokinetic and pharmacodynamic data (i.e., peripheral blood and tumor/skin tissues) are being collected to inform on RO7296692 exposure-response relationship in order to select the optimal biological dose (OBD) required for RO7296682, which may be different from MTD.

4.3.3 Rationale for the Expansion Dose

The RO7296682 dose selected for Part II of BP42595 studying the combination of RO7296682 with atezolizumab is [redacted] mg Q3W.

This dose was selected based on the integration of all available safety, efficacy, PK, and PD data from Study WP41188. While there was neither correlation between drug concentration and clinical response (according to RECIST 1.1.) nor AEs (such as frequency of total reported, related, immune-mediated, and skin-related AEs), a dose-dependent effect on [redacted] was observed. Consequently, the dose recommendation is based on PK/PD modelling with an optimization towards [redacted] with the least possible effect on [redacted] in the periphery.

The anti-tumor activity observed in the first 10 response-evaluable participants with an [redacted], treated with [redacted] mg RO7296682 (and fixed dose of atezolizumab) will be assessed. If the ORR is less than 25%, another RO7296682 dose, which previously cleared in Part I may be explored. In this scenario the [redacted] mg dose cohort will be closed and a new Part II dose cohort will be initiated. The Sponsor is committed to action based upon emerging data and to aim at optimizing the dose

selection process in real-time which may include the exploration of other doses with an expected improved Benefit-Risk profile. To this end, a total of approximately 60 participants are planned to be enrolled in Part II.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last participant's last visit per protocol (includes the safety follow-up visit 135 [± 35] days after last dose of study drug) or the date on which the last data point from the last participant required for statistical analysis is received (last participant, last observation), whichever is the latest date.

Because of the exploratory nature of this clinical study, its conduct can be discontinued at any time at the discretion of the Sponsor.

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

The participants in this study will be adult male and female participants with advanced and/or metastatic solid tumors, who fulfill all eligibility criteria. For a high-level overview of the cancer types across the study, refer to Section 1.2 or Section 4.1.

Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

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

1. Signed written informed consent and ability to comply with the study protocol according to International Council for Harmonisation (ICH) and local regulations.
2. Age ≥ 18 years.
3. Diagnosis of advanced and/or metastatic solid tumors. Participants whose tumors have known sensitizing mutations must have experienced disease progression (during or after treatment) or intolerance to treatment with a respective targeted therapy. More detailed criteria for Parts I, II, and III are defined further below.
4. Measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).

   Previously irradiated lesions must not be counted as target lesions, unless there has been demonstrated progression in the lesion and no other target lesions are available.
5. Life expectancy of ≥12 weeks, as assessed by the Investigator and supported by the ROPRO score. In case the patient's score is above the cut-off of 0.7, the patient may still be enrolled provided that per the Investigator's judgment the clinical benefits of enrollment will outweigh the risks. Please see Section 4.2.4 for rationale.

6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
7. Participants must have progressed on all standard therapies, be intolerant to and/or non-amenable to SoC.
8. Able to provide the most recent archival tumor tissue samples (formalin-fixed-paraffin-embedded [FFPE] blocks preferred; if not available, slides accepted). If no archival samples are available, refer to inclusion criteria #19 and #23 for Part I and Part II, respectively. For Part III, refer to Appendix 6, Appendix 7 and Appendix 8.
9. Able to provide skin punch biopsy at screening and at C2D8.
10. For Part II and Part III able to provide a fresh tumor biopsy at screening and C2D8.
11. Adequate cardiovascular function:
    - Left ventricular ejection fraction ≥ 50%, as determined by multiple-gated acquisition scan (MUGA) or transthoracic echocardiogram (TTE).
    - New York Heart Association (NYHA) Heart Failure Stage ≤ 2.
    - Baseline-corrected QT (QTcF) interval ≤ 470 ms.
    - Resting systolic blood pressure ≤150 mmHg and diastolic blood pressure ≤ 100 mmHg (average of ≥ 3 readings).
    - Resting heart rate (HR) between 45 to 100 bpm.
12. Adequate hematological function:
    - Neutrophil count of ≥ 1.5×10^9 cells/L (1500/μL).
    - Platelet count of ≥ 75×10^9 /L (75,000/μL).
    - Hemoglobin ≥ 9 g/dL (90 g/L, ~ 5.6 mmol/L).
    - Lymphocyte count of ≥0.5×10^9 cells /L (500/μL) (borderline lymphocyte values can also be confirmed with manual counts if machine count is below limit).
13. Adequate liver function:
    - Total bilirubin ≤1.5 ×upper limit of normal (ULN; excluding Gilbert syndrome; see below).
    - AST, ALT, and alkaline phosphatase (ALP) ≤ 2.5 × ULN; with the following exceptions:
        - Participants with documented liver metastases: AST and ALT ≤ 5 × ULN.
        - Participants with documented liver or bone metastases: ALP ≤ 5 × ULN.
        - GGT > 2.5 × ULN (in case of liver metastases: ≥ 5 × ULN) must be discussed and agreed with the Sponsor.
14. Adequate renal function: serum creatinine ≤ 1.5 × ULN or creatinine clearance by Cockcroft-Gault formula ≥ 50 mL/min for participants in whom, in the Investigator‘s judgment, serum creatinine levels do not adequately reflect renal function.
15. Additional adequate laboratory parameters obtained prior to the first study treatment (C1D1):
    - Serum albumin ≥ 25 g/L (2.5 g/dL).

- Prothrombin time (PT) and activated partial thromboplastin time (aPTT) $\leq 1.5 \times$ ULN or $< 2 \times$ ULN for participants with hepatocellular carcinoma.

16. Participants on therapeutic anticoagulation must be on a stable anticoagulant regimen.
17. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    - Not a woman of childbearing potential (WOCBP).
    - WOCBP, who:
        - Agree to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 4 months after the final dose of RO7296682 and for 5 months after the final dose of atezolizumab, whichever is longer.
        - Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal occlusion, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs.
    - Have a negative pregnancy test (blood) within the 7 days prior to the first study treatment administration.

    Male participants: During the treatment period and for at least 28 days after the last dose of RO7296682, agreement to the following:

    - Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year, with partners who are WOCBP.
    - With pregnant female partners, remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing the embryo.
    - Refrain from donating sperm during that period.

Specific Inclusion Criteria for Dose Escalation, Part I

18. Participants with histologically confirmed advanced and/or metastatic OvCa, TNBC, HNSCC, NSCLC, MEL, or EsC.
19. In the absence of sufficient archival tissue, a fresh biopsy from a safely accessible site, per Investigator determination and patient consent, will be requested, providing the patient has more than one measurable target lesion.

    Note: if fresh biopsy cannot be obtained, please contact the Medical Monitor.

Specific Inclusion Criteria for CPI-resistant Participants, Part II

20. Participants with histologically confirmed advanced and/or metastatic HNSCC, NSCLC or MEL.

21. [redacted] positivity established using a validated IHC method and readout (validated laboratory-developed test). For this purpose, the most recent archival sample from a metastatic site (and NOT primary tumor) must be obtained. Please see Section 4.2.1 for rationale.

    Note: In the absence of sufficient or appropriate archival tissue the immune-phenotype must be confirmed using a fresh tumor biopsy, providing the patient has more than one measurable target lesion. Please refer to inclusion criteria #23.

22. For participants to be defined as acquired CPI-resistant, they must have received prior treatment with approved or investigational anti-PD-1/L1 (Note: prior treatment with anti-CTLA-4 at any time during anti-cancer treatment is prohibited) and meet the following requirements:
    - CPI administration as (neo-) adjuvant therapy is not allowed.
    - For participants with MEL, no line of chemotherapy is allowed between the most recent PD-1/PD-L1 treatment and study treatment. For participants with HNSCC and NSCLC, a maximum of 1 line of chemotherapy is allowed between the most recent PD-1/PD-L1 treatment and study treatment.
    - Participants must have experienced Investigator-assessed initial clinical benefit (SD or better) from most recent CPI therapy for at least 4 months:
        - If a scan within the first 4 months exists and shows progressive disease the patient is not eligible (i.e., the scan result cannot be overruled by Investigator assessment of clinical benefit).
        - Should a subsequent scan for the same line of treatment show clinical benefit after initial radiographic progression (i.e., pseudoprogression) the patient is eligible.
23. Able to provide a freshly collected biopsy of a tumor lesion (primary and/or metastatic) from a safely accessible site, per Investigator determination and patient consent, providing the patient has more than one measurable target lesion. If the patient has only one target lesion, the patient will be excluded from study participation. The biopsied lesion must not be a target lesion. The following rules apply:
    - Bone lesion biopsies, bronchoscopy/trans-bronchial biopsies, and cytology fine needle aspirates are not acceptable.
    - The tumor lesion must not be a metastatic lymph node sample; metastatic lymph node is acceptable ONLY when other accessible tumor sites are not available for biopsy.
    - Fresh biopsies must be obtained within 28 days before the first dose at C1D1.
    - If fresh tissue biopsies cannot be obtained, please contact the Medical Monitor.

For specific inclusion criteria for tumor-specific expansion cohorts, Part III, refer to Appendix 6, Appendix 7, and Appendix 8.

5.2 EXCLUSION CRITERIA

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

1. Pregnancy, lactation, or breastfeeding.
2. Known hypersensitivity to any of the components of RO7296682 and atezolizumab, including but not limited to hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.
3. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
4. Participants who experienced infusion-related reactions (IRRs), skin toxicity, and/or immune-mediated AEs of Grade ≥ 3 in conjunction with previous CPI treatment are excluded (with the exception of endocrinopathy managed with replacement therapy or controlled type 1 diabetes mellitus on a stable insulin regimen).
5. AEs from any prior anti-cancer therapy that have not resolved to Grade ≤ 1 except for alopecia, vitiligo, or endocrinopathy managed with replacement therapy, and Grade ≤ 2 peripheral neuropathy.

   Note: Other Grade 2 AEs that are deemed clinically insignificant by treating physician are permitted.
6. History or clinical evidence of central nervous system (CNS) primary tumors or metastases including leptomeningeal metastases, unless they have been previously treated, are asymptomatic, are stable (without evidence of progression by computed tomography [CT] or magnetic resonance imaging [MRI] for at least 4 weeks prior to the first dose of the study drug), and have had no requirement for steroids or enzyme-inducing anticonvulsants in the last 14 days prior to screening.

   Note: Anticonvulsants are permitted if anticonvulsant therapeutic is established for > 14 days.
7. Participants with another invasive malignancy in the last two years (exceptions are non-melanoma skin cancer, cervical carcinoma in situ, good prognosis ductal carcinoma in situ of the breast, or prostate carcinoma that is in remission under androgen deprivation therapy for > 2 years). Other exceptions may apply and require discussion between the Investigator and the Sponsor.
8. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications.
9. Encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.
10. Severe dyspnea or requiring supplemental oxygen therapy at rest.
11. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina.

12. Participants with known active or uncontrolled infection that, in the opinion of the Investigator, could impact patient safety, or reactivation of a latent infection, whether bacterial, viral (including, but not limited to, hepatitis B, hepatitis C and HIV), fungal, mycobacterial (including but not limited to tuberculosis), or other pathogens (excluding fungal infections of nail beds) or any major episode of infection requiring hospitalization or treatment with IV antibiotics (for IV antibiotics, this pertains to completion of last course of antibiotic treatment), or hospitalization for severe pneumonia within 28 days of first drug administration.
13. Positive HIV test at screening.
14. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
15. Vaccination with live vaccines within 28 days prior to C1D1 or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab.
16. Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, and inherited liver disease.
17. Major surgical procedure or significant traumatic injury within 28 days prior to first RO7296682 and atezolizumab infusion, or anticipation of the need for major surgery before end of treatment period. After major surgery, participant must wait until surgical wounds are fully healed before initiating treatment.
18. Participants with current or history of wound healing complications and/or participants with open wounds until complete resolution.
19. Prior allogeneic stem cell or solid organ transplantation.
20. Dementia or altered mental status that would prohibit informed consent.
21. History of Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug rash with eosinophilia and systemic symptoms.
22. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
    - Participants with a history of autoimmune-mediated hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
    - Participants with controlled type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
    - Participants with controlled eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., participants with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
        - Rash must cover $<$ 10% of body surface area.
        - Disease is well controlled at baseline and requires only low-potency topical corticosteroids.

- No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

23. Prior treatment with CPIs, immunomodulatory agents and/or mAbs, and/or mAb-derived therapies, or immunostimulatory agents is not allowed (approved or investigational), provided that:
    - Less than 4 weeks have elapsed between the last dose and the proposed C1D1.
    - Less than 5 half-lives or 28 days (whichever is shorter) have elapsed since prior treatments with specific immunomodulators, TLR-agonists, inhibitors of IDO/TDO, or agonists (e.g., OX40) and the proposed C1D1.
24. For Part II only: Prior treatment with anti-CTLA4 is prohibited.
25. Prior treatment with a CC chemokine receptor 4 (CCR4)-targeting (e.g., mogamulizumab) or a CD25-targeting agent (e.g., basiliximab) is prohibited. Note: participants previously treated with single agent RO7296682 in the WP41188 study may be included in this study.
26. Treatment with standard radiotherapy, any chemotherapeutic agent, targeted therapy, or treatment with any other investigational drug (defined as treatment for which there is currently no regulatory authority-approved indication) within 28 days or 5 half-lives of the drug (whichever is shorter), prior to C1D1 is prohibited.
27. Treatment with systemic immunosuppressive medications including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor (TNF) agents within 2 weeks prior to C1D1. Participants who have received acute and/or low-dose systemic immunosuppressive medications (e.g., a one-time dose of dexamethasone for nausea or chronic use of $\leq$ 10 mg/day of prednisone or another dose-equivalent corticosteroid) may be enrolled in the study. The use of inhaled corticosteroids and mineralocorticoids (e.g. fludrocortisone) is allowed.
28. Radiotherapy within the last 4 weeks before start of study drug treatment, with the exception of limited palliative radiotherapy (for which no wash out period is required).

5.3 LIFESTYLE CONSIDERATIONS

Participants will be expected to follow protocol requirements for contraception (see Appendix 5), but there are no other lifestyle restrictions during the study. There are no study-specific restrictions to meals and dietary requirements.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently entered in the study. Patients who fail screening due to a ROPRO score above the prescribed threshold will be followed up for survival after the date of screen failure.

The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure. In the event that a fresh biopsy is taken during the screening period and the participant is not enrolled into the study, the FFPE biopsy block can be returned to the site upon site request.

Individuals who fail to meet the criteria for participation (screen failures) may be re-screened, with Sponsor approval. In the event re-screening is permitted, invasive assessments like biopsies do not have to be repeated. Re-screened participants should be assigned a different screening number as compared to that used for the initial screening.

Participants who are re-screened are required to sign a new ICF.

5.5 RECRUITMENT PROCEDURES

An IxRS system will be utilized to manage (pre-) screening and enrollment.

Participants will be identified using pre-screening enrollment logs, clinical database, and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved newspaper/radio/social-media advertisements prior to consenting to take part in this study.

6. TREATMENTS

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

For the purpose of the study, RO7296682 and atezolizumab are considered investigational medicinal products (IMPs). All IMPs required for completion of this study will be provided by the Sponsor or its designee in compliance with local drug management regulations. Pre-medications are considered non-IMPs.

All study treatment administration will be performed at the study center under supervision of site staff. In case of infusion-associated AEs in participants, the signs and symptoms should have fully resolved before the participant is discharged. Cases of accidental overdose or medication error, along with any associated AEs, should be reported as described in Appendix 2, Section 5.2.

6.1 TREATMENTS ADMINISTERED

Administration of RO7296682 and atezolizumab will be performed in a monitored setting, such as an intensive care unit (ICU), where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

The administered treatments are summarized in Table 5. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively.

For more details, refer to the RO7296682 and atezolizumab Investigator's Brochures and the Pharmacy Manual.

Table 5 Summary of Treatments Administered

Study Treatment Name:	RO7296682	[redacted]	Atezolizumab
Dose Formulation:	Solution	Solution	Solution
Unit Dose Strength(s)/Dosage Level(s):	[redacted] mg/mL	[redacted] mg/mL	60 mg/mL
Dose:	Ascending flat doses (Q3W)	Not applicable	[redacted] mg (Q3W)
Route of Administration:	IV infusion	IV infusion	IV infusion
Sourcing:	Provided centrally by the Sponsor		

6.1.1 RO7296682/Atezolizumab and Infusion Rates

For infusion guidelines of atezolizumab, refer to Table 6 and for infusion guidelines of RO7296682, refer to Table 7.

Table 6 Administration of First and Subsequent Atezolizumab Infusions

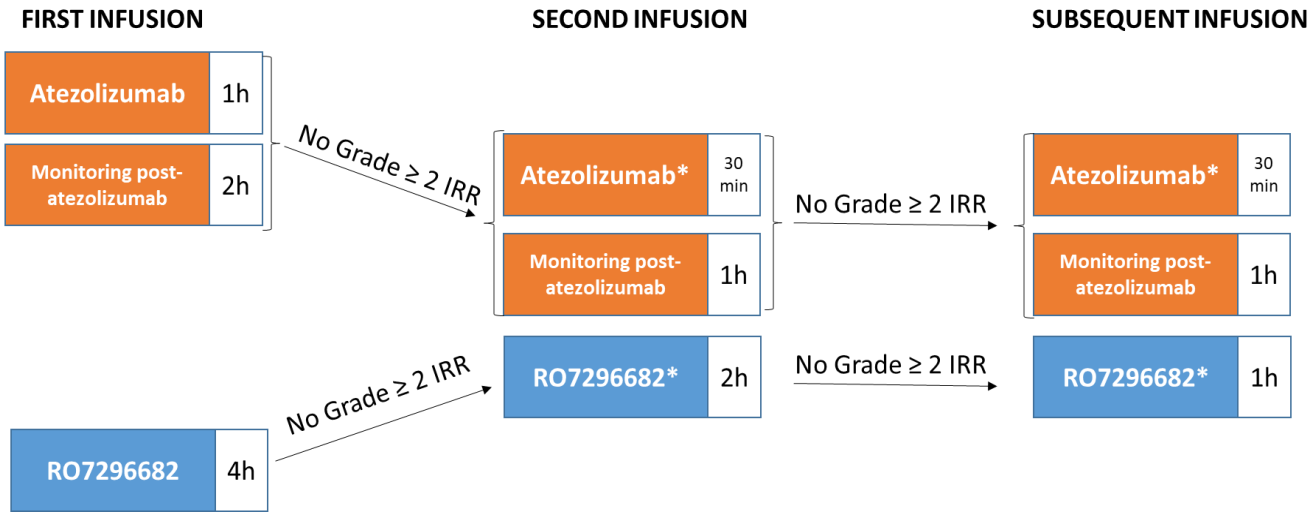
First Infusion	Subsequent Infusions
• Atezolizumab must be administered prior to RO7296682. • No pre-medication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (± 15) minutes. • If clinically indicated, vital signs should be measured every 15 (± 5) minutes during the infusion and at 30 (± 10) minutes after the infusion. • Participants who do not receive a full dose of atezolizumab should not receive RO7296682.	• If the participant experienced Grade ≥ 2 IRR with any previous infusion, pre-medication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Atezolizumab must be administered prior to RO7296682. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated (i.e., absence of Grade ≥ 2 IRRs), or 60 (± 15) minutes if the patient experienced Grade ≥ 2 IRRs with the previous infusion. • Participant should be observed for at least 1 hour before receiving RO7296682.

