Official Title: An Open-Label, Multicenter Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of RO7296682, a CD25-Targeting, T-Regulatory Cell Depleting Antibody in Participants With Advanced and/or Metastatic Solid Tumors

NCT Number: NCT04158583

Document Date: Protocol Version 5: 01 June 2021

PROTOCOL

TITLE:	**AN OPEN-LABEL, MULTICENTER PHASE 1 STUDY TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF RO7296682, A CD25-TARGETING, T-REGULATORY CELL DEPLETING ANTIBODY IN PARTICIPANTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS**
PROTOCOL NUMBER:	WP41188
VERSION:	5
EUDRACT NUMBER:	2019-002830-35
IND NUMBER:	TBD
TEST PRODUCT:	RO7296682
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 12-Aug-2019
DATE AMENDED:	Version 2: 24-Jun-2020
	Version 3: 08-Jul-2020
	Version 4: 13 November 2020
	Version 5: See electronic stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
01-Jun-2021 10:46:43	[redacted]	[redacted]

PROTOCOL ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, MULTICENTER PHASE 1 STUDY TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF RO7296682, A CD25-TARGETING, T-REGULATORY CELL DEPLETING ANTIBODY IN PARTICIPANTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS**
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TEST PRODUCT:	RO7296682
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL AMENDMENT, VERSION 5
RATIONALE

Protocol WP41188 version 4 has been amended. The changes along with a rationale for each change are listed below.

- Section 1.3, Schedule of activities, Table 1 was updated to include [redacted]. Table 2, footnote " g" was clarified by adding the note, "If preliminary data suggest, alternative on-treatment tumor biopsy or healthy skin punch biopsy time points may be considered upon joint agreement between Investigators and the Sponsor" which was already mentioned in the body of the previous protocol version as well. In addition, Table 2 was updated including the collection of [redacted] samples from participants enrolled in Part B Dose Expansion.
- Sections 4.1, 4.1.4 and 9.2: The sample size of 60 participants for the dose escalation part of this study has been increased to 90 participants. The increase in sample size is required to determine the optimal biological dose based on additional patients providing tumor biopsies. The maximum planned dose of 500mg will not be exceeded. The updated sample size of 90 had been determined in order to allow for at least 15 additional paired tumor biopsy sample.
- Section 4.2.2 was updated to provide the rationale for collecting [redacted] samples from participants enrolled in Part B Dose Expansion.
- Section 5.1: Inclusion criteria 9 was updated in order to allow for patients with hemoglobin < 9 g/dL who have experienced acute bleeding events or received transfusion.

Additional minor changes have been made to ensure consistency of the protocol. 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
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATD	anticipated therapeutic dose
AUC	area under the curve
BML	below measurable limit
C1D1	Cycle 1/Day1
CCR4	CC chemokine receptor 4
CL	clearance
C_{max}	maximum concentration
C_{min}	minimum concentration
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CRO	contract research organization
[redacted]	[redacted]
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLCO	diffusion capacity
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
DRF	dose range finding
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

Abbreviation	Definition
EDC	electronic data capture
EEA	European Economic Area
EsC	esophageal carcinoma
EoS	end of study
EoT	end of treatment
EU	European Union
EWOC	escalation with overdose control
FDA	Food and Drug Administration
FEV1	forced expiratory volume
FFPE	formalin-fixed-paraffin-embedded
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HBcAb	total hepatitis B core antibody
HCV	Hepatitis C virus
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
[redacted]	[redacted]
[redacted]	[redacted]
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	international normalized ratio
imAE	immune-mediated adverse event

Abbreviation	Definition
IRB	Institutional Review Board
IRF	independent review facility
IRC	Independent Review Committee
IRR	infusion-related reactions
iRECIST	immune RECIST
IUD	intrauterine device
IV	intravenous
IxRS	interactive (voice/web) response system
LDH	lactate dehydrogenase
LDL	low-density lipoproteins
LPLV	last participant, last visit
LPLO	last participant, last observation
LN	lymph node
MAD	multiple-ascending doses
mCRM	modified continual reassessment method
MD	multiple doses
MEL	melanoma
MoA	mode of action
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition scan
NCI	National Cancer Institute
NGS	next-generation sequencing
NOAEL	no-observed-adverse-effect level
NSAESI	non-serious adverse event of special interest
NSCLC	non-small cell lung carcinoma
NSAIDs	nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
OvC	ovarian cancer
PD	pharmacodynamic
PD	progression of disease
PFS	progression-free survival
PFT	pulmonary function test
PK	pharmacokinetic

Abbreviation	Definition
PR	partial response
PT	prothrombin time
Q3W	every 3 weeks
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia's correction factor
RBC	red blood cell
RBR	research biosample repository
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 Dose
RR	RR interval
SAD	single-ascending dose
SAE	serious adverse event
SC	subcutaneous
SD	stable disease
SDEC	Safety and Dose Escalation Committee
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TBD	tissue biomarker dose
t_{max}	time of maximum concentration observed
Teff	T effector cell
TNBC	triple-negative breast cancer
Treg	T-regulatory cell
TSH	thyroid-stimulating hormone
TTE	transthoracic echocardiogram
ULN	upper limit of normal
US	United States
Vss	volume of distribution at steady-state conditions
WBC	white blood cell
WES	whole exome sequencing
WGS	whole genome sequencing
WOCBP	women of childbearing potential
WONCBP	women of non-childbearing potential

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**AN OPEN-LABEL, MULTICENTER PHASE 1 STUDY TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF RO7296682, A CD25-TARGETING, T-REGULATORY CELL DEPLETING ANTIBODY IN PARTICIPANTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS**
SHORT TITLE	**CD25 TARGETING BY RO7296682 IN PATIENTS WITH ADVANCED AND/OR METASTATIC SOLID TUMOR**
PROTOCOL NUMBER:	WP41188
VERSION:	5
TEST PRODUCT:	RO7296682
PHASE:	1

RATIONALE

In this study, the novel compound RO7296682, which selectively binds to CD25 (the IL-2 receptor α chain) while not interfering with interleukin-2 (IL-2) signaling, will be assessed as a T-regulatory cell (Treg)-depleting strategy for the treatment of cancer.

Tregs can suppress antigen-specific, anti-tumor immune responses, thus allowing for tumor growth. Reducing the number of Tregs, or fully removing them from tumors, may reduce tumor growth in vivo and may foster or restore an immune response to tumor cells in humans.

The high prevalence of CD25 on Tregs, as well as a more than $>$20 to100-fold higher expression of CD25 on Tregs vs. cytotoxic T lymphocytes (CTLs), qualifies CD25 as superior target over other Treg markers. Therefore, RO7296682 has the potential to improve anti-cancer outcomes, particularly in combination with other immune-modifying agents.

In this first-in-human, open-label, multicenter Phase 1 study, WP41188, the safety and tolerability of the monoclonal antibody RO7296682 will be explored and the Maximum Tolerated Dose (MTD) and/or Recommended Phase 2 Dose (RP2D) will be determined. Study WP41188 will also assess the pharmacokinetics (PK), pharmacodynamics (PD), and preliminary anti-tumor activity of RO7296682.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To characterize the safety, tolerability, Maximum-Tolerated Dose (MTD) and/or Recommended Phase 2 Dose (RP2D) of RO7296682	• Nature and frequency of Adverse Events (AEs), (with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0) • Nature and frequency of dose-limiting toxicities (DLTs)
Secondary	
To assess the preliminary anti-tumor activity of RO7296682	• Objective response rate (ORR) • Disease control rate (DCR); defined as ORR + stable disease [SD] rate • Duration of response (DoR) • Progression-free survival (PFS) • All according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1
To investigate the PK profile of RO7296682	• PK profiles and parameters derived for RO7296682 including but not limited to: • Area under the curve (AUC), minimum concentration (C_{min}), maximum concentration (C_{max}), Clearance (CL), Volume of distribution at steady-state conditions (Vss), Half-life ($t_{1/2}$), as appropriate, Time of maximum concentration (T_{max})
To evaluate the anti-drug immune response after treatment	• Incidence and titer of anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at baseline
To assess the PD effect of RO7296682 in blood and tumor tissue	• Treatment-induced changes in Treg levels in blood and/or tumor as compared to baseline. • Treatment-induced changes in Treg/Teff ratio in blood and/or tumor as compared to baseline.

OVERALL DESIGN

Study Design

Study WP41188 is a first-in-human, open-label, multicenter, Phase 1 dose escalation study of single agent RO7296682.

The study consists of 2 parts: Part A (dose escalation) and Part B (dose expansion).

- **Part A: RO7296682 dose escalation in multiple participant cohorts**

- Part A will determine the safety, tolerability, PK/PD profile, and preliminary anti-tumor activity of escalating doses of RO7296682using a minimum of 3 DLT evaluable participants per cohort.
- Incremental increases (and potential decreases) between cohorts will be determined by a Bayesian-based continuous reassessment method (CRM) with overdose control measures.
- Participants with advanced and/or metastatic non-small cell lung cancer (NSCLC), melanoma (MEL), head and neck squamous cell carcinoma (HNSCC), ovarian cancer (OvC), triple-negative breast cancer (TNBC), or esophageal carcinoma (EsC) will be enrolled.
- On treatment biopsies: Once a dose is reached where a reduction to 25% of baseline peripheral Treg level is observed in at least 50% of participants in a given cohort and/or a $\geq$ 4-fold increase of peripheral Teff/Treg is observed in at least 50% of participants in a given cohort, and/or objective clinical response is observed (Complete Response [CR] or Partial Response [PR]), on-treatment biopsies will be collected starting with the following cohort (at the Tissue Biomarker Dose).
- Part A will determine the MTD and/or RP2D based on the safety, tolerability, and PK/PD profile of RO7296682.

- **Part B: RO7296682 single agent dose expansion cohort:**
  - Part B will evaluate safety, tolerability, PK/PD profile and preliminary anti-tumor activity of the MTD and/or RP2D of RO7296682 determined in Part A in participants with MEL, NSCLC, and HNSCC. Based on emerging data, additional indications may be added to this study through a substantial protocol amendment.

Treatment Groups and Duration

RO7296682 will be administered by intravenous (IV) infusion over 4 hours (240 min) at the first infusion. If the first infusion is well tolerated, as defined by an absence of Grade $\geq$2 Infusion-related reactions (IRRs), the subsequent infusions may be given over 2 hours (120 min) after consultation with the Medical Monitor. If the 2-hour infusion is well tolerated, all subsequent infusions may be further reduced to 60 minutes after consultation with the Medical Monitor.

The starting dose will be 0.3 mg and the maximum dose is planned to be 500 mg. Participants will receive IV RO7296682 every 3 weeks (Q3W) and the cycle length will be accordingly defined as 21 days.

Starting from administration of the first dose (Cycle 1/Day 1 [C1D1]), each participant is followed through a 4-week DLT window in Part A. At least 3 DLT evaluable participants will be enrolled in each Part A cohort during the dose escalation. Entry into a cohort will be controlled by a 7-day safety window between participants 1 and 2 in each cohort.

The maximum total number of participants in Part A will be approximately *90* DLT evaluable participants. Part B will conclude when approximately 20 evaluable paired tumor biopsy samples or a maximum total number of 50 participants has been reached.

Participants may continue treatment with RO7296682 for up to 24 months.

At the discretion of the Investigator and in agreement with the Sponsor, intra-patient 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 dose is considered safe.

All participants will be treated with RO7296682 until disease progression, unacceptable toxicities, withdrawal of consent, or withdrawal of the participant by the Investigator.

The Investigational Medicinal Product (IMP) is:

Ro 729-6682/F01 (active) solution for IV infusion; 20mg/mL.

Length of Study

The maximum duration of the study for each participant will be up to 28 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: 90 (± 7) days after last treatment with RO7296682
- 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 (LPLV) per protocol (includes the safety follow-up visit 90 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

No formal third party data monitoring committee is planned. However, ongoing medical data review will be performed regularly by a Safety and Dose Escalation Committee (SDEC) composed of key Sponsor-based functional representatives of the clinical study team, including at a minimum the Medical Monitor, Drug Safety Scientist, and the Biostatistician. In addition, this committee will make decisions regarding dose escalations. The SDEC will meet regularly and additionally as needed at the request of the study Medical Monitor.

PARTICIPANT POPULATION

The study population consists of adult male and female participants with advanced and/or metastatic solid tumors who meet all inclusion criteria and none of the exclusion criteria.

Part A: Participants with TNBC, OvC, MEL, NSCLC, HNSCC, or EsC, which are not amenable to standard treatment.

Part B: Participants with MEL, NSCLC, or HNSCC, who are not amenable to standard treatment. Based on emerging data, additional indications may be added to this study through a substantial protocol amendment.

Inclusion/Exclusion Criteria

Key General Inclusion Criteria

Adult participants are eligible to be included in the study only if all of the following criteria apply prior to dosing on C1D1. For a detailed list of eligibility criteria, see Section 5.

- Diagnosis of advanced and/or metastatic solid tumors (**Part A**: TNBC, OvC, MEL, NSCLC, HNSCC, or EsC; **Part B**: MEL, HNSCC, or NSCLC) who have progressed on all standard therapies, are intolerant to SOC, and/or are non-amenable to SOC. Participants whose tumors have a known sensitizing mutation must have experienced disease progression (during or after treatment) or intolerance to treatment with a respective targeted therapy.
- Measurable disease according to RECIST v1.1
- Life expectancy, in the opinion of the investigator, of ≥ 12 weeks.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Able to provide the most recent archival tumor tissue samples.
- Adequate cardiovascular function.
- Adequate hematological function.

- Adequate liver function.
- Adequate renal function.
- Additional adequate laboratory parameters obtained prior to the first study treatment (C1D1):
  - Serum albumin $\geq$ 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
- Adequate contraception as defined in the protocol.

Key Specific Inclusion Criteria for Part A (only for Participants who reached the "Tissue Biomarker Dose") and Part B Dose Expansion cohorts:

- A freshly collected biopsy of a tumor lesion (primary and/or metastatic) from a safely accessible site, per Investigator determination and patient consent, will be requested, providing the patient has more than one measurable target lesion. The biopsied lesion must not be a target lesion.
- Consent to provide a freshly collected skin punch biopsy.

Key General Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply prior to dosing on C1D1:

- Pregnancy, lactation, or breastfeeding.
- Known hypersensitivity to any of the components of RO7296682, including but not limited to hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.
- 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.
- Participants with another invasive malignancy in the last two years.
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results.
- Encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.
- Severe dyspnea or requiring supplemental oxygen therapy at rest.
- Episode of significant cardiovascular/cerebrovascular vascular disease within 6 months prior to C1D1 of study drug administration.
- Participants with known active or uncontrolled infection, or reactivation of a latent infection.
- Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, and inherited liver disease.
- Major surgical procedure or significant traumatic injury within 28 days prior to first RO7296682 infusion, or anticipation of the need for major surgery until end of treatment period.
- Participants with current or history of wound healing complications and/or participants with open wounds until complete resolution.
- Dementia or altered mental status that would prohibit informed consent.

- History of Stevens-Johnson syndrome, toxic epidermal necrolysis, or DRESS (drug rash with eosinophilia and systemic symptoms).
- 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 (exceptions are listed in Section 5.2).
- Prior treatment with checkpoint inhibitors (CPIs) (e.g. anti-CTLA4, anti-PD1, anti-PDL1), immunomodulatory monoclonal antibodies (mAbs) and/or mAb-derived therapies (approved or investigational) is allowed, provided that
  - at least 4 weeks have elapsed between the last dose and the proposed C1D1
  - at least 5 half-lives or 28 days (whichever is shorter) have elapsed since prior treatment with specific immunomodulators, TLR agonists, inhibitors of IDO/TDO, or agonists (e.g., OX40) and the proposed C1D1
- Prior treatment with a CC chemokine receptor 4 (CCR4)-targeting (e.g. mogamulizumab) or a CD25-targeting agent (e.g. basiliximab) is prohibited.
- 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 the first RO7296882 administration on C1D1.
- Immuno-modulating agents.
- Treatment with systemic immunosuppressive medications.
- 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).
- Adverse events 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.

NUMBER OF PARTICIPANTS

The maximum total number of participants in Part A will be approximately *90* DLT evaluable participants.

Part B will conclude when approximately 20 evaluable paired tumor biopsy samples or a maximum total number of 50 participants has been reached.