First Infusion	Subsequent Infusions
• Participant should be observed for at least 2 hours after the first administration of atezolizumab before receiving RO7296682. • Participants should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the participant experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (± 10) minutes after the infusion.

Table 7 Administration of First and Subsequent RO7296682 Infusions

First Infusion	Subsequent Infusions
• For pre-medication guidelines, refer to Table 8. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 min prior to the infusion. • RO7296682 should be infused over 4 h (± 15 min). • If clinically indicated, vital signs should be measured every 15 (± 5) min during the infusion and at 30 (± 10) min after the infusion. • Participants should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the participant experienced Grade ≥ 2 IRR with any previous infusion, refer to the pre-medication guidelines in Table 8. • Vital signs should be measured within 60 min prior to the infusion. • RO7296682 should be infused over 2 h (± 10 min) if the first infusion was well tolerated (i.e., absence of Grade ≥ 2 IRRs). If the 2 h infusion was well-tolerated, all subsequent infusions may be reduced to 60 (± 10) min. If the participant experienced Grade ≥ 2 IRRs the previous infusion duration should be maintained until absence of Grade ≥ 2 IRRs is observed. • If the participant experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (± 10) min after the infusion.

Figure 3 Infusion Times of Atezolizumab followed by RO7296682



*In case of Grade ≥2 IRRs, refer to Table 6 and Table 7 for infusion durations.

6.1.2 Pre-medication prior to Administration of RO7296682

No pre-medication is foreseen prior to the administration of RO7296682, unless per Investigator judgment and based on the participants' medical history, pre-medication is warranted in the best interest of the participant. In case of IRRs, a list of pre-medication is provided in Table 8. Pre-medications are captured in a dedicated pre-medication eCRF.

For participants having experienced an IRR-like reaction with a single and isolated symptom such as fever, occurring within 24 h after study drug infusion was completed, the use of pre-medication such as paracetamol, antihistamines and corticosteroids is not foreseen prior to subsequent RO7296682 administrations. Pre-medication of those participants at subsequent infusions is at the discretion of the investigator, as is the

treatment and management at the time of an event. The event will be reported as a single AE (e.g. fever).

Table 8 Pre-medication prior to Treatment with RO7296682

First Infusion	Subsequent Infusions
Pre-medication with the following can be considered at Investigator discretion approximately 30 minutes prior to the infusion: • Antihistamines (both an H1-receptor antagonist and an H2-receptor antagonist) and/or • Antipyretics per institutional standard and/or • Anti-emetic	**In case of IRR Grade 1 at previous infusion** Pre-medication with the following is recommended approximately 30 minutes prior to the infusion: • Antihistamines (both an H1-receptor antagonist and an H2-receptor antagonist) and/or • Antipyretics per institutional standard and/or • Anti-emetic **In case of IRR Grade 2 at previous infusion** pre-medication with the following must be administered approximately 30 minutes prior to the infusion: • Antihistamines (both an H1-receptor antagonist and an H2-receptor antagonist) and • Anti-pyretics per institutional standard and/or • Anti-emetic **In case of IRR Grade 3 at previous infusion**, pre-medication with the following must be administered approximately 30 minutes prior to the infusion: • Antihistamines (both an H1-receptor antagonist and an H2-receptor antagonist) and • Anti-pyretics per institutional standard and • Hydrocortisone (200 mg IV or equivalent according to institutional guidelines) and/or • Anti-emetic **In case of IRR Grade 4**, treatment with RO7296682 and must be permanently discontinued and patient discontinued.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study drug packaging will be overseen by the Sponsor's clinical study supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labeling of the study medication will be in accordance with the Sponsor's standard and local regulations. RO7296682, RO7296682 diluent and atezolizumab will be provided by the Sponsor.

The investigational site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced. The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

The study site (i.e., Investigator or authorized personnel [e.g., pharmacist]) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation and final disposition records). Upon arrival of the IMPs at the site, site personnel will complete the following:

- Check the IMPs for damage.
- Verify proper identity, quantity, integrity of seals and temperature conditions.
- Report any deviations or product complaints to the Study Monitor upon discovery.

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the Pharmacy Manual.

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

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. The site must obtain written authorization from the Sponsor before any 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 RO7296682 and atezolizumab Investigator's Brochure for information on IMP formulation, IMP handling, including preparation and storage, and accountability.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

This is an open-label study with no randomization.

The Sponsor will be responsible for allocation of patient numbers, using an IxRS process. The log in information and directions for the IxRS will be provided to each site.

Participants who fulfill all of the inclusion criteria and none of the exclusion criteria are eligible to participate in the study and will be assigned to a treatment group/dose in consultation with the Sponsor.

6.4 TREATMENT COMPLIANCE

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the randomization schedule. This individual will write the date dispensed and participant number on the study treatment vial label and on the Drug Accountability Record. This individual will also record the study treatment number received by each participant during the study.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a participant within 30 days of study screening until the safety follow-up visit must be recorded on the Concomitant Medications eCRF along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency).

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All medication administered to manage AEs should be recorded on the Adverse Event eCRF.

6.5.1 Permitted Therapy

For pre-medication guidelines, refer to Section 6.1.2. Participants who use oral contraceptives with a failure rate of $< 1\%$ (See Appendix 5), hormone-replacement therapy, or other maintenance therapy should continue their use.

The use of limited field palliative radiotherapy during the course of the study should be discussed and agreed by the Investigator on a case-by-case basis with the Medical Monitor in order to exclude overall progressive disease. No delay of study treatment administration is required although participants should not receive study treatment during radiation.

Systemic corticosteroids and TNF-α antagonists may attenuate potential beneficial immunologic effects of treatment with RO7296682 in combination with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives (including antihistamines) should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids are recommended, at the discretion of the Investigator, for the treatment of specific AEs when associated with RO7296682/atezolizumab therapy (for details, refer to Section 8.3.9.1, 8.3.9.2, and 8.3.9.3, and Appendix 12).

6.5.2 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 28 days or 5 half-lives of the study drug (whichever is shorter), prior to initiation of study treatment, unless otherwise specified below:

- Investigational or unlicensed/unapproved agents.
- Immunotherapy/radio-immunotherapy.
- Chemotherapy / targeted therapy.
- Radiotherapy (with the exception of limited field palliative radiotherapy).
- Biologic agents (e.g., bevacizumab, cetuximab).
  Note: Insulin is allowed.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) 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 RO7296682 and/or atezolizumab.
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. See Section 6.5.1 for guidelines on systemic corticosteroids and TNF-α inhibitors.
- Live, attenuated vaccines (e.g., Flu – Mist® influenza vaccine) are prohibited at any time during the study, and for 5 months following the last dose of study treatment.

6.6 DOSE MODIFICATION

If, in the opinion of the Investigator, a toxicity is considered due solely to one of the study treatments, the dose of the other study treatment does not require modification. However, in cases potentially related to both drugs, treatment with both RO7296682 and atezolizumab should be modified or permanently discontinued as appropriate based on the grade of toxicity. Examples of potentially overlapping toxicities that could be related to both drugs include immune-mediated toxicities, IRR/CRS, skin toxicity and immunogenicity.

For Part I (Dose-Escalation):

Dose-Limiting Toxicities (DLTs): Participants who experience toxicities fulfilling the definition of a DLT during the DLT assessment period should be discontinued from study treatment. Nevertheless, the Investigator, after discussion with the Sponsor, will have the option to reduce the dose of RO7296682 to the previous tolerated dose level, if participant is deemed to be deriving clinical benefit. No dose modification for atezolizumab is allowed.

For All Parts:

IMP-related AEs (i.e., attributed to RO7296682 in combination with atezolizumab): AEs attributable to IMPs must resolve to ≤ Grade 1 or baseline for non-hematological toxicities and ≤ Grade 2 for hematological toxicities before resuming treatment. Exceptions may be allowed after a careful potential clinical risk/benefit assessment by the Investigator and approval by the Medical Monitor.

Dose reduction of RO7296682 alone may be allowed with the approval of the Medical Monitor. No dose modification for atezolizumab is allowed.

AEs not attributed to IMPs: A delay of IMP administration for up to two cycles will be acceptable to allow for resolution of toxicity to NCI CTCAE Grade ≤ 2 for hematological toxicities or Grade ≤ 1 for non-hematological toxicities. If in the judgment of the Investigator, a participant is likely to derive clinical benefit from RO7296682 in combination with atezolizumab after a hold of more than 2 cycles, study drug may be re-started with the approval of the Medical Monitor.

Liver Function Tests: For participants with documented liver metastasis and elevated liver function test (LFT) results at baseline, further elevations of LFT results may not require dose interruptions if there are no progressive changes in the ALT and/or AST (less than a doubling) and if there are no progressive elevations in total bilirubin or international normalized ratio.

Investigators are encouraged to contact the Sponsor for further guidance if needed. After Cycle 1 is completed, RO7296682 dose modifications should be discussed with the Sponsor.

6.7 TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not have any plans to provide RO7296682 or any other study treatments to the participants after the end of the study, or when participants discontinue or have been withdrawn from the study. The Sponsor will evaluate whether to continue providing treatment to participants after the main study is over, in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

7. DISCONTINUATION OF STUDY, STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

An excessive rate of withdrawals (either participants discontinuing study treatment or withdrawing from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided and efforts should be taken to

motivate participants to comply with all the study-specific procedures as outlined in this protocol.

Details on study and site closures are provided in Appendix 1 Study Governance Considerations Study.

7.1 DISCONTINUATION OF STUDY TREATMENT

For data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed see the SoA (Section 1.3).

Reasons for discontinuation of study treatment (or withdrawal from the study) may include, but are not limited to, the following:

- Participant withdrawal of consent at any time.
- Any toxicity, which is not manageable with dose delays, dose decrease, and appropriate treatment
- Any medical condition that the Investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study.
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant.
- Pregnancy
- Disease progression when there is a consensus that the participant will not benefit from further study treatment
- Immunoglobulin E (IgE)-mediated hypersensitivity reactions, including anaphylaxis.
- Any event that meets stopping criteria defined in Section 4.1.3.

Participants who discontinue study treatment prematurely will be asked to return to the clinic for a study completion/early termination visit (see Section 8.11.3) and may undergo follow-up assessments (see Section 8.11.4), unless the participant withdrew consent. The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF.

Treatment beyond Disease Progression

- As with other immunotherapies, treatment beyond RECIST v1.1 progression may be considered following discussion between the Investigator and the Sponsor.
- The criteria below are needed for continuing treatment beyond initial apparent progressive disease per RECIST v1.1 (e.g., radiological progression secondary to tumor inflammation):
  - Absence of clinical deterioration or improvement in clinical symptoms.
  - Investigator-assessed potential clinical benefit for the participant.
  - The participant is tolerating study drug.

Participant Replacement Rules

Participants who discontinue study treatments prematurely may be replaced for the following reasons to ensure adequate numbers of evaluable participants:

- For all parts: Participants who withdraw from the study prior to the treatment start may be replaced.
- For Part I:
  - Participants who discontinue from the study before the end of the DLT period for reasons other than DLTs.
  - Participants who did not receive at least two doses of RO7296682 and two doses of atezolizumab during the DLT period, for reasons other than DLT.

7.1.1 Temporary Interruption

Temporary study drug interruption is an acceptable method to manage AEs related to any of the study treatments.

Before permanently discontinuing the study drugs (regardless of whether initiated by the participant, Investigator or Sponsor), an interruption should be considered. Participants who have temporarily interrupted study treatment should be considered to restart as soon as medically justified in the opinion of the Investigator and after discussion with the Medical Monitor.

Temporary interruption in presence of ongoing clinical benefit:

If a participant has achieved clinical benefit (i.e., durable disease control with stable disease [SD], partial response [PR], or complete response [CR]), as determined by the Investigator and the Sponsor after an integrated assessment of radiographic data, biopsy result (if available), and clinical status, study treatment may be paused at the discretion of the Investigator after documented agreement with the Medical Monitor.

While the treatment is paused, assessments per SoA (Section 1.3) will be suspended, except for tumor assessments. The span of the treatment pause is to be included in the calculation of the maximum treatment period duration (24 months from C1D1 to discontinuation visit), as per Section 4.1.1.

Restarting study treatment should be considered as soon as medically justified in the opinion of the Investigator. If during the treatment pause, signs of disease progression emerge, study treatment may be reintroduced after consultation with the Medical Monitor if the study is still open. PK and ADA samples should be collected pre-dose and at the end of the infusion (PK only) on the day that the treatment is reintroduced. For the remaining samples, the SoA will be followed according to the “Subsequent cycles”

category (Section 1.3). Additional unscheduled samples may be collected at the discretion of the Investigator or upon request from the Sponsor if clinically indicated.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants have the right to withdraw voluntarily from the study at any time for any reason. In addition, the Investigator has the right to withdraw a participant from the study for medical conditions that the Investigator or Sponsor determines, may jeopardize the participant's safety if he/she continues in the study.

If possible, information on reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Participants will not be followed for any reason after consent has been withdrawn.

When a participant voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the participant specifically requests for these to be discarded or local laws require their immediate destruction. However, if samples have been tested prior to withdrawal, results from those tests will be used as part of the overall research data. A participant's withdrawal from this study does not, by itself, constitute withdrawal of samples donated to the Research Biosample Repository (RBR).

Participants who withdraw from the study for safety reasons will not be replaced. Participants who withdraw from the study for other reasons may be replaced as described in Section 7.

For data to be collected at the time of study discontinuation and at safety and follow-up visits, and for any further evaluations that need to be completed, see the SoAs (Section 1.3).

Participants will be treated until progressive disease, unacceptable toxicities, or withdrawal of consent.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if the participant 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, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of sites or of study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their time points are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the SoA.

Exceptional measures during the COVID-19 pandemic, such as adjustments in study visits, may be considered if in the overall best interest of the participant.

Adjustments may include:

- Use of alternative facility for assessments (e.g., local laboratory or imaging centers)
- Replacement of a study visit with alternative methods for assessments (such as phone contacts or virtual visits to assess safety)
- Postponement of a study visit or individual assessments

A robust benefit-risk assessment should be performed by the Investigator and discussed with the Medical Monitor. This assessment will be fully documented and any deviations to the protocol will be recorded in accordance with the Sponsor's standard procedure.

8.1 EFFICACY ASSESSMENTS

8.1.1 Tumor and Response Evaluations

Tumor response will be evaluated according to both RECIST v1.1 (Appendix 13) and immune RECIST (iRECIST, Appendix 14). Tumor lesions will be assessed at screening and every 8 weeks (± 7 days) after first dose (i.e., C1D1) -regardless of any treatment delays - for the first year, and then every 12 weeks (± 7 days) thereafter until disease progression. The visit at which a response assessment shows progressive disease may be used as the discontinuation visit. For participants who discontinue treatment for any other reason than disease progression: an end of study CT/MRI scan is only to be performed if it was done ≥ 28 days prior to this day. In addition, a CT/MRI scan to be performed at the safety follow-up visit.

Response will be assessed by the Investigator based on physical examinations and CT scans (or MRI) of chest, abdomen, and pelvis as defined in the SoAs (Section 1.3). CT scans of the neck should be included, if clinically indicated. Ultrasound and x-rays are not acceptable for monitoring target lesions. All measurable disease must be documented at screening and re- assessed at each subsequent tumor evaluation.

A CT or MRI scan (with IV contrast unless contraindicated) of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an ambiguous CT scan. Patients with untreated or actively progressing CNS metastases are not eligible for the study (see Section 5.2). Stable brain metastases must be evaluated at each tumor assessment with the same radiographic procedure as the baseline. Patients without brain metastases do not need brain scans for tumor assessment unless clinically warranted.

Consistency of consecutive CT scans (or MRIs) should be ensured during all assessments for each participant; the same method of assessment (preferable also by same evaluator) and the same technique must be used to evaluate lesions throughout the entire study. Use of CT (or MRI) is required for baseline lesions $<$20 mm and must be documented in medical records and used consistently throughout the study. The same radiographic procedure used to define measurable disease sites at screening must be used throughout the study (e.g., the same contrast protocol for CT scans). Tumor measurements should be made by the same Investigator/radiologist for each participant during the study to the extent that this is feasible. At the Investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

The data collected for RECIST v1.1 will be used by the Sponsor to programmatically calculate time point responses for iRECIST, a recently published set of guidelines developed by the RECIST working group in an effort to harmonize immune-based response criteria across the academic and industrial cancer immunotherapy field (Seymour et al. 2017).

In the absence of clinical deterioration, any initial assessment of radiological progressive disease should be confirmed by a repeat evaluation at the next time point for tumor assessment. As with other immunotherapies, treatment beyond RECIST progression could be considered after approval of the Sponsor (see Section 7 for details on continuing treatment).

All tumor assessments after baseline may be done within one week of the scheduled visit. Confirmation of objective responses (partial response [PR] and complete response [CR]) will be done at the next scheduled visit after at least 28 days from the initial response.

8.1.2 Photography of Cutaneous Lesions

Cutaneous lesions not evaluable by CT or MRI will be documented by anonymized high-resolution, color digital photography, including a ruler to estimate lesion size. Cutaneous lesions may be considered target lesions if they meet RECIST v1.1 criteria (see Appendix 13), otherwise they may be considered non-target lesions.

Photographs of cutaneous lesions will be taken at screening and on the same day as tumor assessment visit or at the first clinic visit following each tumor assessment.

8.2 SAFETY ASSESSMENTS

Planned time-points for all safety assessments are provided in the SoA (Section 1.3).

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious AEs of special interest (NSAESI); measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs, electrocardiograms (ECGs); and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

8.2.1 Physical Examinations

Complete physical exam: A complete physical examination should include an examination of head and neck, eyes, ears, nose, and throat; cardiovascular; dermatology; musculoskeletal; respiratory; gastrointestinal; genitourinary and neurological systems.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Targeted (symptom-directed) physical exam: At subsequent visits (or as clinically indicated), targeted, symptom-directed physical examinations should be performed. Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, dermatological, neurologic, and any system that might be associated with tumor assessment [e.g., lymph nodes, liver, and spleen and those systems associated with symptoms] or potential drug-related toxicity; for details see RO7296682 IB and atezolizumab IB). Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

8.2.2 Height and Weight

Height and body weight must be measured at the time points indicated in the SoA (Section 1.3) and recorded in eCRF. If body weight is assessed three days or less before the day of the planned dosing, this value should be used and recorded in the eCRF.

8.2.3 Vital Signs

Vital signs will be recorded at the time points specified in the SoA (Section 1.3).

Vital signs will include measurements of systolic and diastolic blood pressure, respiratory rate, HR, and body temperature while the participant is in a sitting or semi-supine position.

Blood oxygen saturation will be measured at baseline by pulse oximetry.

For vital sign assessments on infusion days, refer to Section 6.1.1. It is not required to capture vital signs collected during the infusion in the eCRF unless abnormalities are observed.

8.2.4 Electrocardiograms

Triplicate 12-lead ECG measurements will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the HR and measures PR interval, QRS complex, QT interval, and QT corrected for HR (QTc) interval.

At each time point at which triplicate ECGs are required, three individual ECG tracings should be obtained as closely as possible in succession, but no more than 5 minutes apart. The average of the 3 readings will be used to determine ECG intervals (e.g., PR, QRS, and QT). Additional unscheduled ECG assessments should be performed in case of abnormalities and if clinical symptoms occur. ECGs for each participant should be obtained from the same machine whenever possible. To minimize variability, it is important that participants be in a resting position for at least 10 minutes prior to each ECG evaluation. ECGs should preferably be performed prior to any scheduled vital sign measurements, blood draws, and prior to dosing.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the participant's permanent study file at the site. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory. ECG characteristics, including HR, QRS duration, and PR, and QT intervals, will be recorded on the eCRF. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

8.2.5 Transthoracic Echocardiogram or Multiple-Gate Acquisition Scans

TTE or MUGA scans will be performed according to the time points specified in Section 1.3 and more frequent monitoring should be performed in case of left ventricular ejection fraction (LVEF) decline during treatment. This may be further repeated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity. TTE or MUGA scans will be used to monitor the cardiac parameters of function (i.e., LVEF).

8.2.6 Chest X-ray

A chest x-ray will be performed at baseline, if the baseline tumor assessment does not image the chest/thorax, and as clinically indicated during the study treatment period (see Section 1.3).

8.2.7 Clinical Safety Laboratory Assessments

Local Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. A list of local laboratory tests to be performed is provided in Appendix 4 and these assessments must be conducted in accordance with the SoA (Section 1.3).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those, which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

Results of clinical laboratory testing will be recorded on the eCRF.

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor participant safety.

Where the clinical significance of abnormal laboratory results at screening is considered uncertain, screening laboratory tests may be repeated before randomization to confirm eligibility.

Central Laboratory Assessments

Central laboratory assessments must be conducted in accordance with Section 1.3. Samples will be sent to one or several central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

Based on continuous analysis of the data, any sample type not considered critical for safety may be stopped at any time if the data from the samples collected do not produce useful information.

8.2.8 Medical History (including Smoking History) and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, THC and its derivative, nutritional supplements) used by the participant within 30 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity and will be recorded in the eCRF.

Smoking history will be assessed by verifying if participant is a current smoker, former smoker, or has never smoked before.

8.2.9 ECOG

Performance status will be measured using the ECOG Performance Status (PS) Scale (Table 9). It is recommended, where possible, that a participant's performance status will be assessed by the same person throughout the study.

Table 9 ECOG Status

Grade	ECOG Status
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 house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Reference: Oken et al. 1982.

8.2.10 Other Non-Safety Assessment(s): Real wOrld PROgnostic score

The ROPRO score must be measured at the time point indicated in the SoA (Section 1.3) and recorded in a "ROPRO calculator" (system to be determined). For the required parameters, see Table 10. Upon entry, the ROPRO value will be reported to the site in order to verify patient eligibility in the study.

Table 10 Real wOrld PROgnostic score

ROPRO Assessments	Parameters
Demographics	Sex, age
Anthropometric measurements	Height, weight
Smoking	Smoking status
Vital signs	Systolic blood pressure, heart rate, oxygen saturation
Hematology	Hemoglobin, platelets, leukocytes, lymphocytes, neutrophils, eosinophils, monocytes
Clinical chemistry	Urea or blood urea nitrogen, calcium, chloride, glucose, total protein, albumin, total bilirubin, ALP, ALT, AST, LDH
Cancer status	Number of metastatic sites*, tumor stage
ECOG performance	ECOG

* Number of metastatic sites does not equal the number of total lesions but the number of organs, which have tumor lesion(s). For example, a participant with two liver lesions and one lung lesion, has two metastatic sites corresponding to two organs that have tumor lesions.

8.2.11 Optional Symptom Questionnaire for Part II Participants

Participants in Part II of this trial will be offered an optional questionnaire to collect symptoms electronically. The questions have been selected on the basis of expected symptoms because of known or potential atezolizumab and RO7296682 adverse drug reactions.

The electronic questionnaire will be self-administered at home at specified time points during the study (see Section 1.3). The questionnaire, translated into the local language as appropriate, will be completed through use of an app downloaded on the participant's own electronic device. The link to download the app and instructions for completing the instruments electronically will be provided by the site staff. If the participant does not have access to a device capable of installing the app, a web link for the electronic completion of the questionnaire may be provided. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

Participants should be given the following instructions for completing the electronic questionnaire at home:

- Participants should complete the questionnaire in a quiet area with minimal distractions and disruptions.
- Participants should answer questions to the best of their ability; there are no right or wrong answers.

Participants should not obtain advice or help from others to select responses (e.g., family members or friends) when completing the questionnaire.

Adverse event reports will not be derived from this tool by the Sponsor. In addition, the Sponsor will make no attempt to reconcile patient reports of treatment-related symptoms with Investigator reports of AEs. Though the Investigator Sites are not expected to review the data for AEs, they are encouraged to review and to discuss symptoms to keep participant engagement high.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 2. The NSAESI and disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are discussed in Sections 8.3.6 and 8.3.8.

The Investigator and any qualified designees are responsible for ensuring that all AEs (including assessment of seriousness, severity and causality; see Appendix 2) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2.

Procedures used for recording AEs are provided in Appendix 3.

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

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Investigators will seek information on AEs at each participant's contact. All AEs, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF as follows:

After informed consent has been obtained **but prior to initiation of study treatment**, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies). Any other AE should not be reported.

After initiation of study treatment, all AEs, regardless of relationship to study treatment, will be reported until the safety follow-up visit, or participant discontinuation, whichever occurs first. DLTs will be reported during the DLT assessment window.

Post-study AEs and SAEs: The Investigator is not required to actively monitor participants for AEs after the end of the AE reporting period – that is, after the safety follow-up visit.

However, if the Investigator learns of any SAE (including a death) or other AEs of concern that are believed to be related to prior treatment with study treatment, at any

time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor. For the procedure of reporting, see Appendix 2.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all participant evaluation timepoints.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the event is otherwise explained, the participant is lost to follow-up (Section 7.3), or the participant withdraws consent. Every effort should be made to follow all SAEs considered related to study treatment or study-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 8.3.5.

8.3.3.2 Sponsor Follow-Up

For SAEs, NSAESIs, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional event 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 event.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE 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 both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then, file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

For immediate and expedited reporting requirements from Investigator to Sponsor and from Sponsor to Health Authority, investigators, IRB, and IEC, see Appendix 2.

8.3.4.1 Emergency Medical Contacts

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

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 4 months after the last dose of RO7296682/atezolizumab.

Male participants will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study or within 28 days after the final dose of RO7296682.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the pregnancy reporting process as detailed in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs (Appendix 5).

8.3.6 Non-Serious Adverse Events of Special Interest

NSAEIs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2 for reporting instructions).

NSAEIs for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Appendix 3.
- Suspected transmission of an infectious agent by the study treatment, defined as:

  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.

Atezolizumab-specific NSAESIs:

- Pneumonitis.
- Colitis.
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis.
- Hepatitis, including AST or ALT $>$ 10 $\times$ ULN.
- Systemic lupus erythematosus.
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis.
- Events suggestive of hypersensitivity, IRRs, CRS, hemophagocytic lymphohistiocytosis (HLH), and macrophage activation system (MAS).
- Nephritis.
- Myositis.
- Myopathies, including rhabdomyolysis.
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis).
- Grade $\geq$ 2 cardiac disorders.
- Vasculitis.
- Autoimmune hemolytic anemia.
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis).
- *Myelitis*
- *Facial paresis*

8.3.7 Dose-Limiting Toxicities (Immediately Reportable to the Sponsor)

During the DLT/dose-limiting AE (DLAE) assessment window, AEs identified as DLTs/DLAEs, as defined in Section 4.1.3, are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2, Section 5 for reporting instructions).

8.3.8 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Not applicable.

8.3.9 Management of Specific Adverse Events

This section describes the management of specific AEs based on nonclinical toxicology and clinical experience of RO7296682 as well the clinical experience with molecules in the same class. The most common toxicity expected from RO7296682 are IRRs, immune-mediated AEs (imAEs) and skin toxicity. The most common toxicities from CPIs (i.e., atezolizumab) are IRRs and imAEs.

This is the first-in-human evaluation of the combination of RO7296682 and atezolizumab, therefore, the actual risk of combined toxicity is unknown. Nonclinical toxicology studies have not been conducted with the combination of RO7296682 and atezolizumab. Based on nonclinical and/or clinical studies with each molecule as a single agent, as well as on molecules with similar mechanisms of action, there is a potential for overlapping toxicities in participants treated with RO7296682 in combination with atezolizumab. For further details on the identified and potential risks associated with RO7296682 treatment, see the Investigator's Brochure.

Toxicities associated or possibly associated with RO7296682 treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to determine a possible immunogenic etiology. For further details on the potential risks associated with RO7296682 treatment, see the Investigator's Brochure.

Measures will be taken to ensure the safety of participants in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of participants during the study. Administration of RO7296682 will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions as well as life-threatening conditions including intensive care unit.

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional

guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a 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.

For events in which management guidelines are not covered in this protocol, participants should be managed as deemed appropriate by the Investigator according to best medical judgment and local medical guidelines. Clinical judgment may be applied, and a risk/benefit consideration may suggest deviating from these guidelines. In this specific case, decisions on study treatments will be taken by the Investigator upon consultation with the Medical Monitor.

Guidelines for management of specific AEs are provided in Table 11, Table 12, and Appendix 12.

8.3.9.1 Management Guidelines for Skin Toxicity for RO7296682 and/or atezolizumab

Treatment-emergent rash may be associated with RO7296682 and/or atezolizumab.

In study WP41188, skin-related AEs were observed in 42% of the patients treated up to a dose level of [redacted] mg. The majority of cases of rash were mild in severity and self-limited, with or without pruritus (see Investigator's Brochure).

Participants should be advised to implement particular care of the skin and refer to the study staff in case of dermatologic issues especially after biopsy. After biopsy, study staff should protect the skin and ensure that prevention of superinfections is applied.

A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 11.

Table 11 Management Guidelines for Skin Toxicity

Event	Management
Dermatologic event, Grade 1	• Continue RO7296682 and/or atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines). • Recommend taking anonymized standard clinical photography
Dermatologic event, Grade 2	• Hold RO7296682 and/or atezolizumab until resolution to Grade 1 or baseline. • Consider participant referral to a dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with oral and/or higher-potency topical corticosteroids if event does not improve. • Recommend taking anonymized standard clinical photography
Dermatologic event, Grade 3	• Withhold RO7296682 and/or atezolizumab after event onset.[a] • Refer participant to a dermatologist. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1 to 2 mg/kg/day if event does not improve within 48 to 72 hours. • If event resolves to Grade 1 or better, resume RO7296682 and/or atezolizumab. • If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before RO7296682 and/or atezolizumab can be resumed. • If event does not resolve to Grade 1 or better while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact Medical Monitor.[b] • Recommend taking anonymized standard clinical photography
Dermatologic event, Grade 4	• Permanently discontinue RO7296682 and/or atezolizumab and contact Medical Monitor.[b] • Recommend taking anonymized standard clinical photography

[a] RO7296682 and/or atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period must be agreed upon by the Investigator and the Medical Monitor.

[b] Resumption of RO7296682 and/or atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. Participants can be re-challenged with RO7296682 and/or atezolizumab only after approval has been documented by the Investigator (or an appropriate delegate) and the Medical Monitor.

8.3.9.2 Management Guidelines for Infusion-Related Reactions/Cytokine-Release Syndrome for RO7296682 and/or Atezolizumab

Administration of therapeutic antibodies may cause IRRs, which may include symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea, and vomiting. Such reactions typically occur during or shortly after the infusion, predominantly the first infusion. The incidence and severity typically decrease with subsequent infusions.

No premedication is indicated for the administration of Cycle 1 of RO7296682 and/or atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine release syndrome (CRS) with RO7296682 and/or atezolizumab may receive premedication with antihistamines, antipyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating RO7296682 and/or atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of mAbs and may be reported with RO7296682 and/or atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of administration and are generally mild to moderate in severity.

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

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for *the* medical management of IRRs and CRS are provided in Table 12.

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a 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*'s* judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Table 12 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1[a] Fever[b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment,[c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (>2 days) or in participants with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral pre-medication with antihistamines, *antipyretic medications*, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2[a] Fever[b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen[d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in Appendix 12. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize participant (monitoring in the ICU is recommended), permanently discontinue RO7296682 and/or atezolizumab, and contact *the* Medical Monitor. • If symptoms resolve to Grade 1 or better for three consecutive days, the next dose of RO7296682 and/or atezolizumab may be administered. For subsequent infusions, consider administration of oral pre-medication with antihistamines, *antipyretic medications*, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for three consecutive days, contact *the* Medical Monitor.

Event	Management
Grade 3[a] Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor.[f] • Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in Appendix 12. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Hospitalize participant until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit participant to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. For participants who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the Investigator and in consultation with the Medical Monitor.
Grade 4[a] Fever[b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue RO7296682 and/or atezolizumab and contact Medical *the* Monitor.[f] • Administer symptomatic treatment.[c] • Admit participant to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in Appendix 12. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] For participants who are refractory to anti-cytokine therapy, experimental treatments[g] may be considered at the discretion of the Investigator and in consultation with the Medical Monitor. • Hospitalize participant until complete resolution of symptoms.

Table 12 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (Cont.)

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

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

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v 5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

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

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

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

[e] There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune CPIs (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

[f] Resumption of RO7296682 and/or atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the event. Participants can be re-challenged with RO7296682 and/or atezolizumab only after approval has been documented by the Investigator (or an appropriate delegate) and the Medical Monitor. For subsequent infusions, administer oral pre-medication with antihistamines, *antipyretic medications*, and/or analgesics, and monitor closely for IRRs and/or CRS. Pre-medication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit–risk ratio.

[g] Refer to Riegler et al. (2019) for information on experimental treatments for CRS.

8.3.9.3 Management Guidelines immune-mediated Adverse Events for RO7296682 and/or atezolizumab

Most imAEs observed with immunomodulatory agents have been mild and self-limiting; however, such events should be recognized early and treated promptly to avoid potential major complications. Any organ or tissue can be involved, although some imAEs occur much more commonly than others. The most frequently occurring imAEs affect skin, colon, endocrine organs, liver, and lungs. Others are very infrequent, but may be very serious, even lethal, such as neurological disorders and myocarditis.

The following are general recommendations for management of any other AEs that may occur and are not specifically listed in the organ specific imAE toxicity management guidelines in Appendix 12.

- *Participants 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 AEs 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.*
- Although management varies according to the organ system affected, in general, RO7296682 *and/or atezolizumab* therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities. *Corticosteroids (initial dose of 0.5 to 1 mg/kg/day of prednisone or equivalent) may be administered.*
- RO7296682 in combination with atezolizumab therapy may be suspended for most Grade 2 toxicities, with consideration of resuming when symptoms revert to Grade 1 or less. Corticosteroids may be administered.
- *For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.*
- Grade 3 toxicities generally warrant suspension of RO7296682 in combination with atezolizumab and the initiation of high-dose corticosteroids (prednisone, 1 to 2 mg/kg/day, or methylprednisolone, 1 to 2 mg/kg/day). Corticosteroids should be tapered over the course of *over 1 month to 10 mg/day oral prednisone or equivalent, before RO7296682 and/or atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.*
- In general, permanent discontinuation of RO7296682 in combination with atezolizumab is recommended with grade 4 toxicities, with the exception of endocrinopathies that have been controlled by hormone replacement.
- *The Investigator should consider the benefit–risk balance for a given participant prior to further administration of RO7296682 in combination with atezolizumab. Resumption of atezolizumab 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 RO7296682 in combination with atezolizumab should be based on the Investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.*

Please refer to the American Society of Clinical Oncology (ASCO) (Puzanov et al. 2017) and the European Society for Clinical Oncology (ESMO) clinical practice guidelines for management of imAEs (Haanen et al. 2017).

For organ specific imAE toxicity management guidelines, refer to Appendix 12.

8.4 TREATMENT OF OVERDOSE

Study treatment overdose is the accidental administration of a drug in a quantity that is higher than the assigned dose. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects (for further details, see Sections 5 and 5.2 of Appendix 2).

Decisions regarding dose-interruptions or modifications (if applicable) will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

In the event of an overdose, the Investigator should:

- Contact the Sponsor's Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved.
- Obtain a blood sample for (unscheduled) PK analysis as soon as possible after the overdose, if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose, as well as the duration of the overdose, in the CRF.

8.5 PHARMACOKINETICS

Mandatory blood samples to evaluate concentrations of study treatment will be collected from an IV line from the arm opposite to that used for study treatment administration. The date and time of each sample collection will be recorded in the eCRF. RO7296682 and atezolizumab levels will be analyzed by using validated assays. The PK assessments will be performed as outlined in Section 1.3.

During the course of the study, PK sampling time points may be modified on the basis of emerging data to ensure the PK of RO7296682 can be adequately characterized (but without increasing overall blood collection volume for PK). Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then, archived in the Sponsor and site study files, but this will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

Additional PK samples will be taken at the time of treatment discontinuation, if the participant experiences an IRR, or if the participant experiences an AE leading to dose reduction or delay of RO7296682 administration (see Section 1.3 and Section 6.6 Dose Modifications).

Any residual material from PK samples may be used for ADA analyses and characterization, additional study-related exploratory biomarker profiling, identification, assay development purposes, and assay validation during the development of study or compound-related assays after the mentioned intended uses.

The PK blood samples will be destroyed within 2 years after the date of final clinical study report (CSR). Details on sampling procedures, sample storage, and shipment are given in the Study Flow Chart and Laboratory Manual.

8.6 IMMUNOGENICITY ASSESSMENTS

Although RO7296682 and atezolizumab are humanized antibodies, there is a risk that ADAs against RO7296682 or atezolizumab could develop. This could potentially reduce their efficacy and/or potentially result in symptomatic hypersensitivity reactions, in particular immune-complex reactions, or both.

Validated screening, confirmatory, and titer assays will be employed to detect potential ADAs against RO7296682 and atezolizumab at multiple time points before, during, and after treatment. If required, ADA-positive samples will be further characterized in exploratory assays.

Blood samples for ADA determination will be obtained as specified in the SoA (Section 1.3). The date and time of each sample will be recorded in the eCRF.

Additional ADA samples will be drawn at the time of treatment discontinuation or at the safety follow-up visits and in participants who experience a Grade ≥ 2 IRR and in participants with clinical signs of hypersensitivity reaction, in particular immune-complex reactions. In any case, for each collected ADA sample, a corresponding PK sample will be collected at the same time point for the determination of the RO7296682 and/or atezolizumab concentrations. See Section 1.3 for details.

Remaining volumes of ADA samples may be used for assay development/validation experiments, for compound-related exploratory analyses (e.g. PK or biomarker profiling), or to help develop further blood tests, after they are used for the mentioned intended uses.

The ADA blood samples will be destroyed within 2 years after the date of the final CSR.

Details on sampling procedures, sample storage and shipment are documented in the sample documentation.

8.7 PHARMACODYNAMICS AND BIOMARKERS ANALYSES

Samples will be collected at time points specified in Section 1.3 and may be modified or reduced based on emerging data. The number of samples will not exceed what is described in the SoA.

The PD outcome measures for this study are:

- Whole blood samples: Peripheral blood immune cells will be assessed with respect to the changes in the characteristics of lineage [redacted] activation (including but not limited to HLA-DR, etc.), differentiation [redacted] and [redacted] changes. These samples will also be used to undertake RO assessments for RO7296682. These samples will be taken from all participants enrolled in all parts of the study.