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:

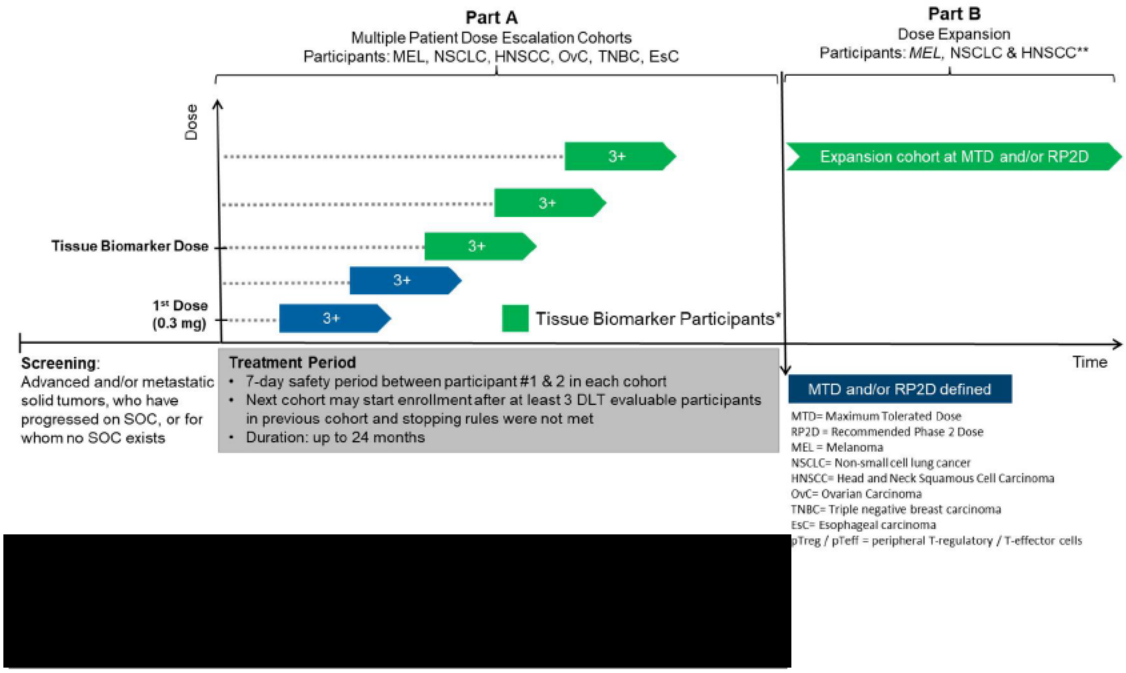
- Investigational or unlicensed/unapproved agents
- Immunotherapy/radio-immunotherapy
- Chemotherapy / targeted therapy
- Radiotherapy (with the exception of limited field palliative radiotherapy).
- Biologic agents (e.g., bevacizumab, cetuximab). Note: Insulin is allowed.
- Chronic use of steroids (excluding topical and inhaled) and concurrent high doses of systemic corticosteroids will not be allowed with the exception of their use to treat AEs (per institutional guidelines). Acute and/or low-dose systemic immunosuppressive medications (e.g. a one-time dose of dexamethasone for nausea or chronic use of ≤ 10 mg/day of prednisone or another dose-equivalent corticosteroid) may be allowed after discussion with and approval by the Medical Monitor.

- Administration of a live, attenuated vaccine within 28 days before C1D1 or anticipation that such a live attenuated vaccine will be required during the study. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed during influenza season only; however, intranasal influenza vaccines (e.g. Flu – Mist®) are live attenuated vaccines, and are not allowed.

1.2 SCHEMATIC OF STUDY DESIGN

An overview of the study design is provided in Figure 1.

Figure 1 Overview of Study Design: Parts A and B



1.3 SCHEDULE OF ACTIVITIES

The schedule of the activities is provided in Table 1 *and details in Table 2*.

Table 1 Schedule of Activities Treatment Period, 21-day Cycles, Q3W

	Screening	Treatment period, 21-day cycles, Q3W dosing																								Post-Treatment			
Cycle	Screening/ Baseline[a]	Cycle 1					Cycle 2			Cycle 3					Cycle 4				Cycle 5		Cycle 6		Subsequent Cycles to 24 Months		End of Treatment (EoT)/ Early Discontin-uation[q]	Safety Follow-up/End of Study (EoS)[r]	Survival Follow up[s]	Unscheduled Safety (for IRR refer to Table 2)[h]
Study visit window				± 1 d	± 2d		+ 2d		± 2d	± 2d		± 1d	± 2d		± 2d		± 2d		± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	28 (± 7) days after last dose	90 (± 7) days after last dose	90 (± 7) days after Safety FU visit and then every 3 months (± 14 days)	
Day	D-28 to D-1[m]	Day 1[c]	Day 2	Day 4	Day 8	Day 15	Day 1[c]	Day 2	Day 8	Day 1[c]	Day 2	Day 4	Day 8	Day 15	Day 1[c]	Day 2	Day 8	Day 15	Day 1[c]	Day 8[h]	Day 1[c]	Day 8[h]	Day 1[c]	Day 8[h]				
Study Week		1			2	3	4		5	7			8	9	10		11	12	13	14	16	17	≥ 19					
ASSESSMENTS[c]																													
Informed Consent[b]	x																												
Eligibility criteria	x																												
Demography	x																												
Medical/Cancer History	x																												
Complete physical exam[d]	x																												
Complete neurological exam[e]	x																												
Royal Marsden Risk Score	x																												
Chest X-ray[p]	x																												(x)
Brain CT MRI[t]	x																												(x)
Echocardiography (TTE/MUGA)	x																												
Height	x																												
Weight[c]	x	x					x			x					x				x		x		x		x	x		(x)
ECOG	x	x					x			x					x				x		x		x		x	x		
Vital Signs[g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)	x	(x)	x	(x)	x	x		(x)
Targeted physical/neurological exam[i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)	x	(x)	x	(x)	x	x		(x)
Triplicate 12-lead ECG[j]	x	pre-dose					pre-dose			pre-dose															x			(x)
Adverse Events[k]	x (continously monitored)																												(x)
Previous and Concomitant Treatments	x (continously monitored)																												(x)
STUDY DRUG ADMINISTRATION																													
Premedication[u]		x					x			x					x				x		x		x					
Administration of RO7296682		x					x			x					x				x		x		x					
TUMOR ASSESSMENT																													
CT/MRI scan[o]	x													x								x	x[q]		x[q]	x		

Table 1 *Schedule of Activities Treatment Period, 21-day Cycles, Q3W (cont.)*

	Screening	Treatment period, 21-day cycles, Q3W dosing																						Post-Treatment			
Cycle	Screening/ Baseline[a]	Cycle 1					Cycle 2			Cycle 3					Cycle 4				Cycle 5		Cycle 6		Subsequent Cycles to 24 Months		End of Treatment (EoT)/ Early Discontinuation[q]	Safety Follow up/End of Study (EoS)[r]	Survival Follow up[s]	Unscheduled Safety (for IRR refer to Table 2)[h]
Study visit window				± 1 d	± 2d		+ 2d		± 2d	± 2d		± 1d	± 2d		± 2d		± 2d		± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	28 (± 7) days after last dose	90 (± 7) days after last dose	90 (± 7) days after Safety FU visit and then every 3 months (± 14 days)	
Day	D 28 to D 1[m]	Day 1[c]	Day 2	Day 4	Day 8	Day 15	Day 1[c]	Day 2	Day 8	Day 1[c]	Day 2	Day 4	Day 8	Day 15	Day 1[c]	Day 2	Day 8	Day 15	Day 1[c]	Day 8[h]	Day 1[c]	Day 8[h]	Day 1[c]	Day 8[h]				
Study Week		1			2	3	4		5	7			8	9	10		11	12	13	14	16	17	≥ 19					
LOCAL LABORATORY ASSESSMENTS[c]																												
Lipids[l]	x																											
Viral serology (HBV, HCV, HIV)[l]	x																											
Auto antibody Panel[n, l]	x						x			x													x			x		(x)
TSH, free T3 (or total T3), free T4[l]	x	x					x			x					x				x		x		x		x	x		(x)
Hematology[l]	x	x	x	x	x	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[l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)	x	(x)	x	(x)	x	x			(x)
Coagulation[l]	x	x			x	x	x			x					x			x	x	(x)	x	(x)	x	(x)	x	x			(x)
Urinalysis[l]	x	x			x	x	x		x	x			x	x	x		x	x	x	(x)	x	(x)	x	(x)	x	x			(x)
Pregnancy Test[m]	x	Urine or serum pregnancy test performed prior to each treatment, with result available prior to dosing																						x	x		
IgE/Tryptase		Collected centrally and locally. Please refer to Table 2																									
CENTRAL LABORATORY ASSESSMENTS																											
PK RO7296682	Refer to Table 2 for sample collection timepoint details																										
ADA RO7296682																											
Receptor Occupancy																											
Blood FACS																											
PD Cytokines																											
[redacted]																											
Soluble tumor and inflammatory markers																											
RBR (DNA and RNA)																											
Blood GEP																											
[redacted]																											
IgE/Tryptase																											
BIOPSIES																											
Archival biopsy	Refer to Table 2 for sample collection timepoint details																										
Tumor biopsy																											
Skin Biopsy																											
Optional biopsy																											
MICROBIOME (optional, Part B ONLY)																											
Stool samples[f]	x																	x									(x)
Post Study																											
New anti cancer treatment																										x	
Survival follow up phone call																										x	

Table 1 Schedule of Activities Treatment Period, 21-day Cycles, Q3W (cont.)

a)	The **screening** period starts with the signing of the Informed Consent Form. Results of standard-of-care tests, tumor assessments or examinations performed prior to obtaining informed consent and within the defined window may be used as screening and baseline assessments; such tests do not need to be repeated for screening purposes.
b)	**Informed consent** must be obtained before any study-specific procedures are conducted. (Note: Two separate consents are embedded within the main Informed Consent Form. In addition, the study contains a separate Informed Consent Form for optional stool samples, in Part B only.)
c)	On treatment days, all assessments should be performed before dose is administered, unless otherwise specified. If body weight and local lab assessments (except for pregnancy test, which must be done on the 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 electronic case report form (eCRF).
d)	**Complete physical exam** should include an evaluation of the head and neck, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.
e)	**Complete neurological exam**: Neurologic examinations should include an assessment of mental status, cranial nerves, muscle strength, sensation, and coordination. Results of the neurological exam should be documented in the participant's chart. Mental status checks do not require completion of a validated mental status questionnaire.
f)	**Stool samples (optional):** Only collected in Part B, dose expansion and provided participant signed the consent for optional stool samples. For details on when samples should be collected, refer to Section 8.9.
g)	**Vital signs:** please refer to the hourly Table 2 for details.
h)	**Optional safety visits** Optional safety visits upon discretion of the Investigator.
i)	**Targeted physical/neurological examinations**: Examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, 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).
j)	**Triplicate 12-lead electrocardiograms (ECGs):** 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. Recordings should be performed prior to blood draws and prior to dosing RO7296682.
k)	**Adverse Events:** Prior first study drug administration only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug all adverse events will be reported as outlined in protocol Section 8.3.1 and Section 8.3.2. Note: All AEs and laboratory safety measurements will be graded per current NCI CTCAE 5.0.
l)	For details on **local laboratory assessments** please refer to Appendix 4 (Clinical Laboratory Tests).
m)	Perform a serum **pregnancy test** for women of childbearing potential within 7 days prior to first dose. Thereafter a urine or serum pregnancy test will be performed prior to each treatment dosing with results available before dose is administered. Results must be obtained and reviewed prior to dose administration.
n)	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 must be repeated. Participants 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.

Table 1 Schedule of Activities Treatment Period, 21-day Cycles, Q3W (cont.)

o)	**Tumor assessments** to be performed according to RECIST 1.1. (Appendix 7). 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. For participants who discontinue treatment for any other reason than disease progression: a) an end of treatment CT/MRI scan is only to be performed if it was done ≥ 28 days prior to this day, b) CT/MRI scan to be performed at the Safety Follow-Up visit.
p)	**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.
q)	**End of Treatment (EoT)/ Early Discontinuation Visit:** Participants who complete treatment or discontinue early, will be asked to return to the clinic within 28 (+/-7) days after the last dose. The visit at which a response assessment shows progressive disease may be used as the discontinuation visit.
r)	**Safety Follow-Up:** Participants who complete the study or discontinue from the study early, will be asked to return to the clinic 90 (± 7) days after the last dose treatment with RO7296682. A tumor assessment is to be performed for participants who discontinued the study for reasons other than disease progression.
s)	**Survival Follow-Up**: The sites will provide to the Sponsor an update on survival status and new anti-cancer treatment 90 (± 7) days after the Safety Follow-Up visit and then every 3 months (± 14 days) thereafter up until 24 months post initial treatment (or until study closure) for each participant enrolled in the study. Contact can be either in person or via a phone call to document.
t)	**Baseline brain CT MRI:** A CT or MRI scan (with IV contrast unless contraindicated) of the head must be performed at baseline to assess CNS metastasis. In the event of an equivocal CT scan, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline. If the participant presents CNS metastasis at baseline, on-treatment tumor assessments must also contain a CT or MRI scan of the head. If participant has no brain metastasis at baseline, then CT/MRI scan of the head is only indicated if symptoms suggest potential brain disease.
u)	**Pre-medication** can be considered prior to the first dose at Investigator discretion. For subsequent infusions, please refer to Section 6.1.2 and Section 8.3.8. For details in case participants experience IRR, refer to protocol section 8.3.8.

Table 2 *Schedule of Activities Q3W, Details*

Cycle	Day	Scheduled Time (h)	Time window[a]	Vital Signs[h]	PK RO7296682[b, c, d, e]	ADA RO7296682[c,d, e]	Receptor Occupancy	PD blood FACS	PD Cytokines	Archival sample	Tumor Biopsy[g]	Skin Biopsy[g]	Optional Biopsy[i]	Blood GEP	[redacted]	Clinical Genotyping (DNA)	RBR (DNA)	RBR (RNA)	IgE/Tryptase[f]
Screening/ Baseline	D-28 to D-1			x			x			x	x	x	Any visit						
Cycle 1	Day 1	Predose		x	x	x	x	x	x					x		x	x	x	
		Half-time of infusion	± 15min	x	x														
		EOI	± 15min	x	x		x	x	x										
		EOI+3	± 30min	x	x														
	Day 2	24	± 2h	x	x														
	Day 4	72	± 24h	x	x		x	x	x										
	Day 8	168	± 48h	x	x			x	x										
	Day 15	336	± 48h	x	x		x	x	x										
Cycle 2	Day 1	Predose		x	x	x	x	x	x					x					
		EOI	± 15min	x	x														
	Day 2	24	± 2h	x	x														
	Day 8	168	± 48h	x	x			x	x		x	x							
Cycle 3	Day 1	Predose		x	x	x	x	x	x					x					
		Half-time of infusion	± 15min	x	x														
		EOI	± 15min	x	x		x	x	x										
		EOI+3	± 30min	x	x														
	Day 2	24	± 2h	x	x														
	Day 4	72	± 24h	x	x		x	x	x										
	Day 8	168	± 48h	x	x														
	Day 15	336	± 48h	x	x		x	x	x										
Cycle 4	Day 1	Predose		x	x	x	x	x	x					x					
		EOI	± 15min	x	x														
	Day 2	24	± 2h	x	x														
	Day 8	168	± 48h	x	x														
Cycle 5	Day 1	Predose		x	x	x	x		x					x					
		EOI	± 15min	x															
Subsequent Cycles[d]	Day 1	Predose		x	x	x	x	x only at cycle of tumor assessment	x only at cycle of tumor assessment		x[g]	x[g]							
		EOI	± 15min	x	x														
End of Treatment (EoT) Visit	28 days (± 7) after last dose	At visit		x	x	x	x												
Safety FU (90d 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 ≥ G2 or hypersensitivity event or AE ≥ G3 leading to dose reduction or interuption		At visit			x	x			x				Any visit						x
DLT		At visit			x	x			x										x
Unscheduled Visit[j]		At visit			x	x	x	x	x										x

Table 2 Schedule of Activities Q3W, Details (cont.)

a)	The **time windows** can be used for flexibility. For example if Day 2 occurs on a Friday, Day 4 can be conducted on the following Monday and Day 8 on the Thursday.
b)	During the course of the study, PK/PD sampling time points may be modified based on emerging data to ensure that PK/PD of RO7296682 can be adequately characterized. In this case, no new additional PK/PD samples will be introduced but sampling times may be modified. Blood for PK/PD should be drawn at the indicated time points.
c)	All blood samples for PK assessments will be collected from an IV line in the opposite arm to the one for drug infusion.
d)	Up to Cycle 5: PK and ADA samples should be taken at **indicated time points**. Subsequent cycles until 6 months after first dose of RO7296682: PK and ADA samples will be taken on Day 1 of each cycle. Subsequent cycles after first 6 months of RO7296682 treatment: PK and ADA samples will be taken only **Day 1** at **cycle of tumor assessments.**
e)	Unscheduled 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/CRS event ≥ G2 or hypersensitivity event or AE ≥ G3. - At time of interruption, collect the unscheduled PK sample and clearly record the reason for 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.
f)	**Tryptase** and **IgE** samples will be collected for **local** analysis at onset of the reaction. A second sample for **central** IgE/Tryptase analysis will be collected approximately 48 hours after onset of the reaction.
g)	**Fresh tumor** biopsy and **healthy skin** tissue punch biopsy will be taken at baseline (only once all inclusion/exclusion criteria have been met) and at Cycle 2 Day 8. *If preliminary data suggest, alternative on-treatment tumor biopsy or healthy skin punch biopsy time points may be considered upon joint agreement between Investigators and the Sponsor.* **Part A:** Mandatory pre- and on-treatment biopsies only done after reaching the Tissue Biomarker Dose. **Part B:** mandatory pre- and on-treatment biopsies for all participants.
h)	**Vital Signs** will include measurements of systolic and diastolic blood pressure, respiratory rate, heart rate, and body temperature while the participant is in a sitting or semi-supine position. Vital signs during the infusion are not required to be captured in the eCRF unless abnormalities are observed.
i)	**Unscheduled Visits** optional samples can be taken at the discretion of the investigator and/or in agreement with the Sponsor.
j)	**Optional biopsies**: 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. For details, see Section 8.8.2.
[redacted]	[redacted]

2. INTRODUCTION

2.1 STUDY RATIONALE

In this study, the novel compound RO7296682, which selectively binds to CD25 (the IL-2 receptor α chain) while not interfering with interleukin-2 (IL-2) signaling, will be assessed as a T-regulatory cell (Treg)-depleting strategy for the treatment of cancer. Tregs can suppress antigen-specific, anti-tumor immune responses, thus allowing for tumor growth. Reducing the number of Tregs, or fully removing Tregs from tumors, may reduce tumor growth in vivo and may foster or restore an immune response to tumor cells in humans.