- Serum and/or plasma samples: PD biomarkers such as cytokines, disease-monitoring and inflammation markers (including but not limited to [redacted] will be analyzed. Because these measurements are also safety measure assessments during any IRRs, they will be examined to all participants enrolled in all Parts of the study. In addition, PD plasma ctDNA changes will be assessed on samples from participants enrolled in Parts II and III of the study.
- Archival tissue: For all participants enrolled in all parts of the study, the most recent archival tumor material must be provided to allow for immune contexture and for immune-phenotyping characterization as described for the fresh biopsies below and for the genetic and genomic analyses described in Section 8.7.1.2. In Part II specifically, only participants with [redacted], as assessed by their most recent archival tissues, will be eligible for the study (see Section 5.1). Archival tumor material will also be used to establish the individual tumor genetic alterations expected to be reflected on the ctDNA.
- Fresh tumor biopsy: Mandatory fresh tumor biopsy samples must be obtained for all participants enrolled in Part II and Part III at baseline and on treatment from a safely accessible site and after participant's consent (see Section 1.3). In Part II specifically, the samples collected at baseline will reflect the most recent immune phenotype ([redacted]) of the participant. Should the immune phenotype of the fresh biopsy be other than [redacted] (as evaluated by the archival sample), the particular participant will be assessed in a separate efficacy analysis population. Furthermore, in Part II and Part III the samples will be assessed for treatment-induced changes in immune cell numbers, lineage and activation characteristics, as well as changes in tumor markers such as PD-L1 and expression of FcγR, TCR Vβ repertoire. (The analyses will be performed with respect to changes in the characteristics of lineage [redacted], activation [redacted] differentiation [redacted] expression of FcγR, TCR Vβ repertoire).
- Healthy skin punch biopsy: Mandatory fresh skin biopsy samples must be obtained at baseline and on treatment for all participants enrolled in all Parts of the study after participant's consent (see Section 1.3). These samples will be assessed for treatment-induced changes in immune cell numbers, composition, and functional immune cell characteristics. The analyses will be undertaken by immunohistochemistry and/or genetic and genomic methods (see Section 8.7).

Residual plasma/serum samples (e.g. from PK and/or PD assessments) may be used for retrospective and longitudinal testing of bacterial or viral infection (including SARS-CoV-2) by serological methods. This testing may be performed for each participant. In addition to serving as an important safety measure, these analyses will inform as to any association of bacterial or viral infection and response to RO7296682 in combination with atezolizumab. In addition, residual blood, serum/plasma, tissue, and stool samples may also be used for additional (assay) validation experiments after the specified

analyses were performed. Details on sampling procedures, sample storage, and shipment are given in the Study Flow Chart and Laboratory Manual.

These samples will be destroyed within 2 years after the date of final CSR unless the participant gives specific consent for the remainder of the sample(s) to be stored for optional exploratory research within the RBR (see Section 8.9).

8.7.1 Genetic and Genomic Analyses

Whole blood samples for genetics will be taken at the time points mentioned in SoA (Section 1.3). These samples will be destroyed no later than 2 years after the date of final CSR, unless the participant gives specific consent for the remainder of the residual material to be stored for optional potential exploratory research within the RBR (see Section 8.9).

The results of such specimen analysis will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future. The specimens will also be made available for future biomarker research towards further understanding of RO7296682, treatment of related diseases and AEs.

8.7.1.1 Clinical Genotyping

A mandatory clinical genotyping whole blood sample will be taken for DNA extraction from every participant. If the sample is missed on Day 1, it can be collected at any other scheduled visit.

The DNA may be used to identify biomarkers that are predictive of response to treatment with RO7296682 in combination with atezolizumab, and will help to better understand the pathogenesis, course, and outcome of the studied cancer types. Genes associated with immunity, including but not limited to KIR, HLA, etc. and how these affect the PK, PD, efficacy, or safety of the study treatment will be explored. This may include genome sequencing to investigate biomarkers that might predispose the participant for drug-associated autoimmunity or to a positive tumor response following study treatment. These assessments will be performed if safety or efficacy rationales develop. The samples will be destroyed no later than 2 years after the date of final CSR, unless the participant gives specific consent for the remainder of the residual material to be stored for optional potential exploratory research within the RBR (see Section 8.9). Details on sampling procedures, sample storage, and shipment are given in the Study Flow Chart and Laboratory Manual.

Data arising from all biosamples including samples for analyses of inherited DNA will be subject to the confidentiality standards described in Section 1.4 of Appendix 1.

8.7.1.2 Whole Genome/Exome/Targeted DNA Analysis

Archival tumor tissue, fresh tumor tissue sample, and blood will be provided at the visits specified in the SoAs (Section 1.3). These may be sent to one or more laboratories for DNA and/or RNA extraction for exploratory research to enable germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing (NGS), or other genomic analysis methods on genomic biomarkers (including, but not limited to, cancer related genes and biomarkers associated with common molecular pathways, or immune-related markers [e.g., TCR sequence/TCR Vb, ctDNA], microsatellite instability and tumor mutation burden).

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

Given the complexity and exploratory nature of these analyses, data and analyses will not be shared with Investigators or study participants unless required by law. Participants will not be identified by name or any other personally identifying information. Data arising from all biosamples, including samples for analyses of inherited DNA, will be subject to the confidentiality standards described in the sample documentation.

Transcriptome Analysis

Tissue biopsy/blood (other matrix possible) will be collected as outlined in the SoA (Section 1.3) for RNA extraction and subsequent gene expression profiling to enable:

- Identification of PD biomarkers.
- Identification of response predictive biomarker.
- Assessment of treatment response (PD).

8.8 PHARMACODYNAMICS AND BIOMARKER SAMPLES

The samples collected during the study may also be used for research purposes to identify biomarkers useful for predicting and monitoring response to RO7296682 in combination with atezolizumab, identifying biomarkers useful for predicting and monitoring safety, assessing PD effects, and investigating mechanism of therapy resistance of RO7296682 in combination with atezolizumab. Additional markers may be measured in case a strong scientific rationale develops.

Samples should be collected as specified in the SoAs (Section 1.3).

Based on continuous analysis of the data in this study and other studies, any sample type and/or analysis not considered critical for safety may be stopped at any time if the data from the samples collected do not produce useful information.

Unless otherwise specified below, samples (including blood, slides, extracts, etc.) will be destroyed no later than 2 years after the date of final CSR. For participants who consent to the RBR, leftover samples will be transferred to the RBR (Section 8.9).

Any remaining blood and tissue samples after the specified analyses may also be used for additional (assay) validation experiments. Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to the drug target, disease process, pathways associated with disease state, and/or mechanism of action of the study treatment.

8.8.1 Mandatory Samples

The following samples for PD and biomarker research are required and will be collected from all participants in all parts of the study:

- Whole blood will be collected and assessed with respect to the analyses described in Section 8.7 for list of analyses.
- Serum and/or plasma will be collected and assessed with respect to the analyses described in Section 8.7 for list of analyses. In the event of an AE temporally related to study drug administration, additional samples will be collected.
- For clinical genotyping, from every participant in the study, a baseline mandatory whole blood sample will be taken for DNA extraction and assessed with respect to the analyses described in Section 8.7 for list of analyses. If the sample is missed on D1, it can be collected at any other scheduled visit.

Archival tumor (for list of analyses, refer to Section 8.7). FFPE archival tumor tissue is to be obtained from all participants, if available (if not available, slides are acceptable). In the case of unavailable archival sample, a fresh biopsy needs to be provided. **Note**, in Part II, archival tumor tissue from a metastatic site (and NOT primary tumor) is required in order to assess the participant's eligibility; see Section 5.1. Prior to signing the main consent form, patients must sign the **pre-screening Informed Consent Form** in order to allow for confirmation of their tumor inflammation phenotype in the archival sample.

Healthy skin punch biopsy (for detailed list of analyses, refer to Section 8.7).

The following samples for PD and biomarker research are required and will be collected only in Part II and Part III of the study:

- Fresh tumor biopsy: (refer to Section 8.7 for analyses description) Samples (each time point consisting preferably of at least three core specimens) will be collected on two occasions (once at baseline and once during the study treatment period [C2D8]) from a safely accessible site and after participant's consent. Collection of tumor biopsies will be guided by ultrasound or CT scan using a 16-gauge needle to provide cores of at least 20 mm in length. Bone lesion biopsies, bronchoscopy/trans-bronchial biopsies, and cytology fine needle aspirates are not acceptable. The baseline and on-treatment biopsies should preferably be taken from

the same accessible, “non-critical” tumor lesion (metastasis) to ensure comparability. The location of each biopsy will be documented in relation to each tumor lesion, as determined by imaging. If feasible, on-treatment biopsies may be repeated if the initial biopsy did not contain sufficient tumor material for analysis. If preliminary data suggest, alternative on-treatment, tumor biopsy time points may be considered upon joint agreement between Investigators and the Sponsor.

- Healthy skin punch biopsy (refer to Section 8.7 for analyses description). A punch biopsy will be collected at baseline and on treatment (C2D8) from healthy skin.

Based on continuous analysis of the data in this study and other studies, any sample type and/or analysis not considered critical for safety may be stopped at any time if the data from the samples collected does not produce useful information, or at the Sponsor’s request.

The blood and tissue samples will be destroyed within 2 years after the date of final closure of the clinical database. Remainder of archival tumor blocks will be returned where possible. Other residual tissue material (slides, extracts, on-study blocks, etc.) and residual samples (blood, serum, plasma, DNA, RNA) will be destroyed within 2 years after the final CSR is available unless the participant gives specific consent for the remainder of the sample(s) to be stored for optional exploratory research.

8.8.1.1 Optional Samples

Optional tissue biopsies may be taken at any time point and at any part of the study per Investigator’s discretion, for example due to skin related AEs, disease progression, or long-lasting SD, if the participant consents to these samples being taken to aid the understanding of immune resistance or homeostasis mechanisms. At the discretion of the Investigator, obtaining a healthy tissue alongside the symptomatic/pathological site would be desirable in order to serve as control tissue. In the case of skin-related AEs, skin biopsies should be obtained from the sites of symptomatic skin as well as from an unaffected site of the skin serving as control tissue for histological- and immuno-histochemical examination.

Assessments as well as biological samples, which are not protocol-specified and are conducted by the Investigator in response to an AE (e.g., laboratory tests, etc.) can be performed at any time during the study and the results may be shared with the Sponsor in order to further inform about the safety profile of RO7296682.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. A separate signature will be required to document a participant’s agreement to allow any remaining samples to be used for exploratory research.

Optional tumor and/or healthy tissue samples will be destroyed within 2 years after the date of final closure of the clinical database.

8.9 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

8.9.1 Overview of the Research Biosample Repository

The Roche RBR is a centrally administered group of facilities for the long-term storage of human biologic samples, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage and analysis of the 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 during C1D1 from participants who give specific consent to participate in the optional RBR.

Collected RBR samples will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy or progressive disease.
- To identify safety biomarkers that are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation.
- To increase knowledge and understanding of disease biology and drug safety.
- To study treatment 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.

RBR samples will be stored and used until no longer needed or until they are depleted. The RBR storage period will be in accordance with the IRB/EC‑approved ICF and applicable laws (e.g., Health Authority requirements).

8.9.2 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 study treatment, diseases or drug safety:

- C1D1 RBR samples.
- Leftover plasma samples.
- Leftover serum samples.
- Leftover blood samples.
- Leftover tissue (fresh tumor, fresh skin, archival tumor) samples.
- Leftover blood samples for DNA extraction.

Optional Stool Samples

Participants will be given the option of consenting to provide stool samples. Dietary intake is a central determinant of changes in the microbiota, which influences the immunological responses in the intestine and thereby affects potential AEs during immunotherapies. A nutritional assessment will therefore be performed at baseline to better correlate the profiles of the microbiota to safety-relevant immune responses.

Upon consent, participants will be requested to provide optional stool samples at the following time points:

- At screening, any time prior to C1D1.
- On-treatment, every 12 weeks (±14 days).
- Upon occurrence of colitis, as assessed and confirmed by the Investigator.

Screening stool samples of participants who are not enrolled in the study will be destroyed.

Additional stool samples may be requested at any time point per Investigator's discretion, for example when resuming treatment post colitis.

For sampling procedures, storage conditions, and shipment instructions, see the sample flowchart and additional instruction documents.

8.9.3 Leftover of Sample Derivatives such as DNA and RNA

The samples collected for DNA extraction include, but is not limited to genomic analysis and may be sent to one or more laboratories for analysis of germline or somatic mutations via WGS, WES, NGS, or other genomic analysis methods.

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

Samples may be sent to one or more laboratories for analysis for of germline or somatic mutations via WGS/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 AEs.

Participants will not be identified by name or any other personally identifying information. 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 all samples, dates of consent and sample collection should be recorded on the associated RBR page of the eCRF. Details on processes for collection and shipment of these samples can be found in separate sample documentation.

RBR samples will be stored and used until no longer needed or until they are depleted. The RBR storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g., Health Authority requirements).

The repository samples will be subject to the confidentiality standards (as described under Confidentiality and in Appendix 1).

8.10 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.11 TIMING OF STUDY ASSESSMENTS

8.11.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Pre-screening ICFs and ICFs for enrolled participant and for participants who are not subsequently enrolled will be maintained at the study site.

All screening and pre-treatment assessments (related to entry criteria), must be completed and reviewed to confirm that participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

An Eligibility Screening Form documenting the Investigator's assessment of each screened participant with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site.

8.11.2 Assessments during Treatment

Under no circumstance will participants who enroll in this study and have completed treatment as specified, be permitted to re-enroll in the study.

All assessments must be performed as per SoAs (Section 1.3). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the SoAs.

8.11.3 Assessments at Study Completion/Early Termination Visit

End of Treatment/Early Discontinuation: Participants who complete the treatment or discontinue from the study early, will be asked to return to the clinic 28 (± 7) days after the last dose of study drug or last data point. The visit at which a response assessment shows progressive disease may be used as the Early Discontinuation visit. Assessments should be completed as detailed in the SoA (Section 1.3).

8.11.4 Follow-Up Assessments

Safety Follow-Up/End of Study: Participants who complete the treatment or discontinue from the study early, will be asked to return to the clinic 135 (± 30) days after the last dose of study drug or last data point determined for an End of Treatment Visit. Assessments should be completed as detailed in the SoA (Section 1.3).

Survival Follow-Up: The sites will provide to the Sponsor (using a designated section of the eCRF) with an update on survival status 90 (± 7) days after the Safety Follow-Up visit and then every 3 months (± 2 weeks) thereafter up until 24 months post initial treatment (or until study closure) for each participant enrolled in the study. Patients who screen-failed due to the ROPRO score will also be followed up for survival.

After the study completion/early termination visit, AEs should be followed as outlined in Sections 8.3.1 and 8.3.3.

8.11.5 Assessments at Unscheduled Visits

For activities that required to be performed in case of an unscheduled visit, refer to the SoA (Section 1.3).

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

There is no formal statistical model or pre-planned formal hypothesis testing in this study.

9.2 SAMPLE SIZE DETERMINATION

Part I:

The maximum total number of participants in the dose escalation portions of Part I will be approximately 60 DLT-evaluable participants on a Q3W schedule. The exact sample size cannot be pre-determined and depends on the number of cohorts needed to reach

a MTD and/or RP2D. However, the simulations presented in Section 3 of Appendix 11 show simulated sample sizes in a variety of toxicity scenarios.

Part II:

Approximately 60 CPI-experienced participants with NSCLC, HNSCC, and MEL will be enrolled in Part II in order to have around 10 participants per indication and aim for at least 30 response-evaluable participants with an [redacted], which is confirmed in the fresh baseline biopsy. With around 10 participants per indication, there will be sufficient number for decision making to open Part III cohorts (Table 18). Participants with MEL, NSCLC and HNSCC which are not amenable to standard treatment, will be enrolled in Part II; however, if emerging data suggest alternative indications should be pursued, then participants with ovarian, esophageal, TNBC or other indications as deemed fit may be considered.

Part III

In Part III, each tumor-specific cohort for NSCLC, HNSCC, and MEL may be opened for approximately 20 response-evaluable participants given that any of the gating criteria defined in Section 9.5 are met based on the corresponding indication in single agent dose expansion of WP41188, Part I of this study, or Part II of this study. The futility interim analysis will be performed when the first 10 response-evaluable participants have mature data in each tumor-specific cohort. The detail of the futility analysis is provided in Section 9.5.

For the CPI-experienced HNSCC cohort in Part III, the sample size of 20 response-evaluable participants allows to declare futility with a probability of 92% under the assumption that the true ORR is 5%, based on the posterior probability for ORR to be below 20% with a 70% confidence level.

For CPI-experienced NSCLC cohort in Part III, the sample size of 20 response-evaluable participants allows to declare futility with a probability of 87% chances under the assumption that the true ORR is 10%, based on the posterior probability for ORR to be below 25% with a 70% confidence level.

For CPI-experienced MEL cohort in Part III, the sample size of 20 response-evaluable participants allows to declare futility with a probability of 83% under the assumption that the true ORR is 15%, based on the posterior probability for ORR to be below 30% with a 70% confidence level.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 13.

Table 13 Analysis Populations

Analysis Population	Description
Efficacy	All participants who received at least one dose of RO7296682 in combination with atezolizumab, and who have at least one baseline and one on-study tumor assessment. Participants who received at least one dose of RO7296682/atezolizumab and discontinued the study because of progression before the first on-study tumor assessment will be considered response-evaluable.
DLT evaluable	DLT evaluable participants are those who have completed the DLT period with two administrations of RO7296682/atezolizumab without DLT, or participants reported with a DLT. This population will be used in the determination of the MTD and/or RP2D.
Safety	All participants who received at least one dose of study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis.
Pharmacokinetic	All participants who have received at least one dose of study treatment and who have data from at least one post-dose sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.
Immunogenicity	The immunogenicity analyses will include all participants with at least one ADA assessment, irrespective of whether or not the participant receives any treatment. Excluded cases will be documented together with the reason for exclusion.
Pharmacodynamic	All participants who had at least one pre-dose and one post-dose PD assessment will be included and analyzed according to the treatment they actually received.

9.4 STATISTICAL ANALYSES

The data will be analyzed by the Sponsor and/or designated contract research organization. Any data analysis carried out independently by the Investigator should be submitted to the Sponsor before publication or presentation. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and PK and biomarker measurements. The baseline value of any variable will be defined as the last available value prior to the first administration of study drug.

9.4.1 Demographics and Baseline Characteristics

Demography and baseline characteristics (including age, sex, participant disposition, previous therapies, and medical history) will be analyzed using descriptive statistics. The

analysis will be based on the safety analysis population. Data will be summarized by dose cohort within each part.

This is a non-randomized dose escalation and dose expansion study; therefore, comparability of treatment groups does not apply.

9.4.2 Efficacy Analyses

The primary and secondary efficacy analyses listed in Table 14 will include all participants in the efficacy population with participants grouped according to dose cohort (and schedule if applicable) within each study part.