RO7296682 is a glycoengineered monoclonal antibody (mAb) against CD25. It is designed to mediate FcγRIIIa-dependent, CD25-targeted cell cytotoxicity (aka, antibody-dependent cellular cytotoxicity [ADCC]) and antibody-dependent cellular phagocytosis (ADCP). The Fc region of RO7296682 is afucosylated to increase FcγRIIIa affinity, and, thus, to outcompete human IgG1 isotypes and trigger ADCC more effectively (Buettner et al. 2018, and Kellner et al. 2017).

CD25 is a highly expressed cell surface lineage marker of Tregs and is critical for their survival (Sakaguchi et al. 2008). The high prevalence of CD25 on Tregs, as well as a $>$20 to100-fold higher expression of CD25 on Tregs vs. cytotoxic T lymphocytes (CTLs), qualifies CD25 as superior target over other Treg markers. Other T-cell markers (such as CCR4 or Ox40) have a lower prevalence on Tregs with a more uniform and indiscriminate expression on CTLs and Tregs.

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 CTLs. An additional key feature of RO7296682 is that it binds CD25 while not blocking IL-2 signaling, particularly in activated Teffs (see Section 2.1 of RO7296682 Investigator's Brochure (IB) for details). Therefore, RO7296682 has the potential to improve anti-cancer outcomes, particularly in combination with other immune-modifying agents

In this first-in-human, open-label, multicenter Phase 1 study, WP41188, the safety and tolerability of RO7296682 will be explored and the Maximum Tolerated Dose (MTD) and/or Recommended Phase 2 Dose (RP2D) will be determined. Study WP41188 will also assess the pharmacokinetics (PK), pharmacodynamics (PD), and preliminary anti-tumor activity of RO7296682. RO7296682 will initially be explored in non-small cell lung cancer (NSCLC), melanoma (MEL), head and neck squamous cell carcinoma (HNSCC), ovarian cancer (OvC), triple-negative breast cancer (TNBC), and esophageal carcinoma (EsC). The rationale for the study design is provided in Section 4.2.

2.2 BACKGROUND

Tregs have been postulated to be one of the major suppressive factors in the tumor microenvironment and their presence is linked to poor outcomes in many tumors (see e.g. Togashi et al. 2019). Although checkpoint inhibitors (CPIs) have led to major improvements in patient outcomes, particularly in NSCLC and MEL, many patients do not respond to therapy, have a suboptimal response, or relapse after a period of response. The mechanisms behind resistance or relapse are still incompletely understood. Immunosuppressive effects mediated by Tregs are among the main mechanisms under discussion and investigation (Sharma et al. 2017).

High levels of Tregs are associated with poor prognoses in several human cancers, such as NSCLC and MEL (Jenkins et al. 2018, Fridman et al. 2012, Liu et al. 2016). RO7296682 was designed to selectively deplete CD25-high Tregs via enhanced ADCC while not interfering with IL-2-mediated Teff signaling. A detailed description of the chemistry, pharmacology, and safety of RO7296682 is provided in the RO7296682 IB.

2.3 BENEFIT/RISK ASSESSMENT

RO7296682 is hypothesized to provide a significantly improved chance of addressing the large unmet medical need that remains for many cancer patients, including CPI-naïve and CPI-experienced/resistant patients. Depleting CD25-expressing Tregs without impacting the number and function of T-effectors, and without interfering with IL2 signaling, has the potential to translate into clinical benefit in cancer patients.

Due to its characteristics, RO7296682 is expected to shift the overall balance of the tumor immune system into a condition enhancing the probability to have an immune response against the tumor. Available non-clinical data demonstrate that RO7296682 or its mouse surrogate is active and induces tumor reduction in different tumor mouse models as well as depletes Tregs in peripheral blood and tissues.

[redacted]

This is the first study in which RO7296682 will be administered to humans and as such, its actual dose risks are unknown. It is anticipated that the safety profile of RO7296682 will be distinct from previously generated anti-CD25 compounds that were originally designed to reduce the number of Teffs and thereby (in contrast to RO7296682) act as immunosuppressive agents.

Potential risks anticipated with RO7296682 may be related to its immune enhancing effects (i.e. immune-related toxicity) and to the depletion of the resident Tregs,

particularly in the skin, where it was demonstrated that Tregs play a role in the skin barrier and in the wound healing process (Ali and Rosenblum 2017) See also corresponding section on potential risks in the RO7296682 IB. [redacted]

In summary, Tregs are considered one of the resistance mechanism of the antitumor immune response. Targeting Tregs through RO7296682 therefore has the potential to provide substantial anti-tumor immune response via a change in the Teff/Treg ratio and may also enable a multitude of combinations with other immunotherapies or with established anti-cancer agents for future clinical development. The existing nonclinical data with RO7296682 provides an acceptable risk-benefit balance for the clinical investigation of RO7296682 in patients with advanced cancers who have progressed on a cancer therapy for whom no effective standard therapy exists.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 3.

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
To characterize the safety, tolerability, maximum-tolerated dose (MTD) and/or Recommended Phase 2 Dose (RP2D) of RO7296682	• Nature and frequency of AEs (with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0) • Nature and frequency of dose-limiting toxicities (DLTs)
Secondary	
To assess the preliminary anti-tumor activity of RO7296682	• Objective response rate (ORR) • Disease control rate (DCR); defined as ORR + stable disease [SD] rate • Duration of response (DoR) • Progression-free survival (PFS) All according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Objectives	Endpoints
To investigate the PK profile of RO7296682	PK profiles and parameters derived for RO7296682 including but not limited to: • Area under the curve (AUC), minimum concentration (C_{min}), maximum concentration (C_{max}), Clearance (CL), Volume of distribution at steady-state conditions (Vss), Half-life ($t_{1/2}$), as appropriate, Time of maximum concentration (T_{max})
To evaluate the anti-drug immune response after treatment	• Incidence and titer of ADA during the study relative to the prevalence of ADA at baseline
To assess the PD effect of RO7296682 in blood and tumor tissue	• Treatment-induced changes in Treg levels in blood and/or tumor as compared to baseline. • Treatment-induced changes in Treg/Teff ratio in blood and/or tumor as compared to baseline.
Exploratory	
To characterize PD effects and duration of PD response following RO7296682 administration	• Changes in number, frequency, activation status, and distribution of blood and tumor infiltrating lymphocytes (TILs)
To evaluate the relationship between RO7296682 exposure and PD biomarkers	[redacted]
To evaluate preliminary anti-tumor activity of RO7296682 according to immune RECIST (iRECIST)	• Objective response rate (ORR) • Disease control rate (DCR); defined as ORR + SD rate All according to immune RECIST (iRECIST) In addition: • Duration of response (DoR) • Progression free survival (PFS) • Overall survival (OS) if data are mature
To explore potential effects of ADA	• Relationship between ADA status and PK/PD, safety, and efficacy

Objectives	Endpoints
To explore biologic markers that might act as predictors of safety and/or anti-tumor activity of RO7296682	[redacted]
To explore degree of target binding of RO7296682 (in association with PK) via a receptor occupancy (RO) assay	• Evaluate RO via ex-vivo assay
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 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 WP41188 is a first-in-human, open-label, multicenter, Phase 1 dose escalation study of single agent RO7296682 in participants with advanced and/or metastatic NSCLC, MEL, HNSCC, OvC, TNBC, or EsC. An overview of the study design is provided in Section 1.2.

All participants will be treated with RO7296682 until disease progression, unacceptable toxicities, withdrawal of consent, or withdrawal of the participant by the Investigator. Participants may continue treatment with RO7296682 for a maximum of 24 months. This period may be adjusted based on the emerging safety and response profile. As with other immunotherapies, treatment beyond progressive disease (i.e. due to pseudo-progression) according to RECIST Version 1.1 can be considered after initial dose, following consultation and agreement between the Sponsor and Investigator.

For the maximum number of participants, please refer to Section 9.2.

The study consists of 2 parts: Part A is a single agent dose escalation and Part B is a single agent dose expansion.

- **Part A: RO7296682 dose escalation in multiple participant cohorts**

Part A will determine the safety, tolerability, PK/PD profile, and preliminary anti-tumor activity of escalating doses of RO7296682 using a minimum of 3 DLT evaluable participants per cohort (see Section 9.3 for definition of DLT analysis population). The starting dose will be 0.3 mg and the maximum dose is planned to be 500 mg. Participants will receive intravenous (IV) RO7296682 every 3 weeks (Q3W) and the cycle length will be accordingly defined as 21 days. Incremental increases (and potential decreases) between cohorts will be determined by a Bayesian-based continuous reassessment method (CRM) with overdose control measures. Entry into a cohort will be controlled by a 7-day safety window between participants 1 and 2 in each cohort. Please refer to Section 4.1.2.1 for details on the DLT window. At least 3 DLT evaluable participants will be enrolled in each Part A cohort during the dose escalation. For intra-patient dose escalation, please refer to Section 4.1.2.2.

Part A will enroll participants with NSCLC, MEL, OvC, HNSCC, TNBC, or EsC 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.

[redacted] The criteria to start collecting on-treatment biopsies may be changed based on emerging data through a protocol amendment. Such biopsies will be collected, provided they are clinically feasible, lesions are accessible, and the participant's consent for these biopsies has been obtained. This will be agreed upon between the Sponsor and Investigators. Part A will determine the MTD and/or RP2D based on the safety, tolerability, and PK/PD profile of RO7296682. The maximum total number of participants in Part A will consist of approximately *90* DLT evaluable participants.

- **Part B: RO7296682 single agent dose expansion cohort:**

Part B will evaluate safety, tolerability, PK/PD profile, and preliminary anti-tumor activity of the MTD and/or RP2D of RO7296682 determined in Part A in participants with MEL, NSCLC, and HNSCC. Approximately 20 evaluable paired tumor biopsy samples will be obtained. Part B will conclude when approximately 20 evaluable paired tumor biopsy samples or a maximum total number of 50 participants has been reached.

Note: If evolving safety and PK/PD data suggest so, tumor types other than those now indicated will be evaluated. In that case, the exact solid tumor indication(s)

inclusion/exclusion criteria, and schedule of activities will be specified in a substantial protocol amendment.

4.1.1 Length of the Study

The maximum duration of the study for each participant will be up to 28 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 (see Section 4.4)
- Safety follow-up: 90 (± 7) days after last treatment with RO7296682
- 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: Part A

Dose-escalation will be carried out according to a modified continual reassessment method (mCRM) with escalation with overdose control (EWOC) design and dose levels selected will be based on the occurrence of DLTs. This model-based design assigns participants to dose levels and defines the MTD based on the estimation of the target toxicity level by a model depicting the dose-toxicity relationship. [redacted]

4.1.2.1 Part A: Single Agent Dose Escalation

The primary objective of Part A will be to determine the MTD and/or RP2D and DLT profile in multiple participant cohorts. Part A starts with an initial dose of 0.3 mg (see Section 4.3 for dose justification). [redacted]

The DLT period starts from the first administration of RO7296682 and ends 7 days after the second administration of RO7296682. [redacted]

The first participant at each dose level must have completed at least 7 days from the first dose without DLT 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 be maintained between the second and third participants. 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 this is achieved, all subsequent participants in a cohort can be enrolled, with no fixed observation period between participants. After the third evaluable participant in each cohort has completed the DLT observation period, the logistic regression model will be updated with the treatment outcome (i.e., the occurrence of DLT) and a new estimate of the MTD will be derived and the recommended dose will be either the new estimate of the MTD or the maximum dose allowed by safety constraints. Selection of the new dose level must be agreed by the Investigator and the Sponsor, as well as being guided by the EWOC recommendation. Please refer to Section 4.1.5 for the communication strategy.

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 pre-defined stopping criteria are satisfied (see Section 4.1.4) or the pre-determined sample is reached, whichever comes first.

Built-in safety constraints are in place to prevent exposing participants to undue risk of toxicity:

- [redacted] – see also the RO7296682 IB. Indeed, a 3-fold has been assumed in a recent Food and Drug Administration (FDA) Oncology review of first-in-human studies for immune-activating agents as it 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). In the absence of DLTs a further increase of 10% of the 3-fold cap (i.e. 3.3-fold vs. 3-fold) will be considered within the allowed built-in safety constraints if the resulting dose increment lead to a dose level which can be more easily administered to the patient (example: 1 mg instead of 0.9 mg).

- 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 1 DLT has been observed, a dose increment of up to 100% (i.e. up to 2-fold) is allowed.

If deemed necessary to further characterize the safety, PK, and/or PD profile of RO7296682, additional participants may be enrolled.

[redacted] For the definition of the SDEC, see Appendix 1.

Part A Single Agent dose escalation may be halted prior to identification of MTD and upon sufficient characterization of the investigational medicinal product in regards to safety, PK, and PD.

4.1.2.2 Individual Dose Increase for Participants in a Dose-Escalation Cohort

At the discretion of the Investigator and in agreement with the Sponsor, intra-patient 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 dose is 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 h infusion for the first higher dose of RO7296682).

4.1.3 Dose-Limiting Toxicities

A DLT is defined as a clinically significant AE (classified according to the NCI CTCAE v.5.0, as applicable) or significant laboratory abnormality if all of the following events apply:

- occurring during the DLT assessment period as defined in Section 4.1.2.1; and
- considered to be related to study treatment RO7296682 by the Investigator, and
- is not attributed to disease progression or another clearly identifiable cause

During the dose escalation phase, participants who withdraw before the end of the DLT period, for reasons other than DLTs, and participants who did not receive two doses of RO7296682 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 7.1 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.

The following AEs are considered DLTs:

Hematological toxicities defined as:

- Grade 4 neutropenia (ANC of <500/μL) lasting ≥ 7 days
- Grade ≥ 3 febrile neutropenia
- Grade 4 thrombocytopenia lasting ≥48 hours
- Grade 3 thrombocytopenia associated with significant bleeding episode and/or bleeding episodes requiring platelet transfusions
- Grade 4 anemia

Any non-Hematological toxicities Grade ≥3 except for:

- Grade 3 nausea, vomiting, or diarrhea that resolves to Grade ≤ 1 with or without treatment and which resolves within one week
- Grade ≥ 3 fatigue that resolves to Grade ≤ 2 within 7 days
- Grade 3 arthralgia that can be adequately managed with supportive care or that resolves to Grade ≤ 2 within 1 week
- Fever >40 degrees Celsius that occurs within 48 hours of RO7296682 infusion and resolves to < Grade 2 within 48 hours and is fully resolved within 7 days
- Grade ≥3 laboratory abnormality that is asymptomatic and deemed by the Investigator not to be clinically significant
- Grade 3 autoimmune thyroiditis or other endocrine abnormality that can be managed by endocrine therapy or hormonal replacement
- Grade 3 tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Grade 3 transient increase of bilirubin in participants with liver lesions, transaminases (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]) and/or gamma-glutamyl transferase (GGT) that starts within 24 hours of infusion and recovers to Grade 1 or baseline within one week.

Additional DLTs not fulfilling the above criteria

- Any other RO7296682-related toxicity considered significant enough to be qualified as a DLT in the opinion of the Investigator after discussion with the Sponsor.

4.1.4 Stopping Rules Criteria

The algorithm of the mCRM with EWOC incorporates the following parameters to stop the dose escalation under the following circumstances:

In addition, the dose escalation could be halted upon sufficient characterization of RO7296682 in regards to safety and PK, and/or PD and without MTD determination, e.g. if by clinical judgment no clinical benefit can be assumed to be gained from additional cohorts.

4.1.5 Communication Strategy

Study Conduct: Given that this is a first-in-human trial of RO7296682, the SDEC will be utilized during the study to make recommendations regarding study conduct on the basis of trial safety data to ensure enhanced participant safety while receiving study treatment (please refer to Appendix 1 for SDEC members). The SDEC will be in regular contact throughout the study by email/telephone/electronic meetings as per normal interactions during the conduct of a clinical study. When and if appropriate, the SDEC will arrange ad-hoc teleconferences or meetings to discuss the study progress with site representatives and investigators. The Sponsor (i.e., consistent of SDEC members) will be available 24 hours a day to discuss any medical or study-related issues that may arise during the conduct of the study.

In addition to the ongoing assessment of the incidence and nature of DLTs, AEs, serious adverse events, AEs of special interest (AESI), and laboratory abnormalities by the Investigators and the Medical Monitor, the SDEC will review all the cumulative data at regular intervals during the study.

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

Cohort Assignment: Upon completion of all screening evaluations and confirmation that a participant has met all eligibility criteria, investigator sites will confirm the participant's

eligibility by completing the Eligibility Screening Form. Sites will then obtain the cohort assignment from the Sponsor or from an interactive voice/web response system (IxRS) where applicable (see Section 6.3.1).

First Dose of RO7296682: After each participant receives RO7296682, the Investigator(s) must confirm to the Sponsor that the participant has been dosed and provide a brief summary of the status of the participant in terms of safety and tolerability of RO7296682. This will be communicated by email, as soon as reasonably possible and within one business day of dosing of the participant.

Dose Escalation Decision: Once the study opens, regularly scheduled teleconferences will occur with the SDEC, investigators and relevant study site staff. During the teleconferences, all relevant demographic, AE, laboratory, dose administration, available response, and PK and PD data will be reviewed for each participant. Dose-escalation decisions and selection of the dose for the next cohort of participants will be guided by mCRM-EWOC recommendation, in addition to the review of all relevant available data, including DLT information. Study Investigators and the Sponsor should reach a consensus on the next dose level and may include de-escalation and/or expansion of recruitment into particular cohorts. A formal notification of the decision will be communicated to all study sites by the Sponsor after the meeting.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

Part A dose escalation will be carried out according to a mCRM-EWOC design and will be 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 less than the model recommended dose may be selected based on clinical judgment.

The SDEC can always override the Bayesian adaptive design recommendations in the dose-selection process based on clinical judgment taken all available data into account.

4.2.1 Rationale for Study Population

Taking into consideration the prognostic relevance of Treg infiltration in tumor tissue (Jenkins et al. 2018, Fridman et al. 2012, Liu et al. 2016) [redacted] (See Section 2.1 of the RO7296682 IB).

4.2.2 Rationale for Biomarker Assessments

The goal of the Biomarker assessments is to confirm the MoA of RO7296682, characterize PD effects and duration of PD response, evaluate the relationship between RO7296682 exposure and PD biomarkers and identify predictors of safety or anti-tumor activity following RO7296682 administrations.

RO7296682 treatment should result in changes of peripheral blood immune cells and soluble circulating markers. Hence, plasma samples will be collected and analyzed for changes in soluble factors [redacted].

Administration of therapeutic antibodies may lead to changes in peripheral cytokine levels either due to direct target engagement or as a secondary effect of immune cell activation. Hence, [redacted]

[redacted]

Moreover, treatment with RO7296682 is expected to result in alterations of intratumoral residing immune cells and in particular reduction of Tregs. Hence, tumor samples will be

collected from participants enrolled in Part A (for all participants after reaching Tissue Biomarker Dose) and Part B of the study. Mandatory tumor biopsies will be collected on two occasions from tumor lesions (primary and/or metastatic) from a safely accessible lesion, per Investigator's determination and patient consent (see Section 1.3 for the biopsy schedule).

[redacted]

In the event skin tissue is taken due to skin related AEs, skin biopsies should be obtained from the sites of symptomatic skin as well as from an unaffected adjacent site of the skin serving as control tissue.

[redacted] 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 treatment and safety, assess PD effects of RO7296682 treatment, and investigate any mechanisms of resistance to therapy.

Additional biomarkers may be measured if initial data lead to strong scientific rationale for these measurements.

4.2.3 Rationale for Optional Stool Samples Collection in Part B

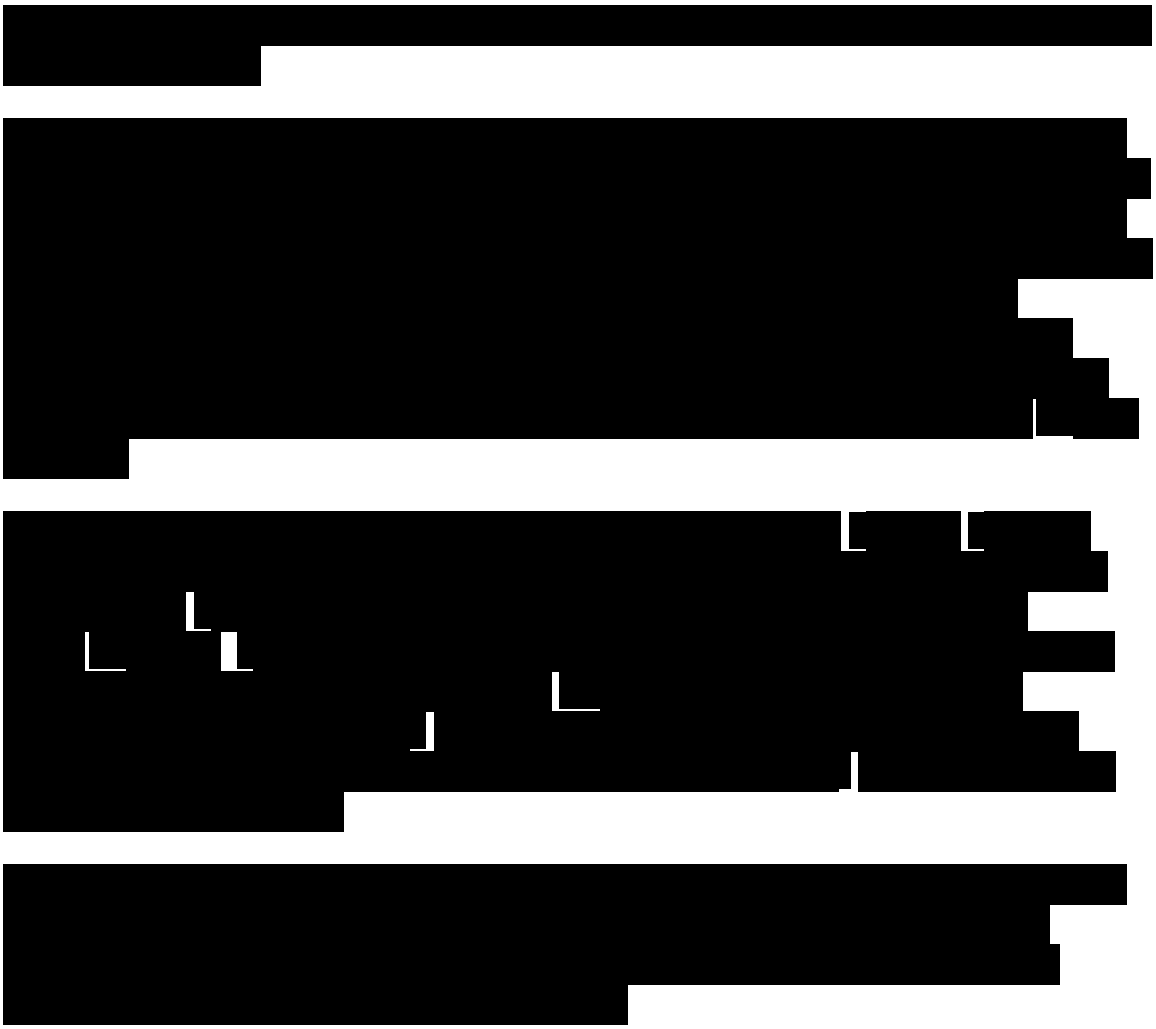
The gut microbiome has been shown to be a key determinant of immune regulation in cancer, in part by influencing T-cell driven anti-tumor responses (Routy et al. 2018). For example, antibiotic treatment is associated with poor survival outcomes to anti-PD-1 therapy in non–small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and urothelial carcinoma (UC) (Elkrief et al. 2019). Conversely, the risk of colitis with CITs

may be predicted based on 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.

In Part B, dose expansion, the study will examine a participant's microbiome at baseline and on-treatment in order to investigate potential changes by RO7296682.

4.3 JUSTIFICATION FOR DOSE

The starting dose of RO7296682 in Study WP41188, i.e. a dose, which is expected to have a minimal pharmacological [redacted]



Flat dosing was selected for this protocol because no strong influence of the body surface area or body weight on overall exposure is expected. Based on the PK data emerging from this clinical study, any potential covariates on exposure to RO7296682 such as but not limited to body surface area, body weight, age, ethnicity and gender will be explored in order to confirm this dosing approach.

[redacted]

[redacted]

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last participant's last visit (LPLV) per protocol (includes the safety follow-up visit 90 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.

Part A: multiple patient dose escalation cohorts

[redacted]

Part B: Dose expansion cohort

[redacted]

Based on emerging data, additional indications may be added to this study through a substantial protocol amendment.

The study population consists of adult male and female participants with advanced and/or metastatic solid tumors, who meet all of the given inclusion and none of the exclusion criteria.

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

Participants enrolled in the study but who do not maintain eligibility or withdraw consent **prior to the first dose** will not be included in the database.

5.1 INCLUSION CRITERIA

General Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply prior to dosing on C1D1.

1. Signed written informed consent and ability to comply with the study protocol according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and local regulations.

Type of Participants and Disease Characteristics

2. Age $\geq$ 18 years

3. Diagnosis of advanced and/or metastatic solid tumors (**Part A**: TNBC, OvC, MEL, NSCLC, HNSCC, or EsC; **Part B**: MEL, HNSCC, or NSCLC) who have progressed on all standard therapies, are intolerant to SOC, and/or are non-amenable to SOC. Participants whose tumors have a known sensitizing mutation must have experienced disease progression (during or after treatment) or intolerance to treatment with a respective targeted therapy.

4. Measurable disease according to 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.

   - Lesions that are intended to be biopsied must not be counted as target lesions.

   Note: In case a patient has just one target lesion, no baseline and/or on-treatment biopsy is required as this would exclude the patient from study participation.

5. Life expectancy, in the opinion of the investigator, of $\geq$ 12 weeks

6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (Section 8.2.11).

7. Able to provide the most recent archival tumor tissue samples (formalin-fixed-paraffin-embedded [FFPE] blocks preferred; if not available, slides accepted).

    - 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.

8. 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 45-100 bpm

9. Adequate hematological function:

    - Neutrophil count of $\geq 1.5 \times 10^9$ cells/L (1500/μl)
    - Platelet count of $\geq 75 \times 10^9$ /L (75,000/μL),
    - Hemoglobin ≥ 9 g/dL (90 g/L, ~ 5.6 mmol/L)
    - Lymphocyte count of $\geq 0.5 \times 10^9$ cells /L (500/μL) (borderline lymphocyte values that are right below the limit with the machine count, lymphocytes can also be confirmed with manual counts if machine count is below limit).

    Note: No transfusion within 2 weeks of first study drug administration and no administration of growth factors like e.g. G-CSF, GM-CSF, EPO within 4 weeks of study drug administration to achieve these levels. *Participants with hemoglobin < 9 g/dL due to an acute bleeding event and/or participants who have received a transfusion following such an event may be enrolled if they are in a stable condition as determined by the Investigator.*

10. Adequate liver function:

    - Total bilirubin ≤ 1.5 × ULN (excluding Gilbert's syndrome, see below)
    - Aspartate aminotransferase (AST), alanine aminotransferase (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
    - Gamma-glutamyl transferase > 2.5 x ULN (in case of liver metastases: ≥ 5 × ULN) must be discussed and agreed with the Sponsor

    Gilbert's Syndrome:

    – Patients with Gilbert's syndrome will be eligible for the study. The diagnosis of Gilbert's syndrome is suspected in people who have persistent, slightly elevated levels of unconjugated bilirubin without any other apparent cause. A diagnosis of Gilbert's syndrome will be based on the exclusion of other diseases based on the following criteria:

      - Unconjugated hyperbilirubinemia noted on several occasions
      - No evidence of hemolysis (normal hemoglobin, reticulocyte count, and LDH)
      - Normal liver function tests
      - Absence of other diseases associated with unconjugated hyperbilirubinemia

11. 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.

12. 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) ≤ 1.5 × ULN or < 2 × ULN for participants with hepatocellular carcinoma

13. Participants on therapeutic anticoagulation must be on a stable anticoagulant regimen.

Contraception

14. Male and/or female participants: The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence for male and/or female enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

    a) Female Participants: 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) as defined in Appendix 5.

    - 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 last dose of RO7296682.

    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 (see Appendix 5).

    – Have a negative pregnancy test (blood) within the 7 days prior to the first study RO7296682 administration.

    b) Male Participants: During the treatment period and for at least 28 days after the last dose of RO7296882, 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 women of childbearing potential (WOCBP, as defined in Section 1 of Appendix 5.

    - 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 Part A (only for Participants who reached the "Tissue Biomarker Dose") and Part B Dose Expansion cohorts:

15. A freshly collected biopsy of a tumor lesion (primary and/or metastatic) from a safely accessible site, per Investigator determination and patient consent, will be requested, providing the patient has more than one measurable target lesion. The biopsied lesion must not be a target lesion (see inclusion criteria 4). 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.

16. Consent to provide a freshly collected skin punch biopsy. Note: if fresh skin punch biopsy cannot be obtained, please contact the Medical Monitor.

5.2 EXCLUSION CRITERIA

General Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply prior to dosing on C1D1:

1. Pregnancy, lactation, or breastfeeding.
2. Known hypersensitivity to any of the components of RO7296682, including but not limited to hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.

Medical Conditions

3. 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.

4. 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.
5. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including diabetes mellitus, history of relevant pulmonary disorders, or other disease with ongoing fibrosis (such as scleroderma, pulmonary fibrosis, emphysema, neurofibromatosis, palmar/plantar fibromatosis, etc.).
6. Encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.
7. Severe dyspnea or requiring supplemental oxygen therapy at rest.
8. Episode of significant cardiovascular/cerebrovascular vascular disease within 6 months prior to C1D1 of study drug administration, including any of the following: hypertensive crisis/encephalopathy, uncontrolled hypertension (systolic $>$ 150 mmHg and/or diastolic $>$ 100 mmHg), unstable angina, transient ischemic attack/stroke, congestive heart failure (for NYHA classification, refer to inclusion criteria), serious cardiac arrhythmia requiring treatment (exceptions are atrial fibrillation, paroxysmal supraventricular tachycardia), history of thromboembolic events (such as myocardial infarction, stroke or pulmonary embolism).
9. Participants with known active or uncontrolled infection, 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 [TB]), 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) within 28 days of first drug administration.
10. Positive HIV test at screening
11. Positive hepatitis B surface antigen (HbsAg) test, and/or positive total hepatitis B core antibody (HbcAb) test. NOTE: Participants with positive total HbcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening can be enrolled.
12. Positive hepatitis C antibody test result prior to starting study treatment. NOTE: Participants with positive hepatitis C antibody test due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C ribonucleic acid (RNA) test is obtained.
13. Vaccination with live vaccines within 28 days prior to C1D1. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed during influenza season only; however, intranasal influenza vaccines (e.g. Flu –

Mist®) are live attenuated vaccines and are not allowed. Seasonal influenza-related AEs must resolve prior to C1D1.

14. Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, and inherited liver disease.
15. Major surgical procedure or significant traumatic injury within 28 days prior to first RO7296682 infusion, or anticipation of the need for major surgery until end of treatment period. After major surgery, participant must wait until surgical wounds are fully healed before initiating treatment with RO7296682.
16. Participants with current or history of wound healing complications and/or participants with open wounds until complete resolution. For individual case assessment, please contact the Medical Monitor.
17. Dementia or altered mental status that would prohibit informed consent.
18. History of Stevens-Johnson syndrome, toxic epidermal necrolysis, or DRESS (drug rash with eosinophilia and systemic symptoms).
19. 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.

Prior/Concomitant Therapy

20. Prior treatment with CPIs (e.g. anti-CTLA4, anti-PD1, anti-PDL1), immunomodulatory monoclonal antibodies (mAbs) and/or mAb-derived therapies (approved or investigational) is allowed, provided that:
    - at least 4 weeks have elapsed between the last dose and the proposed C1D1
    - at least 5 half-lives or 28 days (whichever is shorter) have elapsed since prior treatment with specific immunomodulators, TLR agonists, inhibitors of IDO/TDO, or agonists (e.g., OX40) and the proposed C1D1
21. Prior treatment with a CC chemokine receptor 4 (CCR4)-targeting (e.g. mogamulizumab) or a CD25-targeting agent (e.g. basiliximab) is prohibited.
22. 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 the first RO7296882 administration on C1D1.
23. Immuno-modulating agents:
    - Last dose with immuno-modulating agents such as e.g. etanercept, infliximab, tacrolimus, cyclosporine, mycophenolic acid, alefacept, or efalizumab (or similar agents) within 28 days or 5 half-lives of the drug (whichever is shorter) prior to C1 D1.
    - Regular immunosuppressive therapy (i.e., autoimmune disease, chronic rheumatologic disease), and/or previous recipient of allotransplantation even if not in need of immunosuppressive therapy.
24. 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 after discussion with and approval by the Medical Monitor. The use of inhaled corticosteroids and mineralocorticoids (e.g. fludrocortisone) is allowed.
25. 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).
26. Adverse events from any prior anti-cancer therapy that have not resolved to Grade $\leq$1 except for alopecia, vitiligo, or endocrinopathy managed with replacement therapy, and Grade $\leq$2 peripheral neuropathy. Note: Other Grade 2 AEs that are deemed clinically insignificant by treating physician and in consultation with Medical Monitor are permitted.