Table 14 Efficacy Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
According to RECIST Version 1.1 criteria (Appendix 13) and iRECIST (Appendix 14) • Objective response rate (ORR) • Disease control rate (DCR) • Duration of response (DoR) • On treatment progression free survival (PFS)	No formal statistical model and no formal hypothesis testing are planned in this study. Tumor response data will be reported using descriptive statistics. Response data will be listed. Participants with missing or no response assessments will be classified as not evaluable unless there is documented clinical deterioration, in which case participant will be classified as non-responders. Reasons for the non-evaluability will be summarized (e.g., withdrawal of consent, study discontinuation because of AE or physician decision). ORR and DCR will be summarized by using relative frequencies and 90% confidence interval (CI). Duration of response and PFS (on-treatment) will be summarized by using time-to-event analyses and Kaplan-Meier curves.
• Overall Survival (OS) (if available)	OS data may be tabulated and summarized using time-to-event analyses and Kaplan-Meier curves if data are collected and mature. Summaries will be carried out by cohort (and schedule if applicable) separately for each part.

Objective response rate (ORR) is determined as the rate of participants with an overall response of CR or PR. DCR is determined as the rate of participants with an overall response of either CR, PR, or SD rate. ORR and DCR will be derived for RECIST v1.1 and will be based on Investigators' assessment. Objective response (OR) is defined as a CR or PR as determined by the Investigator. For this protocol, confirmation of response is required at least 4 weeks after a first response occurred. To classify a response as SD, measurements will have to be classified as stable (according to RECIST v1.1) at least once after study entry at a minimum of 6 weeks after study entry. Participants with missing or no response assessments will be classified as not evaluable unless there is documented clinical deterioration, in which case participants will be classified as non-responders.

DoR will be calculated for participants who have a best overall response of CR or PR and defined as the time from first occurrence of a documented OR until the time of

documented disease progression or death (death within 30 days from last study treatment) from any cause, whichever occurs first. Censoring methods will be the same as the one applied for progression-free survival (PFS; on-treatment).

PFS on treatment will be defined as the time from study treatment initiation (C1D1) to the first occurrence of documented disease progression (based on RECIST v1.1 Investigator's assessment) or death from any cause, whichever occurs first. For participants who do not have documented progressive disease or death (within 30 days from last study treatment) during the study, PFS will be censored at the day of the last tumor assessment. Participants without any post baseline assessments or with all post-baseline assessments having unknown result/response but known to be alive at the clinical cut off for the analysis will be censored at the date of study treatment initiation plus one day.

Sensitivity analyses of response endpoints (ORR, DCR, DoR, and PFS) may include the evaluation of response according to iRECIST and the evaluation of response from an independent centralized review.

OS is defined as the time from the first dose of study treatment to the time of death from any cause. Participants who are still alive at the time of analysis will be censored at the time of their last study assessment (for active participants) or at the last date known alive (for participants in follow-up).

9.4.3 Safety Analyses

Unless otherwise specified, all safety analyses listed in Table 15 will be based on the safety population. All safety parameters will be analyzed using descriptive statistics, summarized and presented in tables. Data will be summarized by dose and regimen (if applicable) within each part.

Table 15 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for AEs will be coded by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level. The severity of AEs will be graded according to the NCI CTCAE v5.0. Toxicity grade, seriousness, and relationship to study treatment will be presented, as well as summaries of deaths, AEs leading to death and premature withdrawal from study treatment. A glossary of AEs, medication(s), and procedures will be provided.
Clinical laboratory tests	All clinical laboratory data will be stored in the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI units; Système International d'Unités) by individual listings with flagging of abnormal results.
Vital signs	Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries will be used, as appropriate.
ECG data analysis	ECG data will be presented by individual listings. In addition, tabular summaries will be used, as appropriate.
Concomitant medications	The original terms recorded on the participant's eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by utilizing a mapped term and appropriate drug dictionary level. Concomitant medications will be presented in summary tables and listings.
Nature and frequency of DLTs	DLT events will be presented by individual listings. The MTD will be estimated with an mCRM-EWOC using DLT evaluable participants. The MTD estimate will be presented along with 90% Credible Intervals.

9.4.4 Pharmacokinetic Analyses

Regular PK sampling will be performed in this study to properly characterize the PK of RO7296682 and atezolizumab.

When appropriate, PK parameters will be derived from the serum concentrations of RO7296682 using standard non-compartmental methods.

Individual and mean serum RO7296682 and atezolizumab concentration versus time data will be tabulated and plotted by dose levels and/or group, where appropriate. All PK parameters will be presented by listings and descriptive summary statistics separately by dose levels and/or dosing regimens.

Parameters may include, for example, area under the curve (AUC), clearance (CL), and volume of distribution under steady-state conditions, as appropriate. These parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum). Inter-participant variability and drug accumulation will be evaluated.

For RO7296682, non-linear mixed effect modeling will be used to analyze the concentration-time data. Population and individual PK parameters may be estimated, and the influence of various covariates (such as age, gender, and body weight) on these parameters may be investigated in an exploratory way. Secondary PK parameters (such as C_{max} and AUC) may be derived from the model for each participant included in the PK analysis and will be presented descriptively.

For atezolizumab, a previously developed population PK model for atezolizumab will be used to provide individual parameter estimates using Bayesian feedback methodology. Alternatively, PK data may be compared with available historical data.

Additionally, exploratory analyses on exposure and safety/efficacy relationship may be conducted if deemed necessary. The details of the modeling and exploratory analyses will be reported in a document separate from the CSR.

9.4.5 Immunogenicity Analyses

Antibodies against RO7296682 and atezolizumab will be evaluated in serum samples collected from all participants using appropriate assays. Listings and/or summaries will be prepared. Additional analyses may be conducted as appropriate.

The immunogenicity analyses will include all participants with at least one ADA assessment, irrespective of whether or not the participant receives any treatment (Shankar et al. 2014).

The numbers and proportions of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after study drug administration (post-baseline incidence during both the treatment and follow-up periods) will be summarized by dose levels and/or cohorts as appropriate.

- Participants are considered to be ADA positive if they are ADA negative or missing data at baseline and develop an ADA response following study drug administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is greater than the titer of the baseline sample by a scientifically reasonable margin such as at least 4-fold (treatment-enhanced ADA response).Treatment-induced ADA response can be further categorized in persistent (post-treatment ADA-positive samples over 16 weeks or more or the last ADA time point is positive) and transient (only one ADA-positive sample or the time between the first and last ADA-positive sample is less than 16 weeks and the last ADA sample is negative).
- Participants are considered to be ADA negative if they are ADA negative or missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is greater than the titer of the baseline sample by a scientifically reasonable margin such as at least 4-fold (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

9.4.6 Pharmacodynamic Analyses

All PD parameters will be presented by listings and descriptive summary statistics separately by group or cohorts. Change and percentage of change from baseline will be described and evaluated as evidence of response to treatment.

Part II will evaluate PD effects and preliminary anti-tumor activity of the MTD and/or RP2D of RO7296682 in combination with atezolizumab determined in Part I. To assess the effect of RO7296682 in combination with atezolizumab on the Treg population in blood and tumor tissue, the secondary endpoint is reached if changes of Treg levels in blood and tumor tissues, at a dose at which a [redacted] as compared to baseline is observed in 50% or the participants or changes in the ratio of CD8+ T cells to Tregs in blood and/tumor tissue as compared to baseline, at a dose at which a [redacted] is observed in 50% of the participants.

9.4.7 Other Analyses

Graphical or exploratory analysis will be performed to assess the possible relationship between exposure to RO7296682 in combination with atezolizumab and selected biomarkers, efficacy, or safety parameters, as appropriate.

9.5 INTERIM ANALYSES

Three different gating criteria are defined, each of which can ungate a tumor-specific cohort in Part III (see Section 1.2 for study design). Part III can start when clinical activity is seen already in the ongoing single agent dose expansion study WP41188 (but after Part I completed), after Part I, or based on Part II. For Part III (dose expansions), the pre-planned futility interim analyses will be performed by an IMC (see Section 3.3 of Appendix 1).

Gate based on WP41188 Dose Expansion (RO7296682 single-agent) study

In order to open tumor-specific cohort(s) in Part III (based on the corresponding participants from single agent dose expansion cohort of RO7296682 from WP41188), the gating criteria are defined based on the posterior probability for ORR to be greater than 15% with a 50% confidence level. See gating criteria in Table 16. Per indication at least 2 responders out of a maximum of 16 evaluable tumor-specific participants (or at least 3 responders out of maximum 23 etc.) are needed in the Phase I, single agent expansion cohort (from study WP41188) to open the respective Part III cohort, provided that the MTD/RP2D of RO7296682 in combination with atezolizumab has been determined in Part I. As long as there are at least 2 responders, there is no need to wait until there are 16 response-evaluable participants.

Table 16 Gating Criteria I to Open Part III Tumor-specific Cohort per Indication

Number of required CR/PR in the WP41188 expansion	2	3	4	5	6	7	8
Number of evaluable tumor-specific participants	10-16	17-23	24-29	30-36	37-43	44-49	50

Gate based on BP42595 Dose Expansion Part I (Dose Escalation of RO7296682/ atezolizumab)

In order to open a tumor-specific cohort(s) in Part III (based on the corresponding participants from the dose-escalation Part I of this study), the additional gating criteria are defined based on the posterior probability for ORR to be greater than 20% with a 50% confidence level. See gating criteria in Table 17. Per indication, at least 2 responders out of a maximum of 12 evaluable tumor-specific participants (or at least 3 responders out of maximum 17 etc.) are needed in the Part II to open the respective Part III cohort.

Table 17 Gating Criteria II to Open Part III Tumor-specific Cohort per Indication

Number of required CR/PR in BP42595 Part I	2	3	4	5	6	7	8	9	10
Number of evaluable tumor-specific participants	8-12	13-17	18-22	23-27	28-32	33-37	38-42	43-47	48-50

Gate based on BP42595 Dose Expansion Part II ([redacted], CPI-experienced participants treated with RO7296682/atezolizumab)

In Part II, efficacy will be evaluated in several interim analyses in each indication. The interim analyses will take place to open tumor-specific cohorts in Part III when 5 to 8 evaluable participants have a mature assessment of response in each indication. Additional interim analyses may be needed if the gating criteria based on 5 to 8 evaluable participants are not met and additional participants with a mature assessment of response are included. The exact number of participants per indication in Part II is not pre-defined. The detailed gating criteria to open tumor-specific cohort in Part III per indication are defined based on the posterior probability for ORR to be greater than 20% with a 70% confidence level (see gating criteria in Table 18). Per indication, at least 2 responders out of maximum 8 evaluable tumor-specific participants (or at least 3 responders out of maximum 12 etc.) are needed in the Part II to un-gate the respective Part III cohort.

Table 18 Gating Criteria III to Open Part III Tumor-specific Cohort per Indication

Number of required CR/PR in BP42595 Part II	2	3	4	5	6	7	8	9
Number of evaluable tumor-specific participants	5-8	9-12	13-17	18-21	22-26	27-30	31-35	36-40

Part III Interim Analyses

In Part III, efficacy will be evaluated in one interim analysis in each opened cohort. This futility interim analysis will be assessed after the first 10 response-evaluable participants have mature data in each cohort.

- For the HNSCC cohort, interim futility will be concluded if less than 1 out of 10 response-evaluable participants have CR or PR based on the posterior probability for ORR to be below 20% with a 90% confidence level or final futility will be concluded if less than 3 out of 20 response-evaluable participants have CR or PR based on the posterior probability for ORR to be below 20% with a 70% confidence level.
- For the NSCLC cohort, interim futility will be concluded if less than 1 out of 10 response-evaluable participants have CR or PR based on the posterior probability for ORR to be below 20% with a 90% confidence level or final futility will be concluded if less than 4 out of 20 response-evaluable participants have CR or PR based on the posterior probability for ORR to be below 25% with a 70% confidence level.
- For the MEL cohort, interim futility will be concluded if less than 1 out of 10 response-evaluable participants have CR or PR based on the posterior probability for ORR to be below 20% with a 90% confidence level or interim futility will be concluded if less than 5 out of 20 response-evaluable participants have CR or PR based on the posterior probability for ORR to be below 30% with a 70% confidence level.

Recruitment may not be interrupted while waiting for data maturity. These futility rules are not binding and may be overruled if other endpoints (e.g., DCR rate, DoR, PFS, or OS) show significant improvement over the expected benefit in the population. At any time during the study, parts, cohorts, and arms may be closed based on emerging data external to the study or operational reasons.

9.6 SUMMARIES OF CONDUCT OF STUDY

All protocol deviations will be listed.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

This Section includes the following appendices:

- Appendix 1: Regulatory, ethical, and study oversight considerations
- Appendix 2: Adverse event definitions, follow-up and reporting
- Appendix 3: Procedures for recording adverse events
- Appendix 4: Clinical laboratory test
- Appendix 5: Contraceptive guidance and collection of pregnancy information
- Appendix 6: Study details for Part III, NSCLC (Cohort A)
- Appendix 7: Study details for Part III, HNSCC (Cohort B)
- Appendix 8: Study details for Part III, MEL (Cohort C)
- Appendix 9: Study details for Part III, additional tumor-specific cohort(s)
- Appendix 10: Details on Real wOrld PROgnostic score
- Appendix 11: Statistics for combination therapy dose-escalation
- Appendix 12: Management guidelines for imAEs
- Appendix 13: New response evaluation criteria in solid tumors, version 1.1
- Appendix 14: Modified RECIST v1.1 for immune-based therapeutics (iRECIST)
- Appendix 15: Cockcroft-Gault formula/creatinine clearance

Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

1. REGULATORY AND ETHICAL CONSIDERATIONS

1.1. COMPLIANCE WITH LAWS AND REGULATIONS

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

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the participant (e.g. advertisements, diaries etc.), and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (Section 2.3.1 of this Appendix).

The Investigator should follow the requirements for reporting all AEs to the Sponsor. Investigators may receive written IND safety reports or other safety‑related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with Health Authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

1.3. INFORMED CONSENT

The Sponsor's Master ICF (and ancillary sample ICFs such as a Child's Assent or Caregiver's ICF, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. 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, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study

center. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant or the participant’s legally authorized representative.

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

The ICFs should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to take part. The final revised IRB/EC-approved ICFs must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

If the ICFs are revised (through an amendment or an addendum) while a participant is participating in the study, the participant or a legally authorized representative may be re-consented by signing the most current version of the ICFs or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised ICFs, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study. The study team will provide guidance for which participants need to re-consent in the event of an update to the ICF.

A copy of each signed ICF must be provided to the participant or the participant’s legally authorized representative. All signed and dated ICFs must remain in each participant’s study file or in the site file and must be available for verification by study monitors at any time.

Participants who are re-screened are required to sign a new ICF.

Consent to Participate in the Research Biosample Repository

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

The Investigator should document whether or not the participant has given consent to participate by completing the RBR Sample Informed Consent eCRF.

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

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

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 ICF 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 will not be applicable at that site

Withdrawal from the Research Biosample Repository

Participants who give consent to provide samples for the RBR have the right to withdraw their samples at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her samples, the Investigator must inform the Medical Monitor and Site Monitor in writing of the participant’s wishes using the RBR Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the study is closed. A participant's withdrawal from Study BP42595 does not, by itself, constitute withdrawal of samples from the RBR. Likewise, a participant’s withdrawal from the RBR does not constitute withdrawal from Study BP42595. Data already generated before time of withdrawal of consent to RBR will still be used.

1.4. CONFIDENTIALITY

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; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her 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 the participant.

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

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Study 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 other summary reports will be provided upon request.

Confidentiality for Research Biosample Repository

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

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

Data derived from RBR sample analysis on individual participants will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Participants will not be identified by name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, genetic data and analyses will not be shared with Investigators or participants unless required by law.

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

Monitoring and Oversight Research Biosample Repository

Samples collected for the RBR 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 ICF. The Sponsor's monitors and auditors will have direct access to appropriate parts of records relating to participant participation in 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 samples.

1.5. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (i.e., LPLV).

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF 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 in the CRF.

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

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

Study monitors will perform ongoing source data verification 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, ICH GCP, and all applicable regulatory requirements.

2.1.2. Clinical Outcome Assessment Data

Not applicable.

2.1.3. Source Data Records

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

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

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

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

2.1.4. Use of Computerized Systems

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

2.1.5. 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.

2.2. RETENTION OF RECORDS

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion or discontinuation of the study, or for the length of time required by relevant national or

local health authorities, whichever is longer. After that period, the documents may be destroyed, subject to local regulations. 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.

2.3. STUDY RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully reconstructed, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval.

Roche shall also submit an Annual Safety Report once a year to the IEC and CAs according to local regulatory requirements and timelines of each country participating in the study.

2.3.1. Protocol Amendments

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

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or any non-substantial changes, as defined by regulatory requirements.

2.3.2. 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 for approval prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

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 multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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

2.3.3. Dissemination of Clinical Study Data

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (for more details, see Section 2.3.5), and redacted clinical study reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met.

For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses.

2.3.4. Management of Study Quality

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring participant safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Details regarding the applied approach for the study will be provided in the integrated Risk Based Quality Management Plan.

2.3.5. Site Inspections

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

3. ADMINISTRATIVE STRUCTURE

No formal Independent Review Committee, Steering Committee, Data Monitoring Committee or Data Safety Monitoring Board are planned for this study at this moment.

For Part I, Dose-Escalation, as indicated in Protocol Section 4.1.4 "Communication Strategy," the Sponsor will organize a Safety and Dose Escalation Committee (SDEC)

with the Investigators to discuss the safety and tolerability of RO7296682 in combination with atezolizumab and to discuss the dose(s) for the next cohort.

For Part II: ongoing medical data review will be performed by the Sponsor together with the investigators.

For Part III (Dose Expansions) ongoing medical data review will be performed by an Internal Monitoring Committee (IMC). Please see Section 3.3 of this appendix.

In addition to these communications, the Sponsor and investigators will be in regular contact throughout the study by email/telephone/fax, as per normal interactions during the conduct of a clinical study, and the Sponsor will arrange regular teleconferences and meetings to discuss study status.

3.1. INDEPENDENT REVIEW COMMITTEE (IRC)

Not applicable, see Section 3.3 of this appendix.

3.2. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

Not applicable, see Section 3.3 of this appendix.

3.3. INTERNAL MONITORING COMMITTEE (IMC)

In Part III of this study, an IMC will be used to review accumulating clinical data in order to assess subject risk and benefit on an ongoing basis. The IMC activities included, but are not limited to, data monitoring at pre-planned interim analyses for safety, efficacy and/or futility. At a minimum, the IMC consists of a Statistician, Safety Scientist, Clinical Scientist and Clinical Pharmacologist. If required, additional functional representatives may be members of an IMC. The IMC will review all accumulating clinical data at regular intervals, as defined in the IMC charter.

At the time of each review, the IMC may recommend that the trial continues as planned, the trial stops, additional analyses need to be performed, enrollment be held pending further safety evaluations and opening or closing of expansion cohort(s). The IMC may also recommend a protocol amendment.

4. STUDY AND SITE CLOSURE

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

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

The Sponsor will notify the Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

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 study-site closure visit has been performed.

The Investigator may initiate study-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:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

Appendix 2
Adverse Events: Definitions and Procedures for Evaluating, Follow-up and Reporting

1. DEFINITION OF ADVERSE EVENTS

According to the E2A ICH guideline for Good Clinical Practice, an **adverse event** is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events Meeting the AE Definition:

- Deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., ECG, x-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment (see Appendix 3, Section 4).
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE unless the progression is unexpectedly accelerated and not in line with the natural history of the disease. If the “Lack of efficacy” would not require safety reporting 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 AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/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 an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

2. DEFINITION OF SERIOUS ADVERSE EVENTS

If an event is not an AE per definition above, then it cannot be a serious adverse event (SAE) even if serious conditions are met (e.g., hospitalization for signs/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 which hypothetically might have caused death if it was more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see Appendix 3).

  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 AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- **Results in persistent or significant disability/incapacity.**

  Disability means substantial disruption of the participant'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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**.
- **Other significant events**:

  Medical or scientific judgment should be exercised in deciding whether SAE 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.

3. RECORDING OF ADVERSE EVENT AND/OR SERIOUS ADVERSE EVENT

When an AE/SAE 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 AE/SAE information in the CRF.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Medical Monitor in lieu of completion of the eCRF.

There may be instances when copies of medical records for certain cases are requested by 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 Sponsor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

3.1. ASSESSMENT OF SEVERITY

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to a pre-defined grading criteria [e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event.

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale

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

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

Note: Based on the NCI CTCAE (v5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 6 of this Appendix for reporting instructions), per the definition of serious adverse event in Section 2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 6 for reporting instructions), per the definition of serious adverse event in Section 2. Grade 4 laboratory abnormalities would only be reported as SAEs if these meets one or more of the conditions outlined in Section 2 (Definition of Serious Adverse Events) of Appendix 2.

3.2. ASSESSMENT OF CAUSALITY

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment.
- Course of the event, considering especially the effects of dose-reduction, discontinuation of study treatment, or reintroduction of study treatment.
- Known association of the event with the study treatment or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

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

4. FOLLOW-UP OF AES AND SAES

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Medical Monitor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological 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 Medical Monitor with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list

of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events.
- NSAESI.
- Pregnancies (see Section 8.3.5).
- DLTs during the DLT assessment window (see Section 4.1.3; see the eCRF completion guideline for further guidance).

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

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

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

5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS, NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST AND DOSE-LIMITING TOXICITIES

Events that Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Events that Occur after Study Treatment Initiation

For reports of serious adverse events and non-serious adverse events of special interest (Section 8.3.6) that occur after initiation of study treatment (Section 8.3.1), investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest/ Serious Adverse Event eCRF form and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Reporting of Post-Study Adverse Events and Serious Adverse Events

After the end of the adverse event reporting period (see Section 8.3.1), 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 SAE that is believed to be related to prior study treatment, the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the SAE Reporting Form using the fax number or email address provided to investigators.

5.2 REPORTING REQUIREMENTS FOR 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, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). For RO7296682 and atezolizumab, AEs associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with RO7296682 and atezolizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and should be recorded as described below:

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

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

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

The Sponsor will promptly evaluate all serious adverse events and NSAESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable Health Authorities based on applicable legislation.

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

Drug	Document
RO7296682	RO7296682 Investigator's Brochure
Atezolizumab	Atezolizumab 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.

Appendix 3
Procedures for Recording Adverse Events

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

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

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

1.1. INFUSION-RELATED REACTIONS

AEs that occur during or after study drug administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., “infusion-related reaction” and "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as “systemic reaction”. Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a participant experiences both a local and systemic reaction to the same dose of study drug, 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.

1.2. OTHER ADVERSE EVENTS

For AEs other than infusion-related reactions (see Section 1.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, AEs occurring 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. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events 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 subsequent fracture, all three events should be reported separately on the eCRF.

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

3. PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution, between participant evaluation time-points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent AE is one that resolves between participant evaluation time-points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

4. ABNORMAL LABORATORY VALUES

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

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- 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., alkaline phosphatase and bilirubin 5 × the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) 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 if 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5. ABNORMAL VITAL SIGN VALUES

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

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the Investigator’s judgment.

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

6. ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST in combination with either an elevated total bilirubin or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of potential severe liver injury.

Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>$ 5 $\times$ ULN value in combination with total bilirubin $>$ 2 $\times$ ULN (of which $\geq$35% is direct bilirubin).
- Treatment-emergent ALT or AST $>$ 5 $\times$ ULN value in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Appendix 2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 8.3.6).

7. DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5 of Appendix 2) that are attributed by the Investigator solely to progression of cancer should be recorded only on the Death Attributed to Progressive Disease eCRF. All other on-study deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5 of Appendix 2).

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

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”).

9. LACK OF EFFICACY OR WORSENING OF TUMOR

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

10. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Appendix 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 insertion of access device for study treatment administration).
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
  - The participant has not suffered 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 AE instead:

  - Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

Appendix 4
Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the local laboratory and the results must be captured in source documentation and entered into the eCRF. If local laboratory assessments (except for pregnancy test, which must be performed prior to each treatment day with results available prior to dosing) are performed ≤ 3 days before the day of the planned dosing, these values can be used and recorded in the eCRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2, respectively, of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Leukocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
Clinical chemistry	• Sodium, potassium, chloride, bicarbonate, glucose, urea or blood urea nitrogen, creatinine, creatinine clearance (required at screening only, determined by Cockcroft-Gault formula, see Appendix 15), total protein, albumin, magnesium, phosphate, calcium, bilirubin (total and direct), alkaline phosphatase, ALT, AST, GGT, urate, LDH, CRP, ferritin.
Coagulation	• INR or PT, aPTT.
Viral serology	• HIV (specific tests HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody), hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), hepatitis C virus (HCV) antibody. For participants with positive HCV antibody perform HCV RNA test.
Lipids	• Cholesterol, LDL cholesterol, high-density lipoproteins (HDL) cholesterol, triglycerides.
Thyroid hormones	• TSH, free T3 (or total T3 for sites where free T3 is not performed), free T4.
Pregnancy test	• All women of childbearing potential (including those who have had a tubal occlusion/ ligation) will have a blood pregnancy test at screening within 7 days before the first dose of study treatment on C1D1. Urine or serum pregnancy test performed prior to each treatment, with result available prior to dosing. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test. • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential).

Laboratory Assessments	Parameters
Urinalysis	• Specific gravity. • Dipstick: pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase. • If there is a clinically significant hematuria (confirmed by a positive repeated sample and in the absence of other explanation, e.g. menses), urine will be sent to the laboratory for microscopy. Culture and sensitivity analysis is indicated if urinary tract infection is suspected. • Microscopic examination (sediment, red blood cells, white blood cells, casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal.
Auto-antibody panel	• Anti-nuclear antibody (ANA), circulating anti-neutrophil cytoplasmic antibody (cANCA); and perinuclear anti neutrophil cytoplasmic antibody (pANCA). In case of positive ANA test, the anti−double-stranded DNA antibody test to be performed: ○ The auto-antibody panel will be assessed at Screening, pre-dose Cycles 2 and 3, and every 6 cycles thereafter. In participants who develop signs and/or symptoms suggestive of auto-immune disease while on treatment, the auto-antibody panel (including anti-dsDNA antibody) must be repeated. ○ Patients with confirmed positive serology of at least one of the auto-antibody panel during the course of the study should be discussed between Sponsor and Investigators, and if judged clinically relevant, could be referred to a specialist to exclude an underlying auto-immune disease.
IgE and Tryptase	• Tryptase and IgE samples will be collected for local analysis if a participant experiences a Grade ≥2 IRR, or with clinical signs of hypersensitivity reaction. If tryptase and/or IgE are elevated, a second sample for central IgE/Tryptase analysis will be collected approximately 48 hours after onset of the reaction.

Investigators must document their review of each laboratory safety report.

Additional Statistical Considerations for Clinical Laboratory Data

Standard Reference Ranges and Transformation of Data

Potential analysis considerations for analyzing laboratory data includes the use of standard reference ranges and potential transformation of data for specific laboratory tests.

In this scenario, Roche standard reference ranges, rather than the reference ranges of the Investigator, can be used for specific parameters. For these parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges, e.g., enzyme tests

that include AST, ALT, and alkaline phosphatase and total bilirubin. Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

Definition of Laboratory Abnormalities

For all laboratory parameters included in the analysis described above, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled “H” for high or “L” for low in participant listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for these laboratory parameters. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a participant, the midpoint of the standard reference range will be used as the participant’s baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as “HH” for very high or “LL” for very low.

Appendix 5
Contraceptive Guidance and Collection of Pregnancy Information

1. DEFINITIONS

- **Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

- **Women in the following categories are considered to be Woman of Non-Childbearing Potential**

a) Pre-menarchal

b) Pre-menopausal female with one of the following:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

c) Post-menopausal female

– A post-menopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

– Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

2. CONTRACEPTION GUIDANCE

- **Female Participants**

Female participants of childbearing potential are eligible to participate if they agree to use highly effective method of contraception consistently and correctly as described in Table 1 below.

Per ICH M3(R2), highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly as described in Table 1 below.

Table 1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User-Dependent[a] (Failure rate of < 1% per year when used consistently and correctly)

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  ○ Oral
  ○ Intravaginal
  ○ Transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation:
  ○ Oral
  ○ Injectable

Highly Effective Methods That Are User-Independent (Failure rate of < 1% per year)
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[a] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion/ ligation **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

3. PREGNANCY TESTING

For WOCBP enrolled in the study, blood sample and urine pregnancy tests will be performed according to Schedule of Activity tables (see Section 1.3). If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.

4. COLLECTION OF PREGNANCY INFORMATION

Male participants with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study (see Section 8.3.5 Pregnancy). This applies only to male participants who receive RO7296682 and atezolizumab.

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. The Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. 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 update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy when available. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female participants who become pregnant

The Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study (see Section 8.3.5 Pregnancy). Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, which will be forwarded to the Sponsor. Monitoring of the participant should continue until conclusion of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, and should not be recorded on the AE eCRF, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Appendix 2. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study treatment.

5 ABORTIONS

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Any induced abortion due to maternal toxicity and/or embryo-fetal toxicity should also be classified as serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Elective or therapeutic abortion not associated with an underlying maternal or embryofetal toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

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

Appendix 6
Study Details for Part III, NSCLC (Cohort A)

Background and Rationale for Part III, NSCLC Cohort

Lung cancer remains the leading cause of cancer death in the United States. Treatment of advanced-stage or metastatic non-small cell lung cancer (NSCLC) without EGFR mutations or ALK rearrangements has undergone significant advancement with the development of CPIs against PD-1/PD-L1 e.g., pembrolizumab, nivolumab, atezolizumab or durvalumab in the first line setting. Despite the recent advancements, patients respond poorly to CPIs and ultimately develop resistance mechanisms resulting in disease progression. Removing Tregs is postulated to increase the anti-tumor immunity of participants who do not respond to or progress following CPI treatment.

Should clinical benefit be observed in this or other trials fulfilling the gating criteria outlined in section 9.5, a NSCLC-specific cohort will be opened in order to investigate the signals further and in a wider population, without restrictions of [redacted] type or a specific prior CPI response pattern (i.e. as in Part II). As outlined in Section 4.2.1 of the protocol, given the high FoxP3 content (surrogate marker for Tregs) in this tumor type, Treg depletion through RO7296682 is postulated to increase anti-tumor activity in combination with anti-PD-L1 (atezolizumab).

Specific Inclusion Criteria for Part III, NSCLC Cohort

Participants are eligible to be included in the study only if all of the appropriate inclusion criteria listed in protocol Section 5.1 and all of the following criteria apply:

1. Participants with histologically confirmed advanced and/or metastatic NSCLC previously treated with CPI ± platinum based chemotherapy, including PD-L1/PD-1/CTLA-4 inhibitors (investigational or approved) sequentially or concurrently with chemotherapy.
   - CPI administration as (neo-) adjuvant therapy is not allowed.
2. Participants whose tumors have known sensitizing mutations must also have experienced disease progression (during or after treatment) or intolerance to targeted therapy.
3. Able to provide archival tissue and fresh skin punch biopsy, as per inclusion criteria #7 and #8 in protocol Section 5.1, respectively.
4. Able to provide a freshly collected biopsy of a tumor lesion (primary and/or metastatic) from a safely accessible site, per Investigator determination and patient consent, providing the patient has more than one measurable target lesion. If the patient has only one target lesion, the patient will be excluded from study

participation. The biopsied lesion must not be a target lesion. The following rules apply:

- Bone lesion biopsies, bronchoscopy/trans-bronchial biopsies, and cytology fine needle aspirates are not acceptable.
- The tumor lesion must not be a metastatic LN sample; metastatic LN is acceptable ONLY when other accessible tumor sites are not available for biopsy.
- Fresh biopsies must be obtained within 28 days before the first dose at C1D1.
- If fresh tissue biopsies cannot be obtained, please contact the Medical Monitor.

Appendix 7
Study Details for Part III, HNSCC (Cohort B)

Background and Rationale for Part III, HNSCC Cohort

Head and neck cancer describes a range of tumors that arise in the head and neck region, which includes the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid, and salivary glands. The worldwide incidence of head and neck cancer exceeds half a million cases annually. Despite the wide diversity in Head and Neck cancers, the majority arise from squamous cell in origin. Subjects with advanced and/or metastatic head and neck cancer present a therapeutic challenge. Conventional cytotoxic drugs and molecularly targeted compounds have shown some activity in metastatic and recurrent HNSCC, yet the prognosis of such patients is poor. Therefore, single agent and/or combination therapy together with best supportive care is palliative for these patients.

Should clinical benefit be observed in this or other trials fulfilling the gating criteria outlined in Section 9.5, a HNSCC-specific cohort will be opened in order to investigate the signals further and in a wider population, without restrictions of [redacted] type or a specific prior CPI response pattern (i.e., as in Part II). As outlined in Section 4.2.1 of the protocol, given the high FoxP3 content (surrogate marker for Tregs) in this tumor type, Treg depletion through RO7296682 is postulated to increase anti-tumor activity in combination with anti-PD-L1 (atezolizumab).

Specific Inclusion Criteria for Part III, HNSCC Cohort

Participants are eligible to be included in the study only if all of the appropriate inclusion criteria listed in protocol Section 5.1 and all of the following criteria apply:

1. Participants with histologically confirmed advanced and/or metastatic HNSCC previously treated with CPI ± platinum based chemotherapy, including PD-L1/PD-1/CTLA-4 inhibitors (investigational or approved) sequentially or concurrently with chemotherapy.
    - CPI administration as (neo-) adjuvant therapy is not allowed.
2. Participants whose tumors have known sensitizing mutations must also have experienced disease progression (during or after treatment) or intolerance to targeted therapy.
3. Able to provide archival tissue and fresh skin punch biopsy, as per inclusion criteria #7 and #8 in protocol Section 5.1, respectively.

4. Able to provide a freshly collected biopsy of a tumor lesion (primary and/or metastatic) from a safely accessible site, per Investigator determination and patient consent, providing the patient has more than one measurable target lesion. If the patient has only one target lesion, the patient will be excluded from study participation. The biopsied lesion must not be a target lesion. The following rules apply:

    - Bone lesion biopsies, bronchoscopy/trans-bronchial biopsies, and cytology fine needle aspirates are not acceptable.

    - The tumor lesion must not be a metastatic lymph node sample; metastatic lymph node is acceptable ONLY when other accessible tumor sites are not available for biopsy.

    - Fresh biopsies must be obtained within 28 days before the first dose at C1D1.

    - If fresh tissue biopsies cannot be obtained, please contact the Medical Monitor.

Appendix 8
Study Details for Part III, MEL (Cohort C)

Background and Rationale for Part III, MEL Cohort

CPIs represent the current paradigm of treatment options in patients with melanoma. However, only a fraction of patients derive durable benefit from CPIs. Ipilimumab was the first CPI approved for use in unresectable or metastatic melanoma. Subsequent to this, nivolumab was approved in advanced melanoma patients without BRAF mutation. The combination of ipilumumab and nivolumab was approved in previously untreated patients with unresectable or metastatic melanoma (Robert et al. 2015), although toxicity is more prominent with the combination therapy. Despite anti-CTLA4 and PD-1 CPI therapies many melanoma patients fail to respond (innate resistance), and more worrying, some patients who initially benefited from CPIs acquired resistance over time. Consequently, there remains a medical need to develop new combination therapies to overcome the resistance mechanisms to immunotherapy.

Should clinical benefit be observed in this or other trials fulfilling the gating criteria outlined in section 9.5, a MEL-specific cohort will be opened in order to investigate the signals further and in a wider population, without restrictions of [redacted] type or a specific prior CPI response pattern (i.e. as in Part II). As outlined in Section 4.2.1 of the protocol, given the high FoxP3 content (surrogate marker for Tregs) in this tumor type, Treg depletion through RO7296682 is postulated to increase anti-tumor activity in combination with anti-PD-L1 (atezolizumab).

Specific Inclusion Criteria for Part III, MEL Cohort

Participants are eligible to be included in the study only if all of the appropriate inclusion criteria listed in protocol Section 5.1 and all of the following criteria apply:

1. Participants with histologically confirmed advanced and/or metastatic MEL previously treated with CPI ± platinum based chemotherapy, including PD-L1/PD-1/CTLA-4 inhibitors (investigational or approved) sequentially or concurrently with chemotherapy.
   - CPI administration as (neo-) adjuvant therapy is not allowed.
2. Participants whose tumors have known sensitizing mutations must also have experienced disease progression (during or after treatment) or intolerance to targeted therapy.

   Note: enrollment will be managed so that no more than approximately 10% of participants will be participants with ocular (uveal) melanoma.
3. Able to provide archival tissue and fresh skin punch biopsy, as per inclusion criteria #7 and #8 in protocol Section 5.1, respectively.

4. Able to provide a freshly collected biopsy of a tumor lesion (primary and/or metastatic) from a safely accessible site, per Investigator determination and patient consent, providing the patient has more than one measurable target lesion. If the patient has only one target lesion, the patient will be excluded from study participation. The biopsied lesion must not be a target lesion. The following rules apply:
    - Bone lesion biopsies, bronchoscopy/trans-bronchial biopsies, and cytology fine needle aspirates are not acceptable
    - The tumor lesion must not be a metastatic LN sample; metastatic LN is acceptable ONLY when other accessible tumor sites are not available for biopsy
    - Fresh biopsies must be obtained within 28 days before the first dose at C1D1.
    - If fresh tissue biopsies cannot be obtained, please contact the Medical Monitor.