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.

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. Similarly, screening stool samples of participants who are not enrolled in the study will be destroyed on site.

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 if agreed by Medical Monitor. Re-screened participant should be assigned a different screening number as compared to that used for the initial screening.

Biopsy samples will only be entered in the electronic case report form (eCRF) and analyzed for enrolled participants.

Participants who are re-screened are required to sign a new Informed Consent Form (ICF).

5.5 RECRUITMENT PROCEDURES

Patients will be identified for potential recruitment by the investigator and referring physicians using pre-screening enrollment logs, clinical databases and Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) approved newspaper/radio/social-media advertisements prior to consenting to take place on this study.

6. TREATMENTS

Study intervention 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 is considered the Investigational Medicine Product (IMP). RO7296682 required for completion of this study will be provided as study medication by the Sponsor or its designee in compliance with local drug management regulations. Pre-medications are considered non-investigational medicinal products (NIMPs).

All study treatment administration will be at the study center under supervision of site staff.

6.1 TREATMENTS ADMINISTERED

The administered treatments are summarized in Table 7. For more details, see the RO7296682 IB and pharmacy manual.

Study medication must be administered in a clinic or hospital equipped for systemic (IV) cancer treatment. Full emergency resuscitation facilities should be immediately available, and participants should be under close observation by the Investigator/site staff at all times. In case of infusion associated AEs, the signs and symptoms should be fully resolved before the patient is discharged.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 and Section 7.1 respectively for RO7296682, and in Section 8.2.

For information and guidance on pre-medication, see Section 6.1.2 and Table 8.

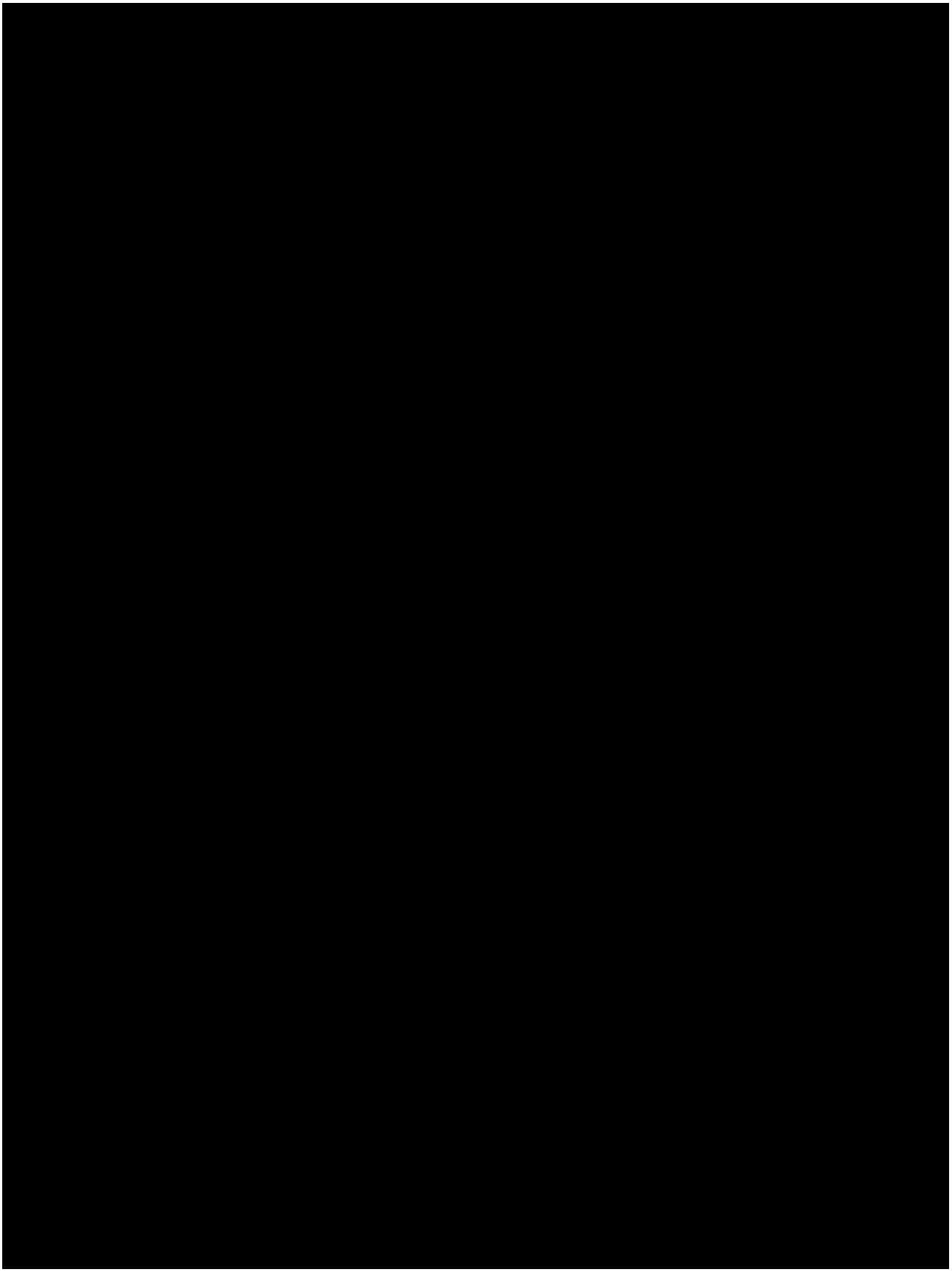
Table 7 Summary of Treatments Administered

	Ro 729-6682/F01 (active)	**Ro 729-6682/F02 (diluent)**
Dose Formulation:	Solution for infusion	Solution for infusion
Unit Dose Strength(s)/Dosage Level(s):	20 mg/mL	0 mg/mL
Dose:	Ascending flat doses with starting dose of 0.3 mg	Not applicable
Route of Administration:	IV infusion*	IV infusion*

- * 0.2 μm in-line filter to be used for drug administration

6.1.1 RO7296682 and Infusion Rates

RO7296682 will be administered by IV infusion over 4 hours (240 min) at the first infusion. If the first infusion is well tolerated, as defined by an absence of Grade ≥ 2 IRRs, the second infusion may be given over 2 hours (120 min). If the 2-hour infusion is well tolerated, all subsequent infusions may be further reduced to 60 minutes. If the previous infusion was not well tolerated, RO7296682 should be infused at the previous infusion rate. In case this infusion is well tolerated again, subsequent infusion may be reduced as previously described. Please refer to Section 6.1.2 and Section 8.3.8 for premedication and IRR management guidelines, respectively. Ro 729-6682/F01 (active) solution for infusion should be used undiluted or diluted in the Sponsor's Diluent Ro 729-6682/F02 solution prior to administration. A 0.2 μm in-line filter must be used with the infusion set during administration.



6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study drug packaging will be overseen by the Roche clinical trial 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.

The study site should follow all instructions included with each shipment of IMP and diluent. 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.

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

The study site (i.e., Investigator or other authorized personnel) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

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 Monitor upon discovery.

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

The Investigator or delegate must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

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

The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure (SOP) 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/or the 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 interactive voice/web response system (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.

6.3.2 Blinding

Not applicable. This is a non-randomized, open-label study.

6.4 TREATMENT COMPLIANCE

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

6.5.1 Permitted Therapy

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a participant during screening until the follow-up visit must be recorded along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency). All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF. All medication administered to manage AEs should be recorded on the Adverse Event eCRF.

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

Radiotherapy

The use of limited field palliative radiotherapy should be discussed by the Investigator on a case-by-case basis with the Medical Monitor in order to exclude overall progressive disease. When applicable, this type of radiotherapy is allowed at any time during the study, except for:

- Days where RO7296682 is administered

Treatment with RO7296682should be on hold for participants who require short courses of palliative radiation for pain control and may be resumed following completion of radiation.

6.5.2 Prohibited Therapy

All medications (prescription and OTC) taken within 30 days of study screening will be recorded on the appropriate eCRF.

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.
- Chronic use of steroids (excluding topical and inhaled) and concurrent high doses of systemic corticosteroids will not be allowed with the exception of their use to treat AEs (per institutional guidelines). Acute and/or low-dose systemic

immunosuppressive medications (e.g. a one-time dose of dexamethasone for nausea or chronic use of ≤10 mg/day of prednisone or another dose-equivalent corticosteroid) may be allowed after discussion with and approval by the Medical Monitor.

- Administration of a live, attenuated vaccine within 28 days before C1/ D1 or anticipation that such a live attenuated vaccine will be required during the study. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed during influenza season only; however, intranasal influenza vaccines (e.g. Flu – Mist®) are live attenuated vaccines, and are not allowed.

6.6 DOSE MODIFICATION

Instructions for RO7296682 administration, change of infusion rate, interruption of infusion, discontinuation of RO7296682 treatment, and management of specific RO7296682-related AEs are provided in Section 6.1, Section 7, and Section 8.3.8.

Dose-Limiting Toxicities (DLTs):

Participants who experience toxicities fulfilling the definition of a DLT while on treatment 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.

RO7296682-related Adverse Events:

AEs attributable to RO7296682 must resolve to Grade 1 or baseline 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 reductions may be allowed with the approval of the Medical Monitor.

Adverse Events not attributed to study treatment:

A delay of RO7296682 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 after a hold of more than 2 doses, study drug may be re-started with the approval of the Medical Monitor

Liver Function Test (LFT):

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 (INR).

Investigators are encouraged to contact the Sponsor for further guidance if needed. After Cycle 1 is completed, 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 or interventions 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 RO7296682 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 (see Section 4 on Study and Site closure in that Appendix).

7.1 DISCONTINUATION OF STUDY TREATMENT

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

Permanent discontinuation

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

- Intolerable toxicity related to study treatment
  - See Section 8.3.8 on management of specific AEs, including skin toxicity, IRRs, and imAE)
  - See Section 6.6 for AEs not fulfilling the criteria in Section 8.3.8
- Pregnancy
- IgE-mediated hypersensitivity reactions, including anaphylaxis
- Any medical condition that the Investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study

- Disease progression when there is a consensus that the participant will not benefit from the study

Treatment beyond disease progression

- As with other immunotherapies, treatment beyond RECIST Version 1.1 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 Version 1.1 (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

Participants who discontinue study treatment 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 study treatment discontinuation should be documented on the appropriate eCRF.

Participant replacement rules

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

- Participants who withdraw from the study prior to the treatment start may be replaced and will not be entered into the database
- Participants who fail to complete their DLT assessment period because of non-drug-related reasons.
- In the case of a major protocol violation, participants will be excluded from the DLT analysis population and the MTD and/or RP2D determination but might continue the treatment if deemed beneficial, and if there is no safety concern associated with the protocol violation criteria and according to clinical judgment.

7.1.1 Temporary Interruption

Before permanently discontinuing study treatment, an interruption should be considered. Participants who have temporarily interrupted study treatment should be considered to restart as soon as medically justified by the Investigator. For dose delay, interruption, and discontinuation guidelines, refer to Section 6.6, Section 7.1, and Section 8.3.8.

If in the judgment of the Investigator, the participant is likely to derive clinical benefit from RO7296682 after a hold of more than 2 doses, study drug may be re-started with the approval of the Medical Monitor.

7.1.2 Resuming Study Treatment

If a participant has a complete response (CR) or achieves maximum clinical benefit as determined by the Investigator and the Sponsor after an integrated assessment of radiographic data, biopsy results (if available), and clinical status, the study treatment may be paused at the discretion of the treating physician after consultation with the Medical Monitor. The participant may remain on study and be followed according to Section 1.3. If the disease relapses or progresses, the study treatment may be resumed after consultation with the Medical Monitor.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants have the right to voluntarily withdraw from the study at any time for any reason.

In addition, the Investigator has the right to withdraw a participant from the study 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 only as described in Section 7.1.

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 Section 1.3.

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.

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

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 were performed within the time-frame defined in the SoA (Section 1.3).

Certain samples for exploratory tests 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 in this study, any sample type or biomarker evaluation not considered to be critical for safety may be stopped at any time if the data from the samples collected do not produce useful information.

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 of 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 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 7) and immune RECIST (iRECIST, Appendix 8). Response will be assessed by the Investigator on the basis of 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 study. 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 calculate programmatically 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 6.7 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 and complete responses) 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 high-resolution, color digital photography, including a ruler to estimate lesion size. Cutaneous lesions may be considered target lesions if they meet RECIST 1.1 criteria (see Appendix 7), 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 serious adverse events (SAEs) and non-serious adverse events 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.

Complete neurological exam: A complete neurological examination, which includes an evaluation of mental status, cranial nerves, muscle strength, sensation and coordination, should be performed and documented in the participant's chart. Mental status checks can be done without the need to complete a validated mental status questionnaire.

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

Targeted (symptom-directed) physical and/or neurological 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, 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). 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, heart rate, and body temperature while the participant is in a sitting or semi-supine position.

Vital signs collected during the infusion are not required to be captured 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 heart rate and measures PR interval, QRS complex, QT interval, and QT corrected for heart rate (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 and blood draws.

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 heart rate, 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.

For TTE or MUGA scans see Section 8.2.7.

8.2.5 Clinical Safety Laboratory Assessments

Local Laboratory Assessments

Local laboratory assessments are provided in Appendix 4 and must be conducted in accordance with Section 1.3. Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts.

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. In circumstances where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated.

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 eCRF.

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 to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

8.2.6 Medical 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.

8.2.7 Transthoracic Echocardiogram or Multiple-Gate Acquisition Scans

Transthoracic echocardiogram (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 LVEF decline during RO7296682 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).

8.2.8 Brain CT/MRI

A CT or MRI scan (with IV contrast unless contraindicated) of the head must be performed at baseline to assess CNS metastasis. In the event of an equivocal CT scan, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline. If the participant presents CNS metastasis at baseline, on-treatment tumor assessments must also contain a CT or MRI scan of the head. If participant has no brain metastasis at baseline, then CT/MRI scan of the head is only indicated if symptoms suggest potential brain disease

8.2.9 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).

8.2.10 Royal Marsden Hospital Risk Score

The Royal Marsden hospital risk score will be derived at time points depicted in SoA (Section 1.3) for each participant. This risk-based score is derived from: (LDH normal = 0 vs LDH > UNL =1 1, albumin > 35 g/L = 0 vs < 35 g/L = 1, site of metastasis < 2 = 0 vs > 2 = 1) (Arkenau et al 2008).

8.2.11 ECOG

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

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.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 2. The non-serious adverse events of special interest (AESI) and disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are discussed in Sections 8.3.6 and Section 8.3.7.

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 last follow-up visit. AEs fulfilling the criteria in Section 4.1.3 and occurring within the DLT period as defined in Section 4.1.2.1 will be reported as DLT.

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 last 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 time-points.

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 to be related to study treatment or trial-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, NSAESI, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of a 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a 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 EC, see Appendix 2.

8.3.4.1 Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical Monitors is available 24 hours a day 7 days a week. Medical Monitors contact details will be available on a separate list generated by the study management team.

8.3.5 Pregnancy

Female participant 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.

Male participant will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 28 days after the last 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, ectopic pregnancy) are considered SAEs (Appendix 5).