Appendix 9
Study Details for Part III, Additional Tumor-Specific Cohort(s) Potentially in Comparison with Standard of Care

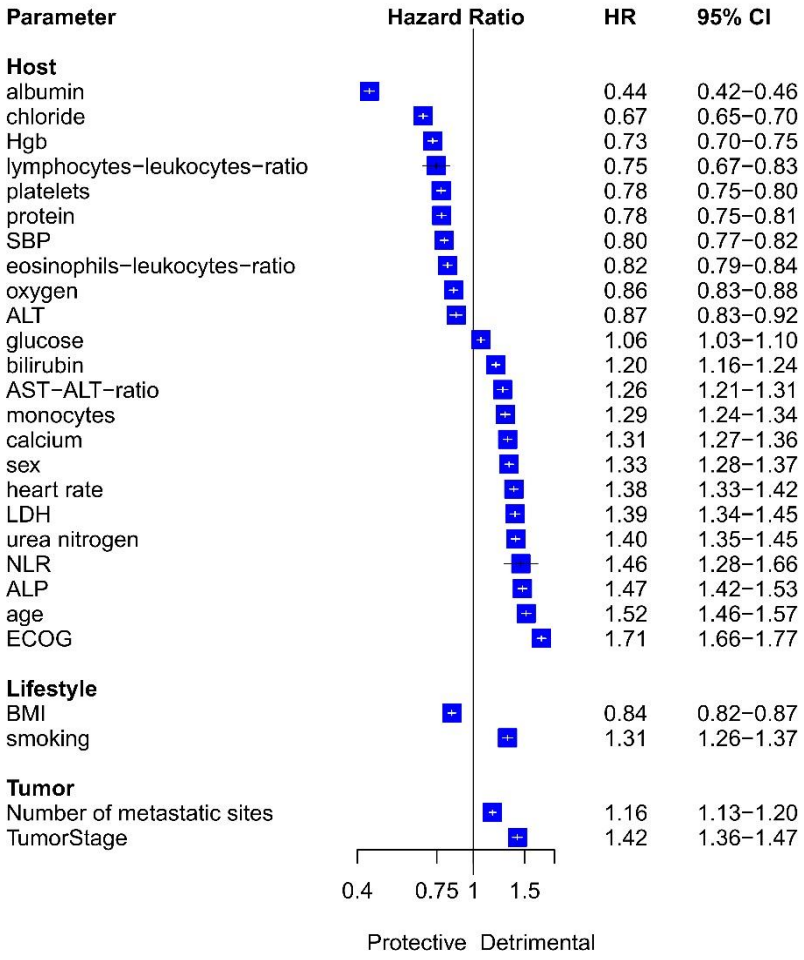
Background and Rationale for Part III, Additional Tumor-specific Cohort(s)

New tumor-specific cohorts may be added based on emerging data from this study or other RO7296682 studies (see Section 9.5 for gating criteria). The cohort details, including but not limited to study objectives, patient eligibility criteria, dosing and schedule requirements, statistical hypothesis, etc. will be outlined in a substantial protocol amendment.

Appendix 10
Details on the Real World Prognostic Score

In a Real World Data cohort of 122,694 patients, demographic, clinical, routine hematology and blood chemistry parameters were analyzed within a Cox proportional hazard framework to derive a multivariate prognostic risk model for overall survival called the Real World Prognostic score (ROPRO; Becker et al. 2020). In total, ROPRO comprised 29 variables (see Table 1), which contributed significantly to overall survival across cancer indications. In the largest cohort (advanced non-small-cell lung cancer), patients with elevated scores (upper 10%) had a 7.91-fold (95% CI 7.45 to 8.39) increased death hazard compared with patients with low scores (lower 10%) ($P<2.23\times10^{-308}$). The ROPRO model performance indicators (generalized-r^2=0.32, C-index=0.747, 3-month-AUC=0.82) strongly outperformed those of the Royal Marsden Hospital score (r^2=0.03, C-index=0.54, 3-month-AUC=0.58). ROPRO was validated in two independent Phase I and Phase III clinical studies.

Table 1 ROPRO Variables



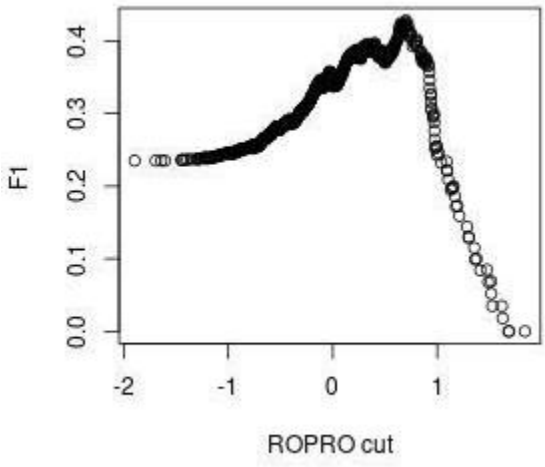
Individual patient ROPRO scores (derived by inputting their measurements for each of the variables into the formula) ranged from -3.49 to 4.12 and 99% were in between -2.21 and 2.09.

As demonstrated in the publication (Becker et al. 2020), increased ROPRO correlates with increased risk for early death. In order to identify a cut-off value of the ROPRO above, which the risk of early death (within 12 weeks of study entry) is particularly high, the study will proceeded as follows:

Four Roche-internal clinical Phase I studies were retrospectively analyzed. In all studies, higher ROPRO was associated with increased hazard of death. Different ROPRO cut-offs were applied and compared to the proportion of patients who died within

12 weeks in the low and high risk patient groups (as defined by the respective ROPRO cutoff). The F-measure (F1) was used, which is the harmonic mean of the precision (probability to die within 12 weeks when the patient is excluded) and recall (probability to be excluded when the patient dies within 12 weeks), to define the optimal ROPRO cutoff. F1 was chosen in order to get a good tradeoff between excluding high-risk patients who will not benefit from the trial and should not undergo unnecessary procedural burden (low false negatives and thus high recall) and not excluding too many patients at the same time that will benefit from the trial (low number of false positives and thus high precision). The F1 measure for different ROPRO cutoffs is shown in Figure 1. The maximum F1 is reached for a ROPRO cut-off of 0.7.

Figure 1 Different potential ROPRO cut-offs and F1 measure. Maximizing F1 results in a ROPRO cut-off of 0.7.



Reference:

Becker T, Weberpals J, Jegg AM, et al. An enhanced prognostic score for overall survival of patients with cancer derived from a large real world cohort. Annals of Oncology. 2020. https://doi.org/10.1016/j.annonc.2020.07.013.

Appendix 11
Statistics for Combination Therapy Dose-Escalation

1. COMBINATION THERAPY DOSE ESCALATION

This appendix provides details of the design that will guide the dose-escalation of RO7296682 in combination with atezolizumab and its operating characteristics through simulations. All analyses were performed using the R statistical software version 3.5.3 (2019-03-11; R Core Team, 2017).

2. RATIONALE FOR MODEL-BASED DESIGN

The modified continuous reassessment method (mCRM) design uses a statistical model that actively seeks a dose level close to the maximum tolerated dose (MTD) by using toxicity data from all enrolled evaluable participants to compute a precise dose-toxicity curve. It locates the MTD efficiently and minimizes the number of participants treated at possibly pharmacological inactive dose levels. Such model-based designs have been successfully applied in many Phase 1 dose-escalation studies (Schöffski et al. 2004; Le Tourneau et al. 2009; Neuenschwander et al. 2008). The simulations in this appendix investigate the operating characteristics of the design as implemented for this study.

In this design, the MTD is defined as the dose maximizing the posterior probability that the dose-limiting toxicity (DLT) rate π (MTD) ϵ [0.2, 0.33] while keeping the probability of overdose {p(MTD) > 0.33} < 0.25.

3. STATISTICAL MODEL

A two-parameter logistic model will be used to fit the dose-toxicity relationship. The probability of DLT at dose d_j, $p(d_j)$ is defined as (1)

$$p(d_j) = \frac{exp(\alpha + \beta x_j)}{1 + exp(\alpha + \beta x_j)} \qquad (1)$$

where

$$x_j = ln\left(\frac{d_j}{d^*}\right)$$

and d* is the reference dose (in this case d* = [redacted] mg)

The model (1) thus can be rewritten as (2):

$$ln\left(\frac{p(d_j)}{1-p(d_j)}\right) = \alpha + \beta x_j \quad (2)$$

where α and β are the parameters to be estimated and assumed to follow a bivariate normal distribution.

3.1 GENERAL MODEL SETTING

3.1.1 Dose Grid

The following dose grid has been used:

From [redacted] by [redacted]; from [redacted], by [redacted]; from [redacted] by [redacted].

3.1.2 Maximum Dose Increments

The following rules for selecting the maximum allowed dose increment will be applied.

- Maximum Dose Increments relative to DLT:
- In absence of a DLT a dose increment of 200% is allowed (i.e., next dose could be as high as 3-fold the previous dose)
- After the first DLT has been observed, the maximum allowed dose increment is reduced to 100% (i.e. up to 2-fold) for later cohorts. If there is only 1 accumulated DLT, no DLT in the most recent 2 cohorts, and provided the current dose is less than [redacted] mg, it is allowed to switch back to a dose increment of 200% (i.e. up to 3-fold). Otherwise, the maximum dose increment of 100% (i.e. up to 2-fold) remains.
    - In addition, based on the emerging data from the single agent dose-escalation study (WP41188), the upper limit to allow switching back to a dose increment of 200% (i.e. 3-fold) will be reset to 6-fold lower than single agent MTD.
- After 2 accumulated DLTs have been observed, a dose increment of 100% (i.e. 2-fold) must be maintained for all subsequent cohorts.

3.1.3 Stopping Rules

The algorithm will recommend ending the dose-escalation if any of the following criteria applies:

- Enough information on MTD:

At least a minimum of 12 participants evaluated *and* at least 6 participants have been accrued near the MTD dose (where near means differing from the MTD by at most 10%)

and the posterior probability that the MTD dose lies within the target toxicity interval is above 50% ***OR***

- Maximum dose is safe:

at least 6 subjects have been observed at the maximum dose or near (differing from the maximum dose by at most 10%) ***and*** it is at least 50% likely that the probability of a DLT for the maximum dose is below 0.2. ***OR***

- Maximum number of participants:

The maximum sample size of 60 DLT evaluable participants has been reached.

3.2 MODEL PRIOR

A minimally informative bivariate normal prior for the parameters of the DLT dose response curve (α, β) is constructed in order to have a weak impact on the final MTD determination (Neuenschwander et al. 2008).

This minimally informative prior "neutral" component will be constructed based on the assumed not toxic and toxic dose levels. It is conservatively assumed that it would be unlikely (less than 10%confidence) that a 15% or higher DLT rates are associated with the first dose ([redacted] mg) of RO7296682 in combination with atezolizumab and that it would be very unlikely (less than 10% confidence) that a 35% or lower DLT rate are associated with the dose of [redacted] mg.

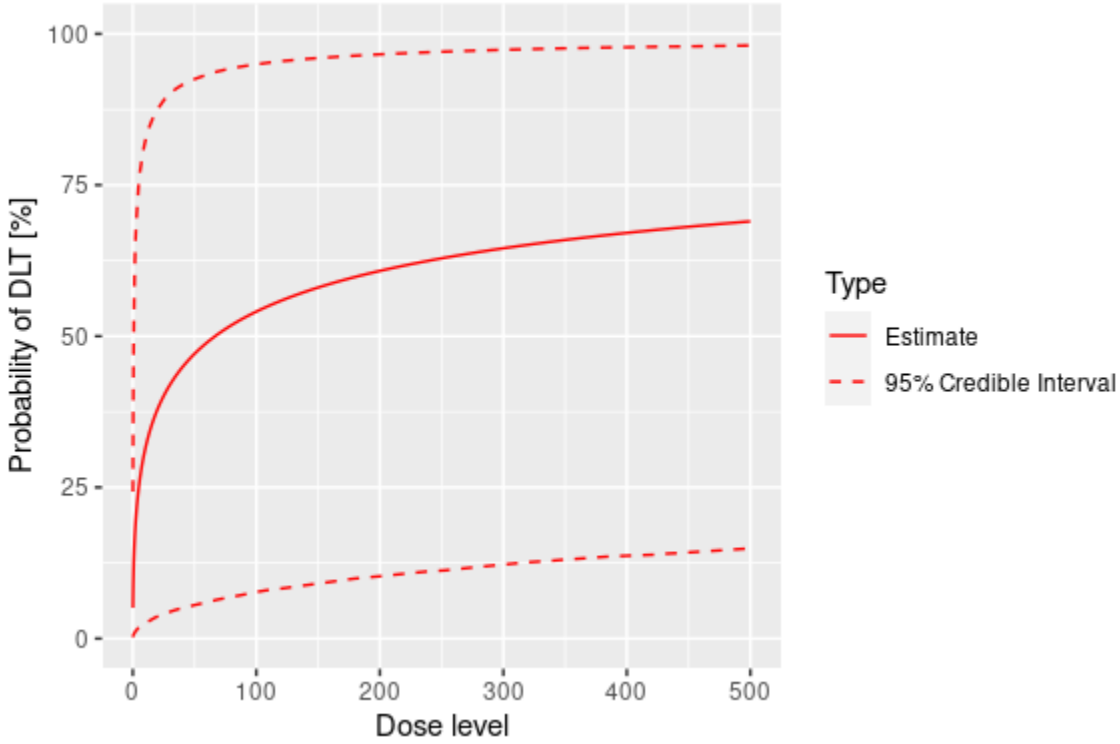
The parameters of the minimally informative prior are listed below (3):

$$\mu = (\alpha, \beta) = (0.05, 0.59)$$
$$\Sigma = \begin{pmatrix} \sigma_\alpha^2 & \sigma_{\alpha\beta} \\ \sigma_{\alpha\beta} & \sigma_\beta^2 \end{pmatrix} = \begin{pmatrix} 1.99701 & 0.05136 \\ 0.05136 & 0.00188 \end{pmatrix} \quad (3)$$

where μ and Σ are the parameters of the bivariate normal distribution.

The prior distribution used to determine the dose-escalation decision for this study is shown in Figure 2.

Figure 2 Minimally Informative Prior



3.3 MODEL PERFORMANCE EVALUATION

To illustrate how the design will perform, different escalation scenarios were explored and the corresponding results are tabulated in Table 1. Each column represents four different situations: which dose would the model recommend, after seeing no DLTs in previous cohorts and when 0, 1, 2, or 3 DLTs are observed in the current cohort. The evaluation is based on cohort size = 3, where stop indicates that the model would stop escalating and the study would be halted.

In general, if there are no observed DLTs, the model will suggest to escalate close to what the maximum increments allow, while in presence of one DLT the increments are more limited (see Table 1). With 2 or 3 DLTs, the model always recommends to de-escalate or STOP. Therefore, the results show that the design will adequately adapt the dose in the presence of observed DLTs.

Table 1 Dose Escalation Mock Runs

Dose Level	Dose (mg)	Next Dose (% Increment) if no DLT	Next Dose (% Increment) if 1 DLT	Next Dose (% Increment) if 2 DLTs	Next Dose (% Increment) if 3 DLTs
1	[redacted]				
2					
3					
4					
5					
6					
7					
8					

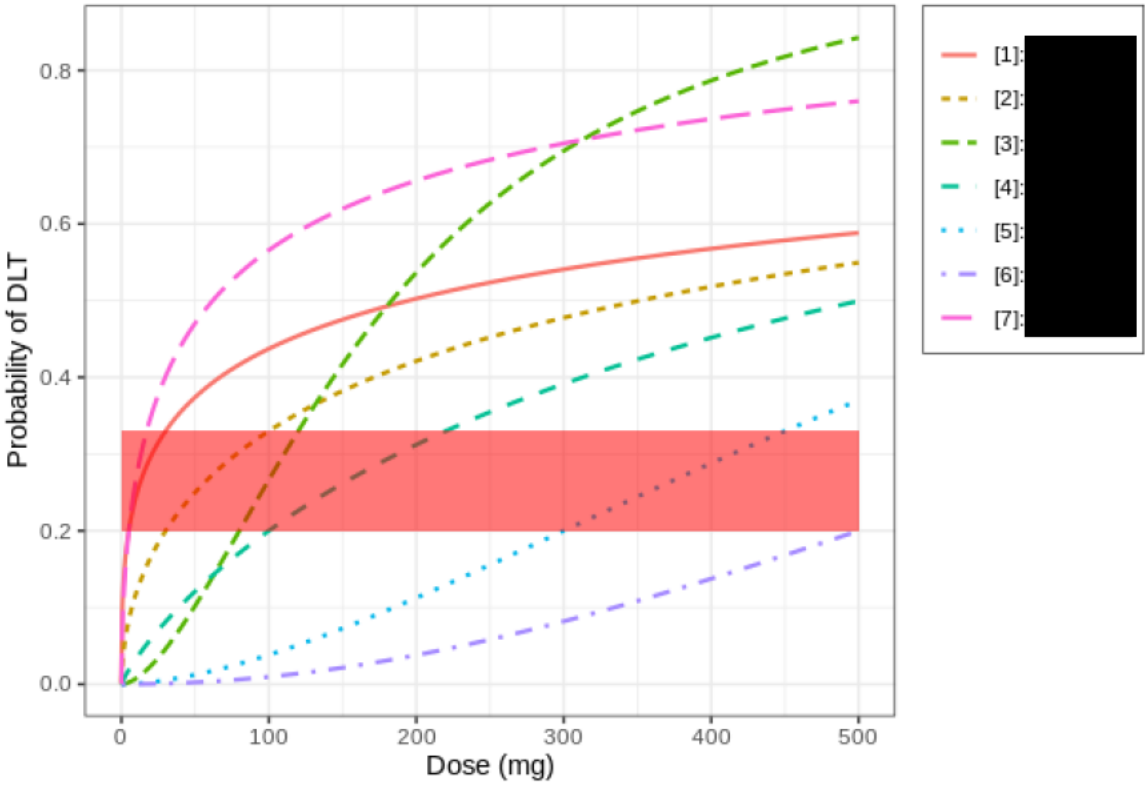
4. SIMULATION STUDY

A simulation study is conducted to evaluate the operating characteristics for the chosen design parameters (priors, reference dose, and stopping rule) under various dose-toxicity scenarios. The different scenarios have been selected in order to cover a wide range of dose-toxicity possibilities and to be able to quantify the risk and benefit, should these scenarios actually occur.

4.1 DOSE-TOXICITY SCENARIOS

In these simulations, the starting dose of [redacted] mg is assumed. Various dose-toxicity scenarios have been selected in order to cover a wide range of dose-toxicity possibilities and to be able to quantify the risk and benefit under different possible dose-toxicity relationships. Scenarios 1 and 7 reflects the toxicity if the compound was to behave very toxic. Scenarios 5 and 6 reflects toxicity of this compound if it is very safe. The other scenarios (2, 3, and 4) are intermediate scenarios. The dose-toxicity curves and target dose intervals are shown in Figure 3.

Figure 3 Simulation Scenarios: Assumed True Dose-Toxicity Relationship



4.2 SIMULATION RESULTS

For each of the scenarios, 1000 trials were simulated.

The design is evaluated using the following criteria: the MTD chosen, proportions of DLT, the number of participants treated at doses higher than the MTD, number of weeks spent estimation and the total number of participants treated. The result of the simulations is summarized in Table 2.

Table 2 Summary for Simulation of Study Results

Scenario	True Target Dose Rage	Overall N of Participants*	Overall N of Weeks*	N Participants Treated above Target Toxicity*	Proportions of DLTs per Trials*	Doses Selected as MTD*
1	[redacted]					
2						
3						
4						
5						
6						
7						

* median (10% quantile, 90% quantile)

3 participants per cohort in simulation but it is not limited to 3 in real study.

9 weeks for each multiple participant cohort.

5. REFERENCES

Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. J Natl Cancer Inst. 2009;101(10):708-20.

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008;27:2420-39.

R Core Team. 2017. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Available from: https://www.R-project.org/.

Schöffski P, Riggert S, Fumoleau P, et al. Phase I trial of intravenous aviscumine (rViscumin) in patients with solid tumors: a study of the European Organization for Research and Treatment of Cancer New Drug Development Group. Ann Oncol. 2004;15:1816-24.

Appendix 12
Management Guidelines for imAEs with RO7296682 and/or Combination Therapy with RO7296682 and Atezolizumab

PULMONARY EVENTS

*Pulmonary events may present as new or worsening d*yspnea, cough, *chest pain, fever, dyspnea*, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Participants will be assessed for pulmonary signs and symptoms throughout the study and will also have CT scans of the chest performed at every tumor assessment.