8.3.6 Non-Serious Adverse Events of Special Interest

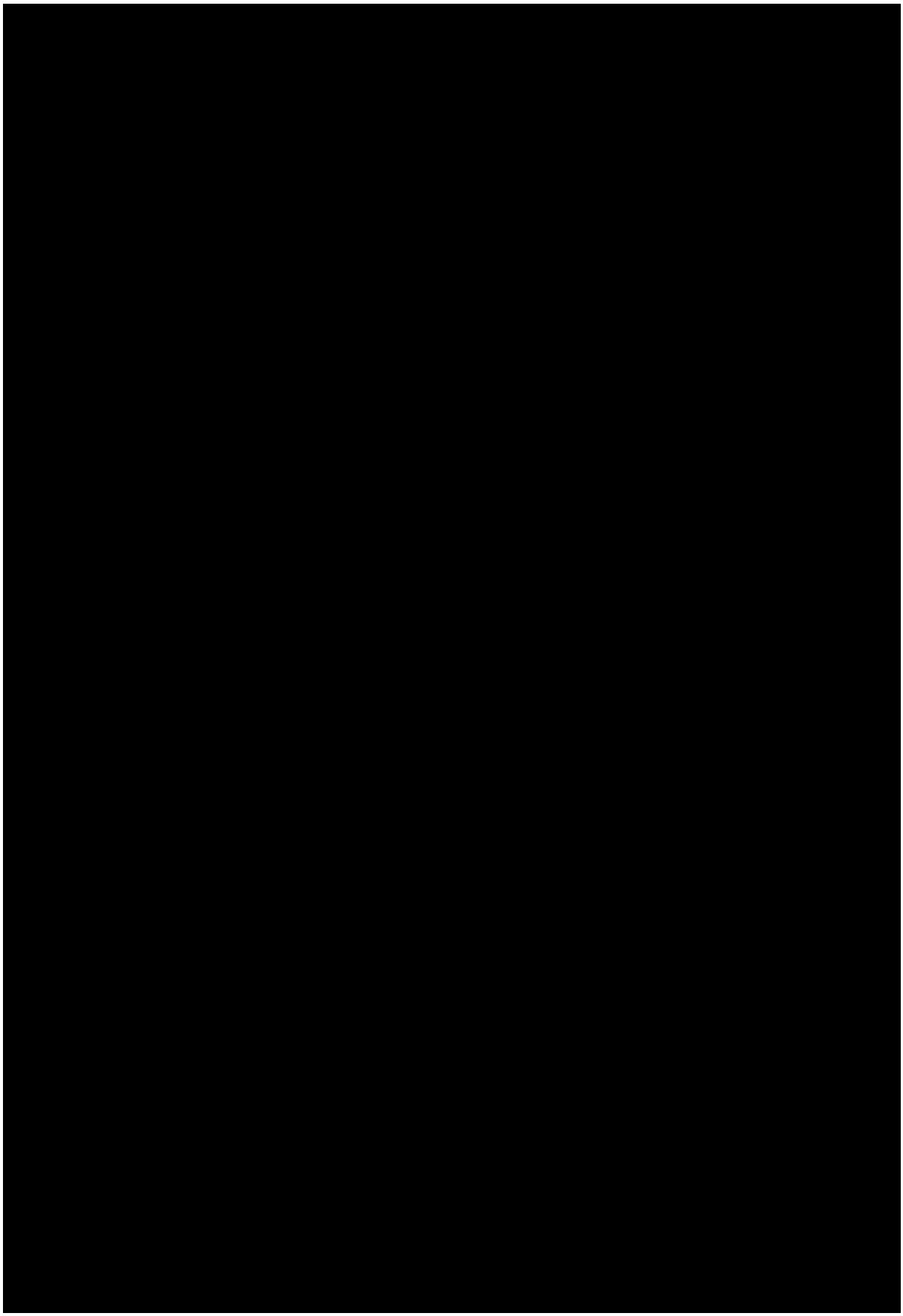
Non-serious AESI are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2 for reporting instructions). Non-serious AESI for this study include the following:

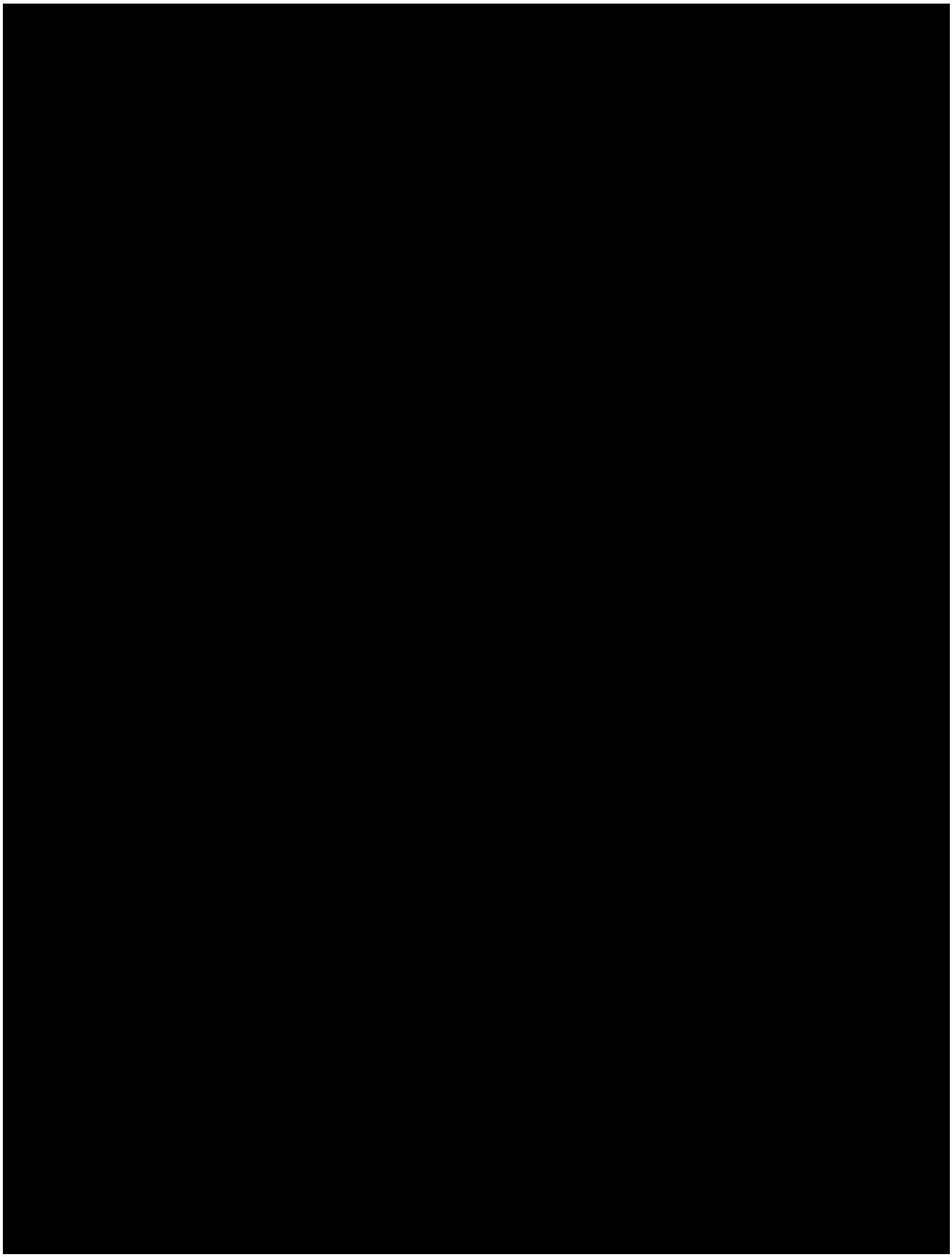
- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Appendix 3.
- Suspected transmission of an infectious agent by RO7296682, as defined as follows:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible 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.

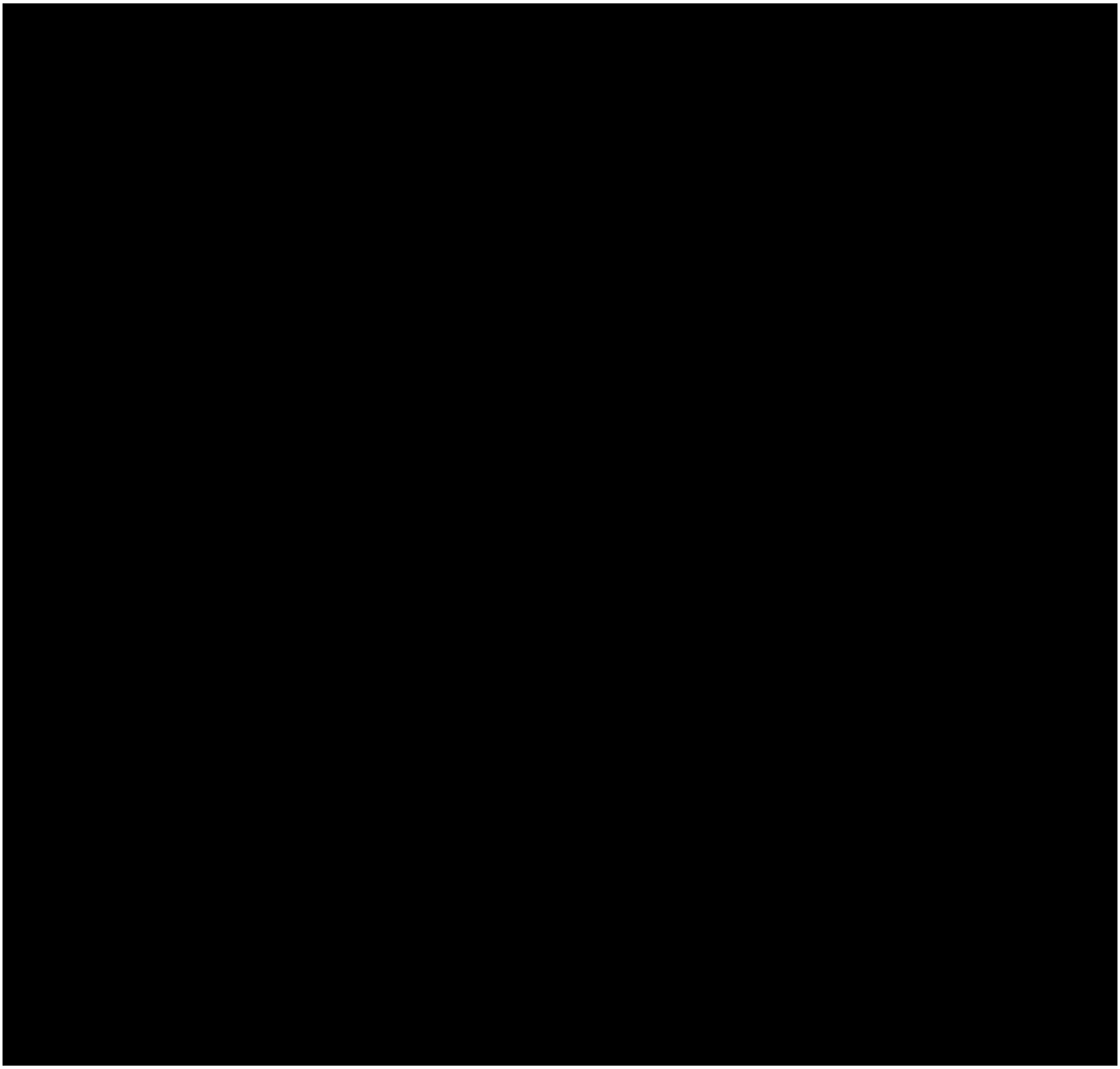
8.3.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

No disease-related events have been identified for this study. Death should be considered an outcome and not a distinct event. For reporting of deaths refer to Section 7 in Appendix 3.

[redacted]







8.3.8.4 Immunogenicity

For immunogenicity, refer to Section 8.6.

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 (see Sections 5 and 5.2 of Appendix 2 for further details).

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:

1. Contact the Sponsor's Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved.
3. Obtain a blood sample for PK analysis within 14 days from the date of the final dose of study treatment, if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose, as well as the duration of the overdose, in the CRF.

For this study, any dose of RO7296682 greater than 150% of the assigned dose level will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

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 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).

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 6.6 Dosage Modifications).

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.

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 is a humanized antibody, there is a risk that ADAs against RO7296682 could develop, potentially reducing its efficacy and/or potentially resulting in symptomatic hypersensitivity reactions, in particular immune-complex reactions.

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

[redacted]

If required, the residual volume of PK samples taken during the study (at any time point) can also be used for additional ADA analyses. 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 $\geq$ 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 concentrations.

Any residual material from samples collected for PK, safety, biomarker assays, and ADA may be used for exploratory biomarker profiling, identification, and PK/PD assay development purposes and additional assessments (e.g. ADA response characterization), as appropriate.

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

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

8.7 PHARMACODYNAMICS AND BIOMARKERS ANALYSES

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 [redacted] differentiation [redacted] and [redacted] changes. These samples will also be used to undertake receptor occupancy assessments for RO7296682. These samples will be taken from all participants enrolled in Parts A and B of the study.

- Serum and/or plasma samples: PD biomarkers such as cytokines and inflammation markers [redacted] will be analyzed. Because these measurements are also safety

measure assessments during any IRRs, they will be examined to all participants enrolled in Parts A and B of the study. Disease-monitoring markers that include but are not limited to [redacted] etc. will also be assessed.

- Fresh tumor biopsy: Mandatory fresh tumor biopsy samples must be obtained for all participants enrolled in Part A cohorts after reaching Tissue Biomarker Dose and Part B cohorts at baseline and on treatment from a safely accessible site and after participant's consent (see Section 1.3). These samples will be assessed for treatment-induced changes in immune cell numbers and activation characteristics, as well as changes in tumor markers such as [redacted]. The analyses will be performed by flow cytometry, molecular, immunohistochemistry and/or genetic and genomic (see Section 8.7.1) methods with respect to changes in the characteristics of lineage [redacted], activation [redacted], differentiation [redacted], expression of [redacted].

- Healthy skin punch biopsy: Mandatory fresh skin biopsy samples must be obtained at baseline and on treatment for all participants enrolled in Part A cohorts after reaching Tissue Biomarker Dose and Part B cohorts 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 8.7.1).
- Archival tissue: For all patients enrolled in in Parts A and B of the study, archival tumor material must be available to allow for the genetic and genomic analyses described in Section 8.7.1 and any immune cell characterization as described for the fresh biopsies above.

Whole blood, serum/plasma, and tissue 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.

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 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 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 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, 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 impact 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 8.9.2). 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 collected at the visits specified in the SoA and may be used for DNA and/or RNA extraction for exploratory research on genomic biomarkers (including, but not limited to, cancer-related genes and biomarkers associated with common molecular pathways, or immune-related markers [e.g., [redacted]], microsatellite instability [MSI] and tumor mutation burden), and for DNA and/or RNA extraction to enable genomic analysis for exploratory research on genetic biomarkers.

8.7.1.3 Transcriptome Analysis

Tissue biopsy/blood (other matrix possible) will be collected (see SoA, Section 1.3) for RNA extraction and subsequent gene expression profiling in-line with our efforts on:

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

8.8 BIOMARKER SAMPLES

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

Whole blood, serum/plasma, and stool and tissue samples will be collected at time points specified in the SoA (Section 1.3). See Section 8.7 for additional details.

8.8.1 Mandatory Samples

The following mandatory samples for PD and biomarker research are required and will be collected from all participants enrolled in Part A after reaching the Tissue Biomarker Dose and Part B in this study:

Tumor: Mandatory tumor biopsy samples (each time point consisting preferably of at least three core specimens) will be collected from all participants enrolled in Part A cohorts after reaching Tissue Biomarker Dose and Part B of the study on two occasions (once at baseline and once during the study treatment period [C2D8]) from a safely accessible site and after patient'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 *or healthy skin punch biopsy* time points may be considered upon joint agreement between Investigators and the Sponsor.

Archival tumor tissue is to be obtained from all participants to allow for the genetic and genomic analyses described in Section 8.8.1. Both archival and fresh tumor biopsy

specimens will be analyzed with respect to changes, as described (Section 8.7), including but not limited to immune and tumor cell characteristics, [redacted] etc.

Healthy skin punch biopsy: Mandatory fresh skin biopsy samples must be obtained at baseline and on treatment for all participants enrolled in Part A cohorts after reaching the Tissue Biomarker Dose and Part B cohorts (see Section 1.3) on two occasions (once at baseline and once during the study treatment period [C2D8]) after participant's consent. The baseline and on-treatment biopsies should preferably be taken from the same area, to ensure comparability. These samples will be assessed for treatment-induced changes in the skin immune contexture by immunohistochemistry and/or genetic and genomic methods (see Section 8.7.1).

Whole blood: From every participant in the study (Parts A and B), whole blood samples will be collected for flow cytometry in order to determine immune cell changes (including but not limited to immune cell subsets, activation and proliferation markers) and also to perform receptor occupancy assessments. A whole blood sample will be taken for [redacted] sequencing ([redacted]). The DNA will be used to determine in peripheral [redacted] the repertoires of [redacted] to analyze [redacted] diversity.

Serum and/or plasma: Blood for serum/plasma isolation will be collected in Parts A and B for investigation of markers and cytokines including but not limited to [redacted] and others, and soluble tumor markers including but not limited to [redacted] etc. In the event of an IRR, an additional sample will be collected.

Clinical genotyping samples: From every participant (Parts A and B), a baseline mandatory whole blood sample will be taken for DNA/RNA extraction. The DNA will be used to determine if alleles at genes associated with immune responses such as chemotaxis, HLA, immunosuppression, etc. affect the PK/PD/efficacy/safety of RO7296682. Data arising from this study will be subject to the same confidentiality as the rest of the study.

Other safety biomarkers: 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. Archival tumor blocks will be returned. 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.

8.8.2 Optional Samples

Tissue Biopsies

Optional tissue biopsies may be taken at any time point per Investigator's discretion and with participant's consent, for example due to skin-related AEs, disease progression, or long-lasting stable disease, 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 informed consent form 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 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 Research Biosample Repository (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.

8.9.2 Sample Collection

DNA and RNA RBR samples will be collected from participants who give specific consent to participate in this optional RBR during C1D1. Collected specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, AEs, or progressive disease.
- To increase knowledge and understanding of disease biology.
- 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.

In addition, 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 or diseases:

- Leftover plasma samples
- Leftover serum samples
- Leftover blood samples
- Leftover tumor samples

Optional Stool Samples

In Part B, dose expansion, 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 impacting potential AEs during immunotherapies. A nutritional assessment may 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

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.

Optional stool samples will be destroyed within 2 years after the date of final closure of the clinical database.

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 whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing (NGS), 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 participants are more likely to respond to a drug or develop AEs. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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. 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 will 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. Given the complexity and exploratory nature of these analyses, WGS/WES data and analyses will not be shared with Investigators or study participants unless required by law.

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 Laboratory Manual.

RBR samples will be stored and used until no longer needed or until they are exhausted. The Research Biosample Repository storage period will be in accordance with the IRB/EC-approved Informed Consent Form 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/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. ICFs for enrolled participant and for participants who are not subsequently enrolled will be maintained at the study site.

All screening, and all 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.

Screening and pretreatment assessments will be performed according to the SoA outlined in Section 1.3. Serum pregnancy test will be done 7 days prior to C1D1. Where the clinical significance of an abnormal screening test result (lab or any other tests) is considered uncertain, the test may be repeated. Screening tumor assessments performed in a reasonable time window prior to Informed Consent Form signature can be accepted if agreed with the Sponsor and if done as standard of care and according to RECIST v1.1 and iRECIST in a qualified facility in which all further scans for the participant will be performed (as defined in Appendix 7 and Appendix 8).

8.11.2 Assessments during Treatment

Under no circumstances 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 SoA (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 schedule of assessments.

Participants will be treated with study treatment, until disease progression, unacceptable toxicity, withdrawal of consent, or withdraw by Investigator. Participants may receive study treatment for a maximum of 24 months since C1D1.

8.11.3 Assessments at Study Completion/Early Termination Visit

End of Treatment/Early Discontinuation: Participants who complete the study 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 90 (± 7) days after the last dose of study drug or last data point determined for an End of Study Visit. Assessments should be completed as detailed in the SoA (Section 1.3).

Survival Follow-Up: The sites will provide to the Sponsor an update on survival status and new anti-cancer treatment 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. Contact can be either in person

or via a phone call to document; the sites will use a designated section of the eCRF for this purpose.

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

8.11.5 Assessments at Unscheduled Visits

For activities that are required to be performed in case of an unscheduled visit, see Section 1.3.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

No formal statistical model and no formal hypothesis testing are planned in this study.

9.2 SAMPLE SIZE DETERMINATION

- Part A:

The maximum total number of participants in the dose escalation portions of Part A will be approximately *90* 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. The simulations presented in Section 3 of [redacted] show however simulated sample sizes in a variety of toxicity scenarios.

- Part B:

Up to a maximum of 50 participants may be enrolled in the expansion cohort in Part B. Participants with MEL, NSCLC and HNSCC which are not amenable to standard treatment, will be enrolled in Part B; but if emerging data suggest alternative indications should be pursued, then participants with ovarian, esophageal, TNBC or other indications as deemed fit may be considered.

- Tumor biopsy samples

[redacted]

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 12.

Table 12 Analysis Populations

Analysis Population	Description
Efficacy	All participants who received at least one dose of RO7296682, and who have at least one baseline and one on-study tumor assessment. Participants who received at least one dose of study drug and discontinued the study because of progression before the first on-study tumor assessment will be considered as response-evaluable.
DLT evaluable	DLT evaluable participants are those who have completed the DLT period with two administrations of RO7296682 during the DLT period and 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 randomized to study treatment (RO7296682) and who received at least one dose of the 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 (RO7296682) 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.

9.4 STATISTICAL ANALYSES

The data will be analyzed by the Sponsor and/or designated contract research organization (CRO). 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 and regimen within each part.

This is a one group, monotherapy dose escalation study; therefore comparability of treatment groups does not apply.

9.4.2 Efficacy Analyses

The primary and secondary efficacy analyses listed in Table 13 will include all participants in the efficacy population with participants grouped according to dose cohort (and schedule if applicable) within each study part.

Table 13 Efficacy Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
According to RECIST Version 1.1 criteria (Appendix 7) and iRECIST (Appendix 8) • 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. Disease control rate 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 Version 1.1 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 Version 1.1) 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 participant will be classified as non-responders.

DoR will be calculated for participants who have a best overall response of CR or PR and will be 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 (on-treatment PFS).

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 Version 1.1 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, DRC, DoR, and PFS) may include the evaluation of response according to iRECIST. As a sensitivity analysis, the analysis described in Table 13 may be applied to a more generic definition of PFS that also includes deaths occurring more than 30 days after last study treatment. Secondary analyses of response endpoints may (if implemented) include the evaluation of response.

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 14 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 14 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.

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

Individual and mean serum RO7296682 concentration versus time data will be tabulated and plotted by dose levels and/or dosing regimens. 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, AUC, 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.

Non-linear mixed effect modeling will be used to analyze the concentration-time data of RO7296682. For RO7296682, 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 Cmax and AUC) may be derived from the model for each individual included in the PK analysis and will be presented descriptively.

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 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.

- 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 may be analyzed and reported.
Additional analyses may be conducted as appropriate.

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 B will evaluate PD effects and preliminary anti-tumor activity of the MTD and/or RP2D of RO7296682 determined in Part A. To assess the effect of RO7296682 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 $\geq$ 4-fold reduction 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 ≥ 4-fold increase 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 and selected biomarkers, efficacy, or safety parameters, as appropriate.

9.5 INTERIM ANALYSES

No formal interim analyses are planned. Participant's safety will be reviewed on an ongoing basis in all parts of the study and formally discussed during part A within the official dose-escalation meetings.

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 11 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 : Cockcroft-Gault formula/Creatinine clearance (ml/min)
- Appendix 7 : Response Evaluation Criteria in Solid Tumors
- Appendix 8 : Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST)
- [redacted]
- Appendix 10 : Preexisting Autoimmune Diseases and Immune Deficiencies

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 (US) or under a US Investigational New Drug (IND) application will comply with US Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union (EU)/European Economic Area (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 Informed Consent Form (and ancillary sample ICFs such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. The Master Informed Consent Form for this study encompasses 1) the consent to participate in the study, 2) the consent for optional collection of samples for RBR, 3) the consent for optional biopsies and 4) the consent for optional stool samples for RBR (only in Part B). 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 Consent Forms must be signed and dated by the participant or the participant’s legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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

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

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

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

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 specimens to be used for exploratory research.

Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their 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 subject 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 Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (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 their 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 trial 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 trial is closed. A participant's withdrawal from Study WP41188 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 WP41188. 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 Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data 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 Roche, 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 Informed Consent Form. Roche 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 Roche. 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 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 eCRF.

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

2.1.2.1 Electronic Clinical Outcome Assessment Data

Not applicable.

2.1.2.2. Paper Clinical Outcome Assessment Data

Not applicable.

2.1.2.3. 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.

2.1.3. 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, clinical outcome assessments (paper or electronic), evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, 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.

2.2. 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 unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

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.

A description of this clinical trial will be available at http://www.clinicaltrials.gov.

2.3.4. 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

3.1. INDEPENDENT REVIEW COMMITTEE (IRC)

See Section 3.3 of this appendix.

3.2. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

See Section 3.3 of this appendix.

3.3. SAFETY AND DOSE ESCALATION COMMITTEE

No formal third party data monitoring committee is planned. However, ongoing medical data review will be performed regularly by a Safety and Dose Escalation Committee (SDEC) composed of key Sponsor-based functional representatives of the clinical study team, including at a minimum the Medical Monitor, Drug Safety Scientist, and the Biostatistician. As part of these regular teleconferences, investigators and relevant site personnel will be invited to attend every SDEC meeting.

This committee will make decisions regarding dose escalations based on the plan described in Section 4.1.2 and Section 4.1.5. The SDEC will meet regularly and additionally as needed at the request of the study Medical Monitor (e.g., based on unexpected safety signals). In addition, study investigators are expected to participate

with the SDEC in regularly scheduled meetings on risk-benefit assessment throughout the trial.

3.4. CLINICAL EVENTS COMMITTEE

See Section 3.3 of this appendix.

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 AEs 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

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 subject 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:

- Any Deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., electrocardiogram [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 Section 4 of Appendix 3).
- Exacerbation of a chronic or intermittent pre-existing condition, including 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. 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 that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/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 SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death attributed to progressive disease).

A SAE is defined as any untoward medical occurrence that at any dose:

- **Results in death.**
- **Is life-threatening**
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it 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 medication 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 the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The Investigator will attempt to establish a diagnosis of the event 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.

SAEs 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_5x7.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 SAE (see Section 6 of this Appendix for reporting instructions), per the definition of SAE in Section 2.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 6 for reporting instructions), per the definition of SAE in Section 2. Grade 4 laboratory abnormalities will only be reported as SAEs if these meet 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 died during participation in the study or during a recognized follow-up period, the Investigator will provide the 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
- Non-serious adverse events of special interest (NSAESI)
- Pregnancies (see Section 8.3.5)
- Dose-limiting toxicities (DLTs) during the DLT assessment window (defined in Section 4.1.3; see Section 5.1 of Appendix 2 for details on reporting requirements)

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

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

Investigators must also comply with local requirements for reporting SAEs 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 electronic data capture (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; see Section 5.1 of Appendix 2,). For RO7296682**,** AEs associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with RO7296682, regardless of whether they result in an AE, should be recorded on the AE 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 SAEs 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 using the following reference document:

- RO7296682 IB

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

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

1.1. INFUSION-RELATED REACTIONS/INJECTION REACTIONS

Adverse events that occur during or within 24 hours 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") 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 adverse events other than infusion-related reactions, 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, adverse events 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 adverse events 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 adverse event is one that extends continuously, without resolution, between participant evaluation time-points. Such events should only be recorded once on the AE 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 AE eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between participant evaluation time-points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the AE 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 times 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 alanine aminotransferase (ALT) or aspartate aminotransferase (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, the Investigator

must report it as an adverse event following the rules of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 8.2 and Section 8.3) 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 8.3.1).

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). A Safety and Dose Escalation Committee will monitor the frequency of deaths from all causes.

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

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 Version 1.1. 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 adverse event 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 adverse event 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 unless otherwise specified. The results must be captured in source documentation and entered into the eCRF.

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

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

All study-required safety laboratory assessments will be performed by local laboratories, with the exception of the following:

- Analysis of IgE and tryptase samples will be performed centrally and locally.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Leucocytes, 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 (by Cockcroft-Gault formula, see Appendix 6), total protein, albumin, calcium, magnesium, phosphorous, uric acid, bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT, [redacted], ferritin.
Thyroid hormones	• TSH, free T3 (or total T3 for sites where free T3 is not performed), free T4
Coagulation	• INR or PT (depending on local laboratory guidelines), activated partial thromboplastin time (aPTT); additional coagulation parameters (i.e., fibrinogen, d-dimer, anti-thrombin III [antigenic or chromogenic], fibrin degradation products) may be assessed according to clinical judgment.
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 lipoprotein (HDL) cholesterol, triglycerides

Laboratory Assessments	Parameters
Pregnancy Test	• All women of childbearing potential (including those who have had a tubal occlusion) will have a blood pregnancy test at screening within 7 days before first dose of study treatment on C1D1, serum or urine tests during treatment period (according to the SoA – see Section 1.3) and on the End of Treatment and Safety Follow-up visit. • Serum human chorionic gonadotropin (hCG) pregnancy test
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, RBCs, white blood cells (WBCs), 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 or AE Grade ≥2 leading to dose interruption or reduction. A second sample for central IgE/Tryptase analysis will be collected approximately 48 hours after onset of the reaction.

The results of each test must be entered into the eCRF. 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 lab 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 this analysis, 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

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 (WONCBP)**

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 a 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 **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) Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
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.

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 embryofetal 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; see Section 5 of Appendix 2)

Appendix 6
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:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age } \langle\text{years}\rangle) \times \text{body weight } \langle\text{kg}\rangle)}{(72) \times (\text{serum creatinine } \langle\text{mg/dL}\rangle)} \times 0.85 \text{ (if female)}$$

Appendix 7
New Response Evaluation Criteria in Solid Tumors—Version 1.1—Modified Excerpt from Original Publication with Addition of Supplementary Explanations

The following text is based on Eisenhauer et al. 2009 (see list of references in Section 3 of this Appendix).

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 CT or 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 in this Appendix below 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 is 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, PET 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) since 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 prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

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

CT, 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 prior to enrollment it is known that a participant is unable to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the subject 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 prior studies if possible. Each case should be discussed with the radiologist to determine if 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.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, and Histology: The utilization of these techniques for objective tumor evaluation cannot generally be advised but will be dependent on the study design.

2 TUMOR RESPONSE EVALUATION

2.1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess OR 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 above in Section 1.1.1 of this appendix).

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 $\geq$ 10 mm by CT scan).

Target lesions should be selected on the basis of 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 since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted in Section 1.1.1 of this appendix, pathological nodes 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 2 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 x 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 of this appendix).

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g., ‘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.
- Progression of Disease (PD): 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 PD.

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 CR criteria are met, since 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 eCRF:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

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

CR: Disappearance of all non-target lesions (and, if applicable, normalization of tumor marker level). All lymph nodes must be non-pathological in size ($<$10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression (see Section 2.3.4 of this appendix) 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' on the basis of 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 on the basis of 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 trials 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 PD for measurable disease: i.e., 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 PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

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 pre-existing lesions). This is particularly important when the participant's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

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

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, 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. Table 1 of this subsection provides a summary of the overall response status calculation at each time-point for participants who have measurable disease at baseline.

When participants have non-measurable (therefore non-target) disease only, Table 2 of this subsection is to be used.

Table 1 Time-Point Response – Target (w/wo 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; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

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; NE = inevaluable; PD = progressive disease; SD = stable disease.

[a] 'Non-CR/Non-PD" is preferred over 'SD' since SD is increasingly used as an endpoint for assessment of efficacy in some trials; to assign this category when no lesions can be measured is not thus advisable.

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 are 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 PD.

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 PD 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” since 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, NE=inevaluable, PD=progressive disease, PR=partial response, SD=stable disease.

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 time 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.

2.4.3 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 eCRF.

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 OR: it is a reason for stopping study therapy. The OR status of such participants is to be determined by evaluation of target and non-target disease as shown in Tables 1-3 in Appendix 7.

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 (i.e., 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.

2.5 FREQUENCY OF TUMOR RE-EVALUATION

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of Phase 2 studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If ‘time to an event’ (e.g., time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any

other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6 CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

2.6.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials [2]. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.6.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

3 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;45:228-247.

Bogaerts J, Ford R, Sargent D, et al, Individual patient data analysis to assess modifications to the RECIST criteria Eur J Cancer 2009;45:248-60.

Appendix 8
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; see list of references at end of this Appendix) 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 time point 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 on the basis of 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 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 time points 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 time points after disease progression per RECIST v1.1. At each time point, non-target lesions should continue to be categorized as "absent" (complete response [CR]), "unequivocal progression" (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 time point 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 (eg, non-lymph node lesions must be $\geq$10 mm on the longest diameter; new lymph nodes must be $\geq$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 time points.

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 time point. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent time point 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 time point.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is $\geq$15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is $\geq$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 time points, 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 time point 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 time points. • 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 time point. • 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 time point.

Abbreviations: 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 TIME POINT

Time point response per iRECIST will be calculated programmatically by the Sponsor. A complete description of the iRECIST criteria can be found in a publication by Seymour et al. (2017).

References:

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

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- e152.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15:7412-20.