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

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue RO7296682 and/or atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider participant referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold after event onset. [a] • Refer participant to pulmonary and infectious disease specialists and consider bronchoscopy or BAL *with or without transbronchial biopsy*. • Initiate treatment with corticosteroids equivalent to 1 to 2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume RO7296682 and/or atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact Medical Monitor.[c, d] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue RO7296682 and/or atezolizumab and contact the Medical Monitor. [c] • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. • Bronchoscopy or BAL with or without transbronchial biopsy is recommended. • Initiate treatment with corticosteroids equivalent to 1 to 2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = Bronchoscopic alveolar lavage.

[a] RO7296682 and/or atezolizumab may be withheld for a longer period (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period must be agreed upon by the Investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before RO7296682 and/or atezolizumab can be resumed.

[c] Resumption of RO7296682.and/or atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. Participants can be re-challenged with RO7296682 and/or atezolizumab only after approval has been documented by the Investigator (or an appropriate delegate) and the Medical Monitor.

[d] *In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.*

HEPATIC EVENTS

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

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 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue RO7296682 and/or atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold RO7296682 and/or atezolizumab after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1 to 2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume RO7296682 and/or atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c]

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue RO7296682 and/or atezolizumab and contact the Medical Monitor.[c] • Consider participant referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1 to 2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

LFT = Liver function test.

[a] RO7296682 and/or atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period must be agreed upon by the Investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤10 mg/day oral prednisone before RO7296682 and/or atezolizumab can be resumed.

[c] Resumption of RO7296682 and/or atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. Participants can be re-challenged with RO7296682 and/or atezolizumab only after approval has been documented by the Investigator (or an appropriate delegate) and the Medical Monitor.

GASTROINTESTINAL EVENTS

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

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

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

Event	Management
Diarrhea or colitis, Grade 1	• Continue RO7296682 and/or atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold RO7296682 and/or atezolizumab after event onset. [a] • Initiate symptomatic treatment. • *If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • Participant referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. *If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • If event resolves to Grade 1 or better, resume RO7296682 and/or atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold RO7296682 and/or atezolizumab after event onset. [a] • Refer participant to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent*. • If event resolves to Grade 1 or better, resume RO7296682 and/or atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c]

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue RO7296682 and/or atezolizumab and contact the Medical Monitor. [c] • Refer participant to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = Gastrointestinal.

[a] RO7296682 and/or atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period must be agreed upon by the Investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤10 mg/day oral prednisone before RO7296682 and/or atezolizumab can be resumed.

[c] Resumption of RO7296682 and/or atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. Participants can be re-challenged with RO7296682 and/or atezolizumab only after approval has been documented by the Investigator (or an appropriate delegate) and the Medical Monitor.

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders may be associated with the administration of RO7296682 and/or atezolizumab. Management guidelines for endocrine events are provided in Table 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. The participant should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• *Continue RO7296682 and/or atezolizumab.* • *Initiate treatment with thyroid replacement hormone.* • *Monitor TSH weekly.*
Grade 2 hypothyroidism	• *Consider withholding* RO7296682 and/or atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely.* • *Consider participant referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled and thyroid function is improving.*
Grade 3 and 4 hypothyroidism	• Withhold RO7296682 and/or atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely.* • *Refer* participant to endocrinologist. • *Admit participant to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status).* • Resume RO7296682 and/or atezolizumab when symptoms are controlled and thyroid function is improving. • *Permanently discontinue RO7296682 and/or atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism.* [c]
Grade 1 hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue RO7296682 and/or atezolizumab. • Monitor TSH every 4 weeks. • *Consider participant referral to endocrinologist.* **TSH <0.1 mU/L:** • Follow guidelines for *Grade 2* hyperthyroidism. • *Consider participant referral to endocrinologist.*
Grade 2 hyperthyroidism	• *Consider withholding RO7296682 and/or atezolizumab.* • *Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.* • *Consider participant referral to endocrinologist.* • *Resume RO7296682 and/or atezolizumab when symptoms are controlled and thyroid function is improving.*

Event	Management
Grade 3 and 4 hyperthyroidism	• Withhold RO7296682 and/or atezolizumab. • Initiate treatment with anti-thyroid drug*s* such as methimazole or carbimazole as needed. • *Refer* participant to endocrinologist. • Resume RO7296682 and/or atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]
Symptomatic adrenal insufficiency, Grade 2 to 4	• Withhold RO7296682 and/or atezolizumab after event onset. [a] • Refer participant to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1 to 2 mg/kg/day IV methylprednisolone and convert to 1 to 2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume RO7296682 and/or atezolizumab. [b] • If event does not resolve to Grade 1 or better or participant is not stable on replacement therapy while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue RO7296682 and/or atezolizumab. • Investigate for diabetes. If *participant* has Type 1 diabetes, treat as a Grade 3 event. If *participant* does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold RO7296682 and/or atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume RO7296682 and/or atezolizumab when symptoms resolve and glucose levels are stable.

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold RO7296682 and/or atezolizumab after event onset. [a] • Refer participant to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1 to 2 mg/kg/day IV methylprednisolone and convert to 1 to 2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume RO7296682 and/or atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c] • Refer participant to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = Magnetic resonance imaging; TSH = Thyroid-stimulating hormone.

[a] RO7296682 and/or atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period must be agreed upon by the Investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7296682 and/or atezolizumab can be resumed.

[c] Resumption of RO7296682 and/or atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. Participants can be re-challenged with RO7296682 and/or atezolizumab only after approval has been documented by the Investigator (or an appropriate delegate) and the Medical Monitor.

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue RO7296682 and/or atezolizumab. • Participant referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold RO7296682 and/or atezolizumab after event onset. [a] • Participant referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume RO7296682 and/or atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue RO7296682 and/or atezolizumab and contact Medical Monitor. [c] • Refer participant to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] RO7296682 and/or atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period must be agreed upon by the Investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7296682 and/or atezolizumab can be resumed.

[c] Resumption of RO7296682 and/or atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. Participants can be re-challenged with RO7296682 and/or atezolizumab only after approval has been documented by the Investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table 6.

IMMUNE-MEDIATED MYOCARDITIS

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

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

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

IMMUNE-MEDIATED PERICARDIAL DISORDERS

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

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

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

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

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

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

Event	Management
Immune-mediated myocarditis, Grade*s* 2-4 *Immune-mediated pericardial disorders, Grades 2 to 4*	• Permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. • Refer participant to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD, *or pericardiocentesis* as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = Extracorporeal membrane oxygenation; IV = intravenous; VAD = Ventricular assist device.

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 7.

Table 7 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue RO7296682 and/or atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold RO7296682 and/or atezolizumab after event onset. [a] • Refer participant to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume RO7296682 and/or atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold RO7296682 and/or atezolizumab after event onset. [a] • Refer participant to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume RO7296682 and/or atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c]

Event	Management
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor.[c] • Refer participant to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = Gastrointestinal; IV = intravenous.

[a] RO7296682 and/or atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period must be agreed upon by the Investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone RO7296682 and/or atezolizumab can be resumed.

[c] Resumption of RO7296682 and/or atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. Participants can be re-challenged with RO7296682 and/or atezolizumab only after approval has been documented by the Investigator (or an appropriate delegate) and the Medical Monitor.

DERMATOLOGIC EVENTS

The majority of cases of rash *reported with the use of atezolizumab* were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 8.

Table 8 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue RO7296682 and/or atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue RO7296682 and/or atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold RO7296682 and/or atezolizumab after event onset. [a] • Refer participant to dermatologist. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume RO7296682 and/or atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor.[c]

[a] RO7296682 and/or atezolizumab may be withheld for a longer period (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period must be agreed upon by the Investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7296682 and/or atezolizumab can be resumed.

[c] Resumption of RO7296682 and/or atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. Participants can be re-challenged with RO7296682 and/or atezolizumab only after approval has been documented by the Investigator (or an appropriate delegate) and the Medical Monitor.

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. Management guidelines for neurologic disorders are provided in Table 9*, with specific guidelines for myelitis provided in Table 10*.

Table 9 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue RO7296682 and/or atezolizumab. • Investigate etiology. • *Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.*
Immune-mediated neuropathy, *including facial paresis,* Grade 2	• Withhold RO7296682 and/or atezolizumab after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • *For general immune-mediated neuropathy:* – If event resolves to Grade 1 or better, resume RO7296682 and/or atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c] • *For facial paresis:* – *If event resolves fully, resume atezolizumab* [b] – *If event does not resolve fully while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated neuropathy, *including facial paresis,* Grade 3 or 4	• Permanently discontinue RO7296682 and/or atezolizumab and contact Medical Monitor. [c] • *Refer participant to neurologist.* • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c] • Refer participant to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1 to 2 mg/kg/day oral or IV prednisone.

[a] RO7296682 and/or atezolizumab may be withheld for a longer period (i.e., $>$12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day oral prednisone. The acceptable length of the extended period must be agreed upon by the Investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over $\geq$ 1 month to the equivalent of $\leq$ 10 mg/day oral prednisone before RO7296682 and/or atezolizumab can be resumed.

[c] Resumption of RO7296682 and/or atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. Participants can be re-challenged with RO7296682 and/or atezolizumab only after approval has been documented by the Investigator (or an appropriate delegate) and the Medical Monitor.

Table 10 Management Guidelines for Immune-Mediated Myelitis

Event	*Management*
Immune-mediated myelitis, Grade 1	• *Continue RO7296682 and/or atezolizumab unless symptoms worsen or do not improve.* • *Investigate etiology and refer participant to a neurologist.*
Immune-mediated myelitis, Grade 2	• *Permanently discontinue RO7296682 and/or atezolizumab and contact the Medical Monitor.* • *Investigate etiology and refer participant to a neurologist.* • *Rule out infection.* • *Initiate treatment with corticosteroids equivalent to 1 to 2 mg/kg/day oral prednisone.*
Immune-mediated myelitis, Grade 3 or 4	• *Permanently discontinue RO7296682 and/or atezolizumab and contact the Medical Monitor.* • *Refer participant to a neurologist.* • *Initiate treatment as per institutional guidelines.*

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.

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

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

Table 11 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. • Refer participant to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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 12.

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue RO7296682 and/or atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold RO7296682 and/or atezolizumab for up to 12 weeks after event onset. [a] • Refer participant to renal specialist. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume RO7296682 and/or atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. • Refer participant to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] RO7296682 and/or atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period must be agreed upon by the Investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7296682 and/or atezolizumab can be resumed.

[c] Resumption of RO7296682 and/or atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. Participants can be re-challenged with RO7296682 and/or atezolizumab only after approval has been documented by the Investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

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

Table 13 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue RO7296682 and/or atezolizumab. • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold RO7296682 and/or atezolizumab after event onset [a] and contact *the* Medical Monitor. • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume RO7296682 and/or atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c]

Event	Management
Immune-mediated myositis, Grade 3	• Withhold RO7296682 and/or atezolizumab after event onset [a] and contact Medical Monitor. • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume RO7296682 and/or atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding RO7296682 and/or atezolizumab, permanently discontinue RO7296682 and/or atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. *Permanently discontinue RO7296682 and/or atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated myositis, Grade 4	• Permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. [c] • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] RO7296682 and/or atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7296682 and/or atezolizumab can be resumed.

[c] Resumption of RO7296682 and/or may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. Participants can be re-challenged with RO7296682 and/or atezolizumab only after approval has been documented by the Investigator (or an appropriate delegate) and the Medical Monitor.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

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

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

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

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

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

- Ferritin $>$ 684 mg/L (684 ng/mL).
- At least two of the following:
  - Platelet count $\leq$ 181 $\times$ 109/L (181,000/μL).
  - AST $\geq$ 48 U/L.
  - Triglycerides $>$ 1.761 mmol/L (156 mg/dL).
  - Fibrinogen $\leq$ 3.6 g/L (360 mg/dL).

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

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

Event	Management
Suspected HLH or MAS	• Permanently discontinue RO7296682 and/or atezolizumab and contact *the* Medical Monitor. • Consider participant referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact *the* Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = Hemophagocytic lymphohistiocytosis; MAS = Macrophage activation syndrome.

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Appendix 13
New Response Evaluation Criteria in Solid Tumors—Version 1.1

1. MEASURABILITY OF TUMOR AT BASELINE

1.1 DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable 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 of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions, which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest x-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also Section 2.2 on “Baseline documentation of target and non-target lesions” for information on lymph node measurement.

1.1.2 Non-measurable Tumor Lesions

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

1.1.3 Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, positron emission tomography scan, or plain films are not considered adequate imaging techniques to measure 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 as 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 as malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.
- “Cystic lesions” thought to represent cystic metastases, can be considered as 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 previous 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.

1.2 TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

1.2.1 Measurement of Lesions

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

1.2.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during 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 diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

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

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

2.2.2 TUMOR RESPONSE EVALUATION

2.1. ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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. Measurable disease is defined by the presence of at least one measurable lesion (as detailed in Section 1.1.1).

2.2. BASELINE DOCUMENTATION 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 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where participants have only one or 2 organ sites involved, a maximum of 2 (one site) and 4 lesions (2 sites), respectively, will be recorded. Other lesions (albeit measurable) in that organ will be recorded as non-measurable lesions (even if size is ≥10 mm by CT scan).

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

Lymph nodes merit special mention because they are normal anatomical structures, which may be visible by imaging even if not involved by tumor. As noted in Section 1.1.1, pathological node, which 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. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan 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, which is reported as being 20 mm × 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 < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', "absent," or in rare cases "unequivocal progression" (see also Section 2.3.4).

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

2.3. RESPONSE CRITERIA

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

2.3.1. Evaluation of Target Lesions

- Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to $<$ 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including baseline (nadir). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.

2.3.2. Special Notes on the Assessment of Target Lesions

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 nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, because a normal lymph node is defined as having a short axis of $<$ 10 mm.

Target lesions that become *too small to measure": while on study, all lesions (nodal and non-nodal) 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 which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure

and may report them as being “too small to measure.” When this occurs, it is important that a value be recorded on the case report form:

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

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked (BML is equivalent to a less than sign $<$).

Lesions that split or coalesce on treatment: when non-nodal lesions “fragment,” the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the “coalesced lesion.”

2.3.3. Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete response (CR): Disappearance of all non-target lesions (and, if applicable, normalization of tumor marker level). All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

Non-CR/non-progressive disease: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive disease: Unequivocal progression (see Section 2.3.4) of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

2.3.4. Special Notes on Assessment of Progression of Non-target Disease

When the participant also has measurable disease: In this setting, to achieve "unequivocal progression" based on the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, 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 based on change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the participant has only non-measurable disease: This circumstance arises in some phase III studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare progressive disease for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the participant should be considered to have had overall progressive disease at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.3.5. 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: i.e., 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 partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

2.4 EVALUATION OF RESPONSE

2.4.1 Time-Point Response (Overall Response)

It is assumed that at each protocol-specified time point, a response assessment occurs. A summary of the overall response status calculation at each time point for participants who have measurable disease at baseline is provided in Table 1.

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

Table 1 Time-Point Response—Target (with/without non-target) Lesions

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 Time-Point Response—Non-Target Lesions only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.4.2 Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the participant is not evaluable at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of progressive disease.

For example, if a participant had a baseline sum of 50 mm with 3 measured lesions and during study only 2 lesions were assessed, but those gave a sum of 80 mm, the participant will have achieved progressive disease status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" because the participant is not evaluable. Similarly, if one or more non-target lesions are indicated as "not assessed," the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Table 3 Best Overall Response when Confirmation is Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2 Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of 'zero' on the case report form (CRF).

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such participants is to be determined by evaluation of target and non-target disease as shown in Table 1, Table 2, and Table 3.

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. In studies where participants with advanced disease are eligible (ie, primary disease still or partially present), the primary tumor should be also captured under target or non-target lesions as appropriate. This is to avoid wrong assessments of complete overall response by statistical programs while the primary is still present but not evaluable.

References

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

Appendix 14
Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immunotherapy-specific response criteria adaptations to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; Eisenhauer et al. 2009) have been developed to allow for unconventional response and progression patterns. These include modified RECIST v1.1 for immune-based therapeutics (iRECIST; Seymour et al. 2017), which was developed by the RECIST working group in an effort to create a common set of criteria that the cancer immunotherapy field could apply to clinical trials.

Response evaluation through use of iRECIST requires collection of tumor assessment data after radiographic progression per RECIST v1.1. Details regarding lesion evaluation are described below. When not otherwise specified, RECIST v1.1 conventions will apply.

Criteria for determining overall response at a single timepoint per iRECIST are also summarized below. Of note, overall response per iRECIST will not be captured in the electronic Case Report Form (eCRF), but will instead be calculated programmatically by the Sponsor based on investigator-assessed individual lesion data recorded in the eCRF.

iRECIST response status is not a specific component of treatment discontinuation criteria, including decisions about whether to continue treatment beyond progression per RECIST v1.1. Investigators should instead take into account radiologic data and clinical status in making such decisions

EVALUATION OF LESIONS TO SUPPORT iRECIST RESPONSE ASSESSMENT AFTER DISEASE PROGRESSION PER RECIST V1.1

iRECIST is an extension of RECIST v1.1 that allows for response assessment following disease progression per RECIST v1.1. RECIST v1.1 rules for categorizing lesions as measurable or non-measurable and measuring lesions (see Appendix 13) also apply to iRECIST. After disease progression per RECIST v1.1, the same target and non-target lesions selected at baseline will continue to be followed, along with any new lesions that develop, to support iRECIST response evaluations, as described below and summarized in Table 1. Once a lesion has been categorized as a target, non-target, or new lesion, it will remain classified as such.

TARGET LESIONS

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

NON-TARGET LESIONS

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

NEW LESIONS

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

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

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

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is ≥15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is ≥10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis

of a lymph node is < 10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is 15 mm. Measurable new lymph node lesions should continue to be measured at all subsequent timepoints, even if the short axis decreases to < 15 mm (or even < 10 mm).

Table 1 Guidelines for Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1

Lesion Type	Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1
Target lesions	• Measurements should be continued according to RECIST v1.1 conventions.
Non-target lesions	• Non-target lesions should continue to be categorized as absent (CR), unequivocal progression (PD), or present without unequivocal progression (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous timepoint should be evaluated to determine whether there has been any further increase in size.
New lesions	• New lesions should be evaluated for measurability per RECIST v1.1. • All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints. • Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint. • All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.

CR = Complete response; PD = Progressive disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.

SUMMARY OF CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Timepoint response per iRECIST will be calculated programmatically by the Sponsor. A complete description of the iRECIST criteria can be found in Seymour et al. 2017.

REFERENCES

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Hodi FS, Ballinger M, Lyons B, et al. Immune-modified response evaluation criteria in solid tumors (imRECIST): refining guidelines to assess the clinical benefit of cancer immunotherapy. J Clin Oncol. 2018;36:850-8.

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

Appendix 15
Cockcroft-Gault Formula/Creatinine Clearance (mL/min)

Creatinine clearance (ml/min) for males

$$\text{Creatinine Clearance} = \frac{(140 - \text{age } \langle\text{years}\rangle) \times \text{body weight } \langle\text{kg}\rangle)}{(72) \times (\text{serum creatinine } \langle\text{mg/dL}\rangle)}$$

Creatinine Clearance (ml/min) for females:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age } \langle\text{years}\rangle) \times \text{body weight } \langle\text{kg}\rangle)}{(72) \times (\text{serum creatinine } \langle\text{mg/dL}\rangle)} \times 0.85 \text{ (if female)}$$

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