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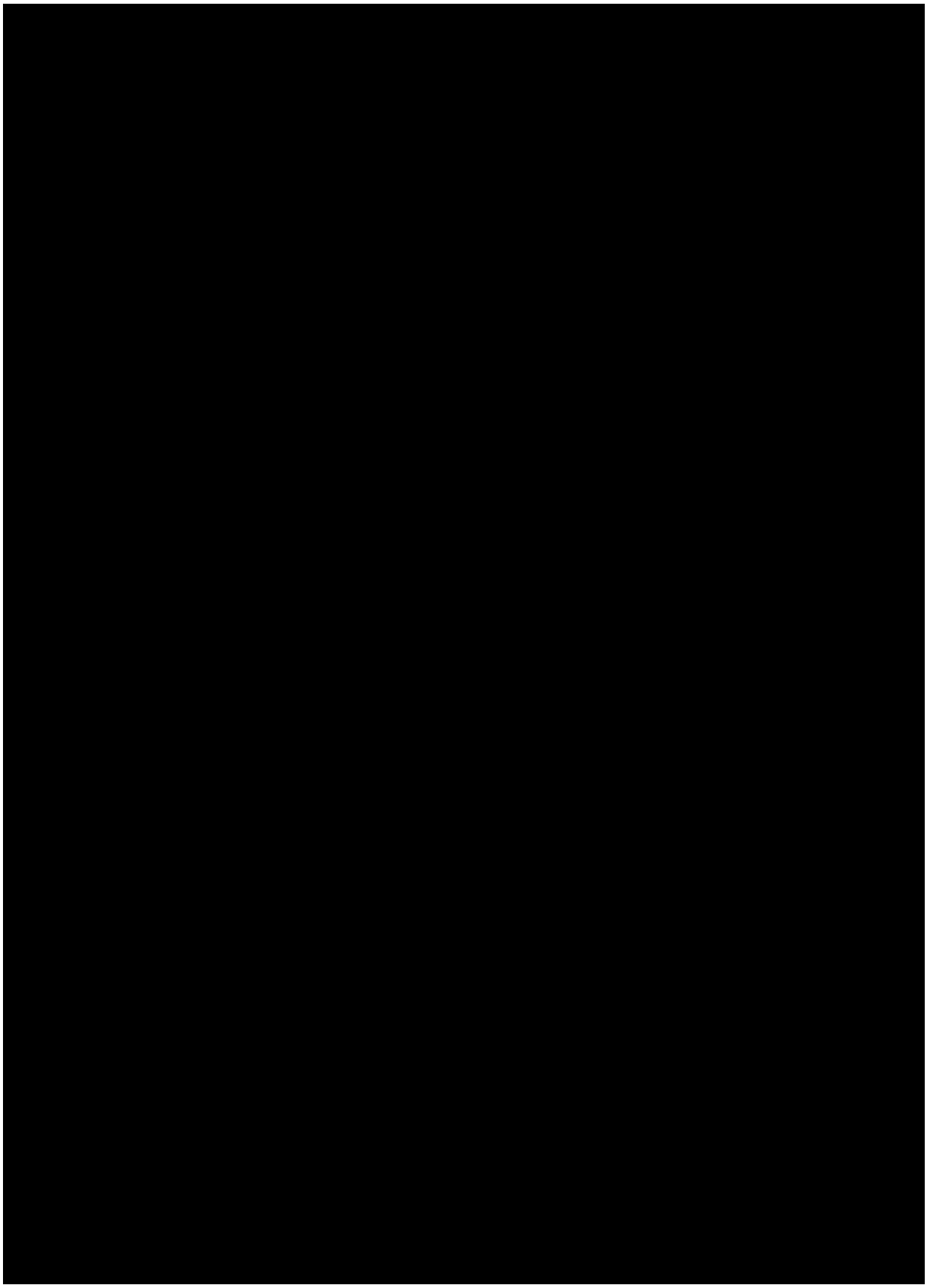

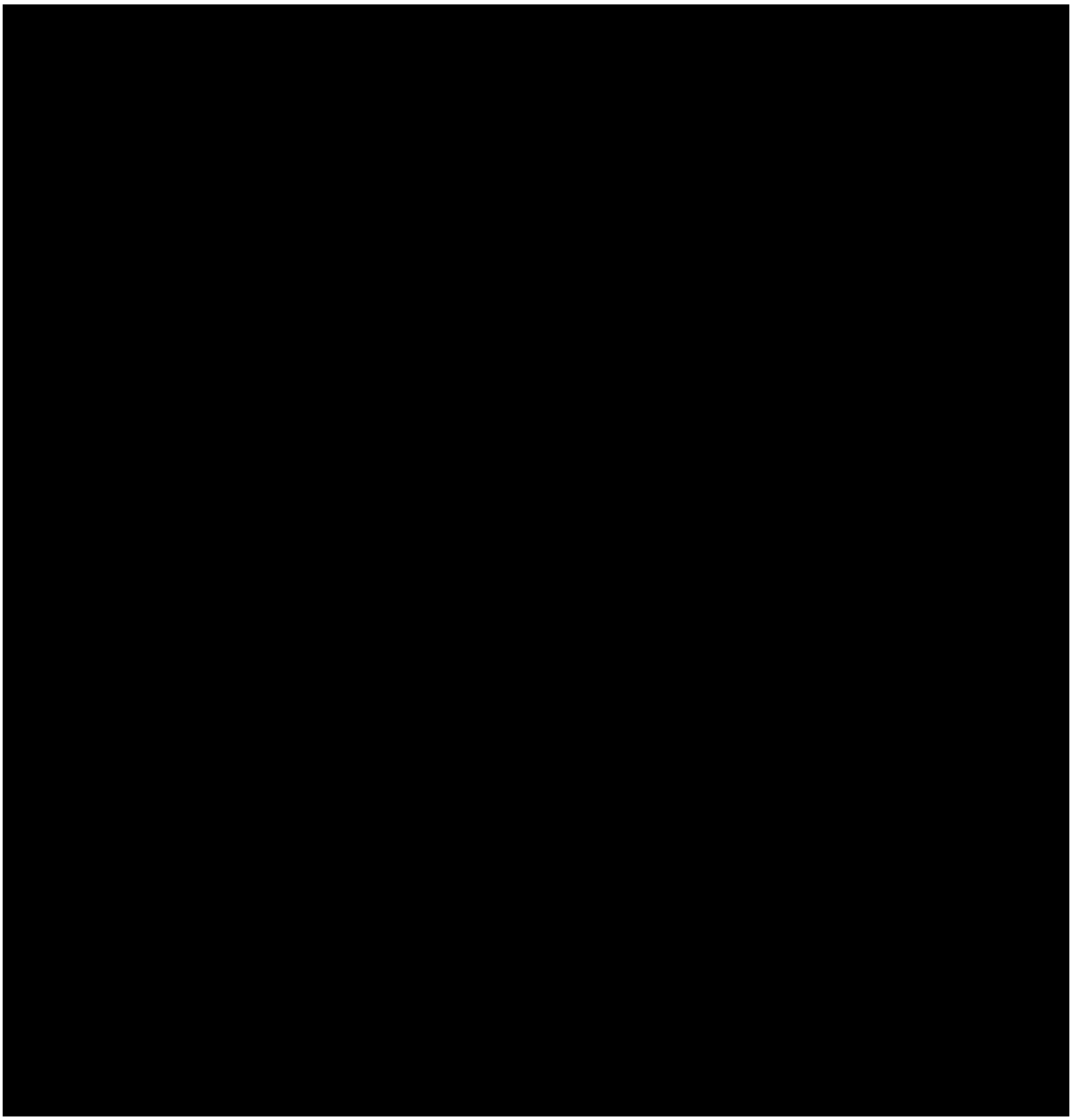

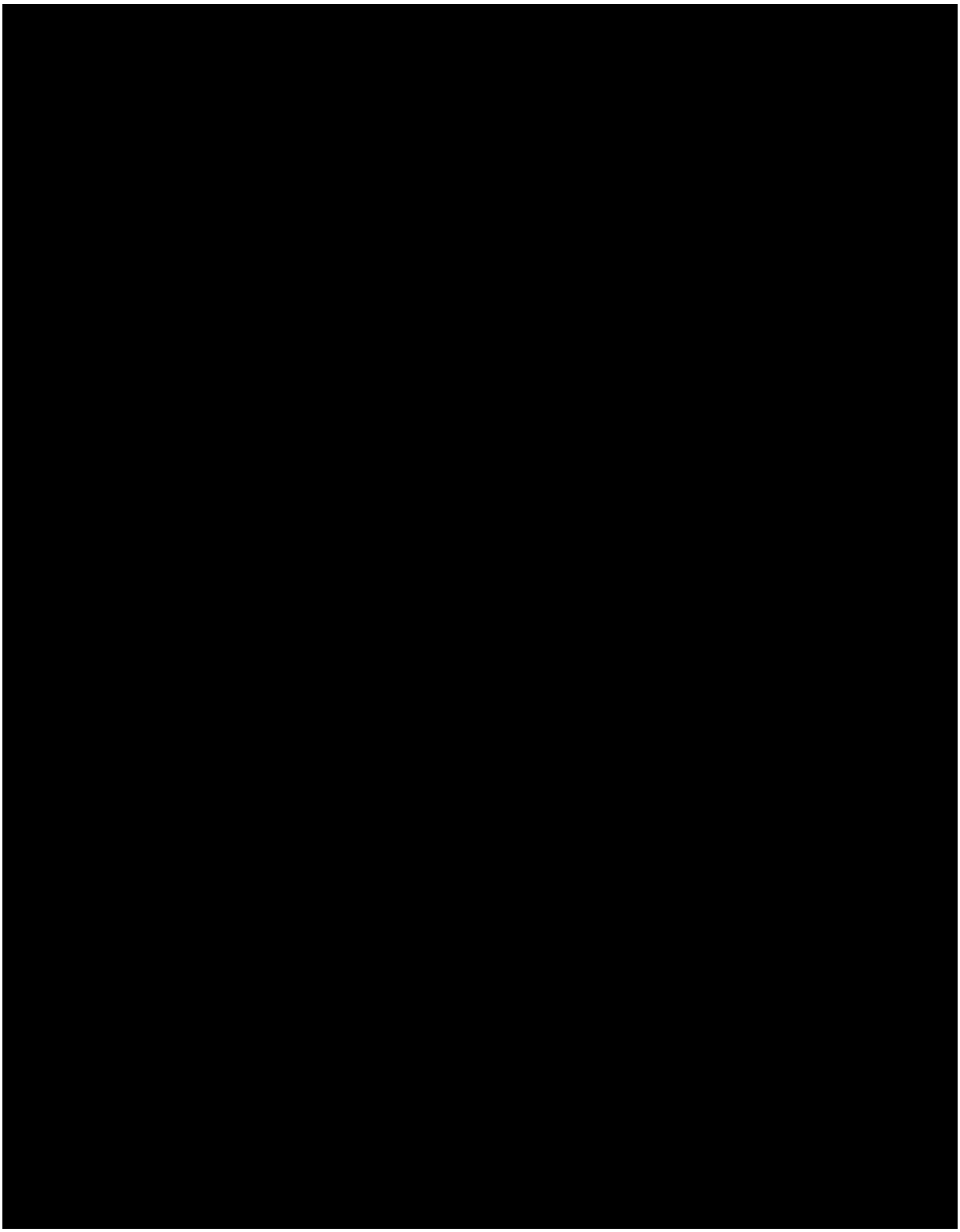

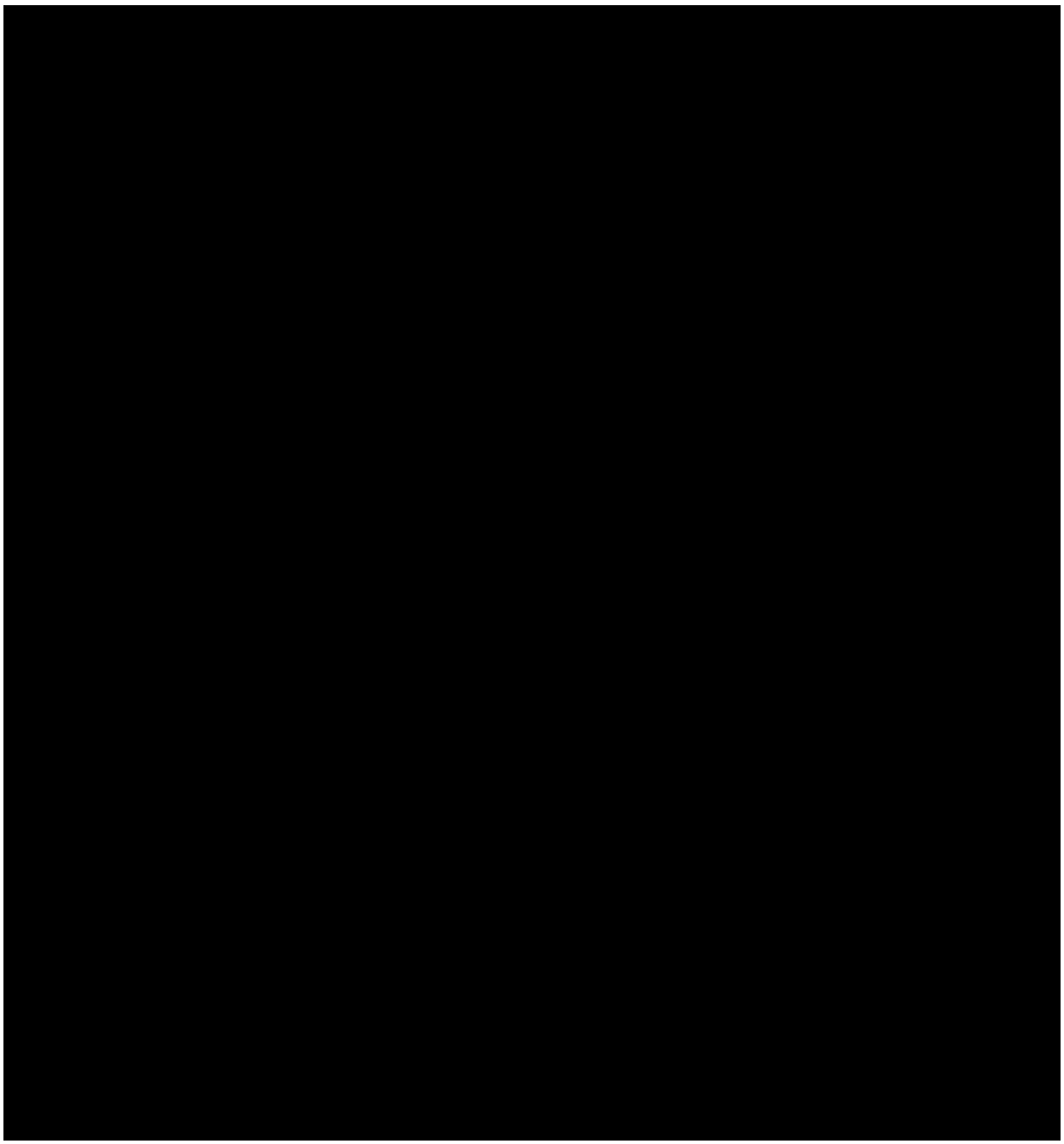

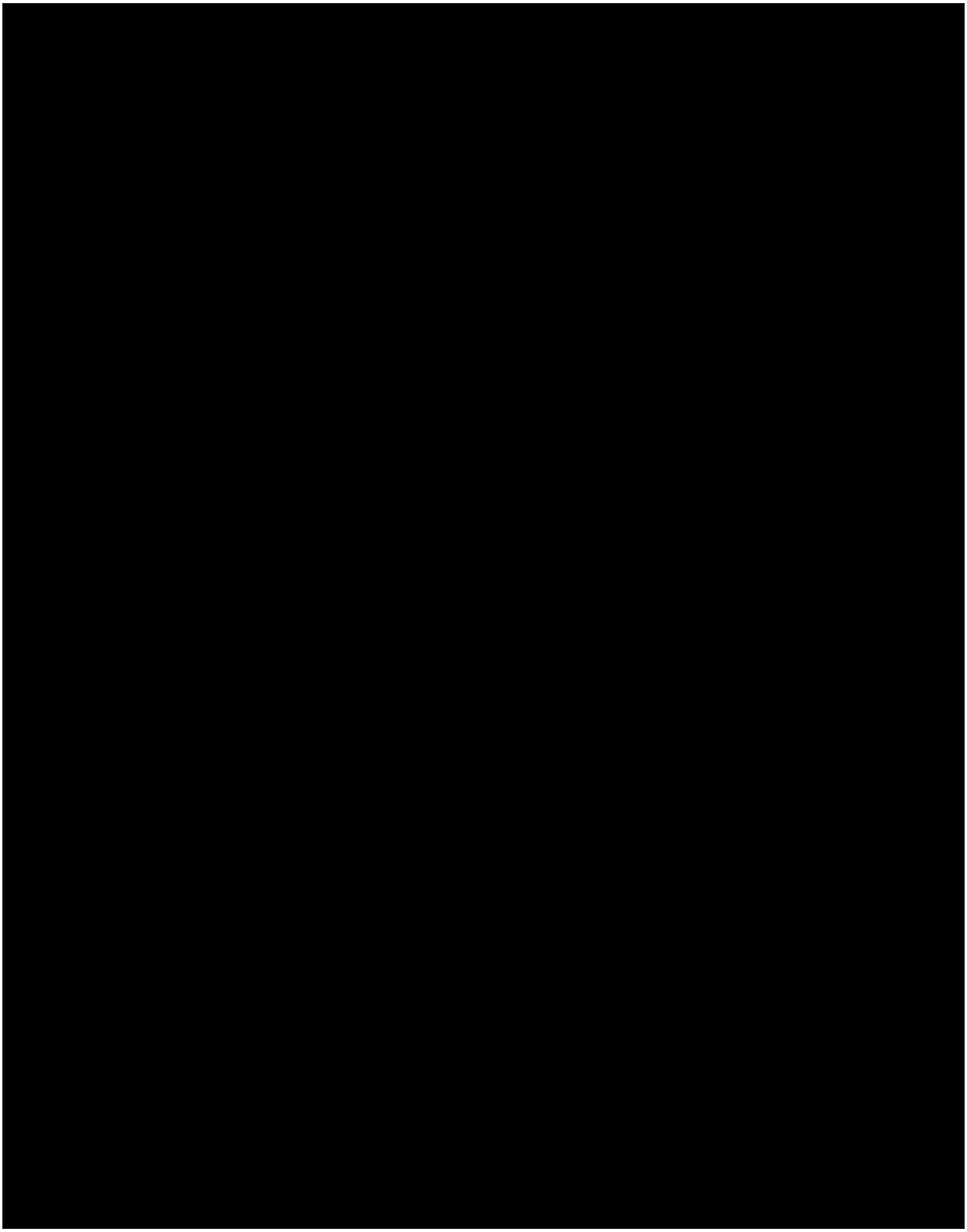

Appendix 10
Pre-existing Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the Table 1 below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Table 1 Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cirrhosis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis